

# NEW APPLICATION



0000171279

RECEIVED

2016 JUN 23 A 10:57

AZ. CORP COMMISSION  
DOCKET CONTROL

Arizona Corporation Commission

DOCKETED

JUN 23 2016

DOCKETED BY	
-------------	--

1 SHAPIRO LAW FIRM, P.C.  
Jay L. Shapiro (No. 014650)  
2 1819 E. Morten Avenue, Suite 280  
Phoenix, Arizona 85020  
3 Telephone: (602) 559-9575  
Jay@ShapsLawAz.com

4 LIBERTY UTILITIES  
5 Todd C. Wiley (No. 015358)  
12725 W. Indian School Road, Suite D-101  
6 Avondale, Arizona 85392  
Telephone: (623) 240-2087  
7 Todd.Wiley@LibertyUtilities.com

8 Attorneys for Liberty Utilities (Litchfield Park Water & Sewer) Corp.

## BEFORE THE ARIZONA CORPORATION COMMISSION

11 IN THE MATTER OF THE  
APPLICATION OF LIBERTY  
12 UTILITIES (LITCHFIELD PARK  
WATER & SEWER) CORP. FOR AN  
13 ACCOUNTING ORDER  
AUTHORIZING THE DEFERRAL OF  
14 COSTS ASSOCIATED WITH EFFORTS  
TO ADDRESS THE POTENTIAL  
15 CONTAMINATION OF WATER  
SUPPLY LOCATED IN MARICOPA  
16 COUNTY, ARIZONA.

DOCKET NO. W-01427A-16-0200

**REQUEST FOR APPROVAL TO  
REMEDiate CERTAIN  
CONTAMINANTS**

**(EXPEDITED RELIEF REQUESTED)**

17  
18 Under Ariz. Rev. Stat. §40-331 and Article 15 of the Arizona Constitution, Liberty  
19 Utilities (Litchfield Park Water & Sewer) Corp (“Liberty Litchfield Park” or “Company”)  
20 requests that the Arizona Corporation Commission (“Commission”) issue an order  
21 directing the Company to undertake any and all necessary measures to remediate  
22 Perfluorooctanoic Acid (“PFOA”) and Perfluorooctane Sulfonate (“PFOS”) potentially  
23 impacting the Company’s water supply located in Maricopa County, Arizona. **Because**  
24 **remediation of these prospective contaminants is immediately necessary, Liberty**  
25 **Litchfield Park respectfully requests that the Commission consider and approve this**  
26 **application on an expedited basis and in no more than 30 days.**

1 In support of this application, the Company states as follows:

2 1. Liberty Litchfield Park is an Arizona public service corporation providing  
3 water and wastewater utility services in portions of Maricopa County pursuant to a  
4 certificate of convenience and necessity ("CC&N") granted by the Commission. At the  
5 present time, the Company provides water utility service to approximately 18,300  
6 customers. Liberty Litchfield Park's present rates and charges for utility service were  
7 approved by the Commission in Decision No. 74437 (April 18, 2014) based on a test year  
8 ending December 31, 2012.

9 2. The Company's central business office is located at 12725 W. Indian School  
10 Road, Suite D-101, Avondale, Arizona 85323, and its telephone number is (623) 935-  
11 9367. The Company's President and primary management contact is Matthew Garlick.  
12 All correspondence regarding this application should be sent to:

13 Gerry Becker, Utility Rates and Regulatory Manager  
14 Liberty Utilities (Litchfield Park Water & Sewer) Corp.  
15 12725 W. Indian School Road, Suite D-101  
16 Avondale, AZ 85323  
17 Telephone: (623) 298-3769  
18 Gerry.Becker@LibertyUtilities.com

19 Jay L. Shapiro  
20 Shapiro Law Firm P.C.  
21 1819 E. Morten Ave., Suite 280  
22 Phoenix, AZ 85020  
23 Tel: (602) 954-9084  
24 Jay@ShapsLawAz.com

25 Todd Wiley  
26 Assistant General Counsel  
Liberty Utilities  
12725 W. Indian School Road, Suite D-101  
Avondale, AZ 85323  
Telephone: (623) 240-2087  
Todd.Wiley@LibertyUtilities.com

1           3.     On May 17, 2016, the United States Environmental Protection Agency  
2 (“EPA”) issued a new Health Advisory lowering the levels of PFOA and PFOS from 400  
3 parts per trillion for PFOA and 200 parts per trillion for PFOS to 70 parts per trillion for  
4 PFOA and PFOS combined. The EPA Health Advisory for PFOA is **attached as**  
5 **Exhibit A** and the EPA Health Advisory for PFOS is **attached as Exhibit B**.

6           4.     EPA established health advisories for PFOA and PFOS based on the  
7 agency’s assessment of the latest peer-reviewed science in order to provide drinking water  
8 system operators, and state, tribal and local officials who have the primary responsibility  
9 for overseeing these systems, with information on the health risks of these chemicals, so  
10 they can take the appropriate actions to protect their residents. See  
11 [https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-](https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos)  
12 [pfoa-and-pfos](https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos).

13           5.     Health advisories issued by EPA provide information on contaminants that  
14 can cause human health effects and are known or anticipated to occur in drinking water.  
15 EPA's health advisories are non-enforceable and non-regulatory and provide technical  
16 information to state agencies and other public health officials on health effects, analytical  
17 methodologies, and treatment technologies associated with drinking water contamination.

18           6.     As stated by the agency, EPA is evaluating PFOA and PFOS as drinking  
19 water contaminants in accordance with the process required by the Safe Drinking Water  
20 Act (“SDWA”). To regulate a contaminant under SDWA, EPA must find that it: (1) may  
21 have adverse health effects; (2) occurs frequently (or there is a substantial likelihood that  
22 it occurs frequently) at levels of public health concern; and (3) there is a meaningful  
23 opportunity for health risk reduction for people served by public water systems.

24           7.     EPA included PFOA and PFOS among the contaminants that water systems  
25 are required to monitor under the third Unregulated Contaminant Monitoring Rule  
26 (“UCMR 3”) in 2012. EPA uses the UCMR program to collect data for contaminants

1 suspected to be present in drinking water but that do not yet have health-based standards  
2 set under SDWA. EPA develops a list of UCMR new emerging contaminants every five  
3 years. A copy of the UCMR 3 Data Summary dated April 2016 is **attached as Exhibit C.**  
4 PFOA and PFOS are listed on page 8 of UCMR 3.

5 8. On or about April 11, 2016, EPA notified Liberty Litchfield Park that the  
6 UCMR 3 study showed elevated levels of PFOA and PFOS in two of the Company's  
7 wells located in the Airline ("AL") well field, specifically wells 2AL and 10AL. At that  
8 time, the existing health advisory levels were 400 ppt for PFOA and 200 ppt for PFOS  
9 (600 ppt combined), but EPA indicated initially that they expected to reduce the health  
10 advisory level to 100 ppt combined for PFOA/PFOS.

11 9. In response to that notice from EPA, on April 20, 2016, Liberty Litchfield  
12 Park had sampling done on Company wells located in the AL well field, including 4AL,  
13 5AL, 9AL and 10AL to determine PFOA/PFOS levels. Well 2AL was not sampled  
14 because it was out of service due to electrical issues on that date. Subsequently, the  
15 Company had sampling done on well 2AL. The sampling results were received on  
16 May 10, 2016 showing levels of PFOA/PFOS in wells 4AL, 5AL, 9AL and 10AL.  
17 Additional test results also showed levels of PFOA and PFOS in well 2AL. At that time,  
18 the Liberty Utilities engineering department began exploring and evaluating treatment  
19 options for perfluorinated compounds.

20 10. After receiving the test results for wells 4AL, 5AL, 9AL and 10AL on  
21 May 10, 2016, Liberty Utilities engineering staff performed blending calculations based  
22 on current usage and well production rates and determined that the combined  
23 concentration of PFOA/PFOS could be maintained below EPA's initial suggested  
24 standard of 100 ppt as long as wells 4AL and 2AL were not used as single production  
25 sources. The Company directed its operations staff not to operate well 4AL unless wells  
26 9AL and/or 5AL were also used so that the combined blending concentration was less

1 than 100 ppt. Well 2AL could not be operated because it lacks a suitable blending source.  
2 At that time, the Company hired Carollo Engineering to produce an independent blending  
3 plan to ensure PFOA/PFOS levels were less than 100 ppt.

4 11. On May 17, 2016, EPA issued the Drinking Water Health Advisory for  
5 Perfluorooctanoic Acid (PFOA). As stated in that Health Advisory, “[t]he U.S.  
6 Environmental Protection Agency (EPA) is issuing a lifetime drinking water Health  
7 Advisory (HA) for PFOA of 0.07 micrograms per liter (ug/l)...”<sup>1</sup> In that Health Advisory,  
8 EPA cited a number of potential health effects associated with exposure to PFOA.

9 12. In that Health Advisory for PFOA, EPA also recommended certain  
10 treatment technologies for PFOA. Specifically, EPA recommended a number of potential  
11 treatment options, including granular activated carbon (“GAC”).

12 13. On May 17, 2016, EPA issued the Drinking Water Health Advisory for  
13 Perfluorooctane Sulfonate (PFOS). As stated in that Health Advisory, “[t]he U.S.  
14 Environmental Protection Agency (EPA) is issuing a lifetime drinking water Health  
15 Advisory (HA) for PFOS of 0.07 micrograms per liter (ug/l)...” In that Health Advisory,  
16 EPA cited a number of potential health effects associated with exposure to PFOS.

17 14. In that Health Advisory for PFOS, EPA also recommended certain treatment  
18 technologies for PFOS. Specifically, EPA recommended a number of potential treatment  
19 options, including GAC.

20 15. Along with the Health Advisories, EPA issued a “FACT SHEET PFOA &  
21 PFOS Drinking Water Health Advisories.” A copy of that Fact Sheet **is attached as**  
22 **Exhibit D**. As stated on that fact sheet, “PFOA and PFOS are fluorinated organic  
23 chemicals that are part of a larger group of chemicals referred to as perfluoroalkyl  
24 substances (PFASs). PFOA and PFOS have been the most extensively produced and  
25

26 <sup>1</sup> For reference purposes, 0.07 micrograms per liter is 70 parts per trillion.

1 studied of these chemicals. They have been used to make carpets, clothing, fabrics for  
2 furniture, paper packaging for food and other materials (e.g., cookware) that are resistant  
3 to water, grease or stains. They are also used for firefighting at air-fields and in a number  
4 of industrial processes.”

5 16. In that Fact Sheet, EPA stated that a “number of options are available to  
6 drinking water systems to lower concentrations of PFOA and PFOS in their drinking  
7 water supply. In some cases, drinking water systems can reduce concentrations of  
8 perfluoraklyl substances, including PFOA and PFOS, by closing contaminated wells or  
9 changing rates of blending of water sources. Alternatively, public water systems can treat  
10 source water with activated carbon or high pressure membrane systems (e.g., reverse  
11 osmosis) to remove PFOA and PFOS from drinking water.” EPA Fact Sheet at 3.

12 17. On May 18, 2016, Liberty Utilities’ engineering staff revised the  
13 Company’s blending plan to maintain levels of PFOA/PFOS below 70 ppt for the Airline  
14 wells.

15 18. On May 19, 2016, Company President (Matthew Garlick) participated in a  
16 conference call scheduled by EPA with ADEQ and local mayors and representatives for  
17 Avondale, Litchfield Park, Glendale and Goodyear. During that call, EPA and ADEQ  
18 directed the Company to take any wells offline that had PFOA/PFOS results in excess of  
19 70 ppt.

20 19. On May 19, 2016, the Company took well 4AL off line as directed by EPA  
21 and ADEQ because the concentration of PFOA/PFOS exceeded the new health advisory  
22 level of 70 ppt. The test results for well 2AL also were above the 70 ppt advisory limit,  
23 but 2AL was already offline and not in use. The concentration levels of PFOA/PFOS for  
24 wells 5AL, 9AL and 10AL were below the revised standard of 70 ppt.

25 20. Liberty Litchfield Park did not cause or contribute to the introduction of  
26 PFOA or PFOS into the Airline wells in any way.

1           21. Liberty Utilities' engineering staff performed blending calculations that  
2 showed that the combined PFOA/PFOS levels at the Airline Reservoir could be  
3 maintained below 70 ppt by operating well 4AL at 450 gpm, 5AL at 1500 gpm, and well  
4 9AL at 1750 gpm. An independent engineer confirmed those blending calculations.

5           22. In an email dated May 20, 2006, ADEQ stated: "ADEQ agrees that the  
6 reasonable and prudent measures to resolve the PFOA and PFOS issue in the affected  
7 wells would be to remove the wells above 70 part per trillion (ppt) from service, blend the  
8 well to a level below 70 ppt and/or install treatment on the wells to reduce the PFOA  
9 and/or PFOS to less than 70 ppt. ADEQ agrees that taking action to reduce the PFOA and  
10 PFOS to less than the 70 ppt in the EPA health advisory and to inform the utilities  
11 customer's about the potential health effects are proactive measures to reassure the  
12 utilities' customers." See email from D. Czecholinski (ADEQ) dated May 20, 2016  
13 **(attached as Exhibit E).**

14           23. On May 25, 2016, EPA published the health advisories for PFOA and PFOS  
15 in the Federal Register. A copy of that Federal Register is **attached as Exhibit F.**

16           24. Unfortunately, blending is not a long-term option for PFOA/PFOS levels in  
17 the Company's drinking water supply from the Airline well field. Wells 2AL and 4AL  
18 are necessary during peak times and to provide water rendered under interruptible bulk  
19 service arrangements with the city of Goodyear and Valley Utilities.

20           25. The Company's peak day of water usage in 2014 was 15.9 MGD and was  
21 16.3 MGD in 2015. Liberty Litchfield Park has a projected peak day of 16.8 MGD in  
22 2016. Current water production capability with wells 2AL and 4AL off-line is only 14.8  
23 MGD. Treatment for PFOA/PFOS with mobile GAC units is necessary at these wells  
24 during the summer months to ensure enough production capacity is available to meet the  
25 expected water usage demands. If treatment is added to wells 2AL and 4AL, the  
26

1 Company's water production capacity will be increased to 17.1 MGD, which is adequate  
2 to meet the expected peak day water usage of 16.8 MGD.

3 26. Under these circumstances, the Company is preparing to install mobile GAC  
4 units at wells 2AL and 4AL to provide immediate remediation of the PFOA/PFOS  
5 contaminants in those wells. The Company obtained and received bids for installation and  
6 use of such mobile GAC units. A copy of the mobile GAC proposal from Evoqua Water  
7 Technologies is **attached as Exhibit G**.

8 27. The expected cost for the mobile GAC units includes one-time  
9 commissioning and decommissioning costs of \$462,130, ancillary improvements of  
10 \$350,000 to the sites and approximately \$17,500 per month for use of the mobile GAC  
11 units. The Company expects to use the mobile GAC units for approximately three (3)  
12 months until permanent GAC treatment can be approved, financed and installed.  
13 The mobile GAC units will act as a preliminary step for the permanent GAC treatment  
14 with the designs, configuration, operational results and/or GAC units being potentially  
15 incorporated into permanent GAC treatment as set forth below.

16 28. Under these circumstances, the Company requests that the Commission  
17 direct the Company to make any and all additions and improvements to or changes in the  
18 existing plant necessary to protect the Company's customers and the public from the  
19 transmission of high levels of PFOS or PFOA through the Company's water supplies.  
20 Such additions and improvements shall include but not be limited to the mobile GAC  
21 treatment measures for wells 2AL and 4AL as necessary and prudent remediation of the  
22 PFOA/PFOS levels in those wells. Consistent with such order, the Commission should  
23 authorize the Company to recover, through rates to be approved in a general rate case, any  
24 and all costs of additions and improvements for remediation of PFOA/PFOS to protect the  
25 Company's customers and the public from contamination by PFOS and PFOA.

26

1           29. The Company believes that this situation is a unique and unusual  
2 circumstance warranting such relief from the Commission. The additions and  
3 improvements subject to this approval are necessary to protect the Company's customers  
4 and the public from PFOS/PFOA contamination, however, there is currently no clear  
5 regulatory requirement that the Company take steps to remediate PFOA/PFOS. Under  
6 these highly unusual circumstances, the Commission should exercise its authority under  
7 Ariz. Rev. Stat. § 40-331 and the Arizona Constitution to direct the Company to take all  
8 necessary steps to remediate the PFOA/PFOS contamination, both preliminary and  
9 permanent, and the Commission should provide the Company with assurance that its  
10 decision to act in the interest of its customers and the general public will not be subject to  
11 post-hoc second-guessing in a rate case over the situation in which the Company finds  
12 itself through absolutely no fault of its own.

13           30. To provide such assurance, the Commission should authorize and allow the  
14 Company to proceed with immediate GAC treatment for wells 2AL and 4AL. As noted  
15 above, any and all costs of the mobile GAC units should be deferred with an order from  
16 the Commission including such costs as capital as part of permanent GAC treatment  
17 because the mobile GAC units will function as a part of the permanent GAC treatment in  
18 terms of design, configuration and permanent treatment of the PFOA/PFOS levels in wells  
19 2AL and 4AL. As a permanent solution for the PFOA and PFOS issues, the Company  
20 presently intends to design, construct and finance permanent GAC treatment using the  
21 mobile GAC units for wells 2AL and 4AL.

22           31. In the event that additional remedial actions are needed in relation to  
23 PFOA/PFOS levels in other Airline wells, the Company would design and construct  
24 additional permanent treatment facilities near the Company's Airline Reservoir in  
25 Maricopa County or by installing GAC units at other well locations. In either event, the  
26 Company would update this docket accordingly and seek Commission approval.

1           32. Under these circumstances, the Company requests that the Commission  
2 approve permanent GAC treatment of wells 2AL and 4AL as necessary and prudent  
3 remediation of the PFOA/PFOS levels in those wells and authorizing the Company to  
4 recover any and all costs for additions and improvements relating to such permanent GAC  
5 treatment in the Company's next general rate case. The Company believes that this  
6 situation is a unique and unusual circumstance warranting such relief from the  
7 Commission.

8           33. Under these circumstances, the Company requests that the Commission  
9 issue an order directing the Company to remediate the PFOA/PFOS concentrations in the  
10 Company's water supply at wells 2AL and 4AL in accordance with the EPA Health  
11 Advisories and reduce the contaminant level to an amount less than 70 ppt by installing  
12 additions or improvements as set forth above.

13           34. In addition to the relief requested above, the Company requests that the  
14 Commission issue an accounting order authorizing the Company to defer any and all  
15 operating expenses incurred by the Company in connection with the Company's response  
16 to the known and potential PFOA/PFOS levels in the Company's water supply, including,  
17 but not limited to: (i) any and all litigation costs incurred by the Company; (ii) any and all  
18 litigation costs related to seeking restitution from third parties; (iii) increases in operation  
19 and maintenance costs from alternative (replacement) water sources; (iv) capital costs of  
20 acquiring and/or constructing alternative (replacement) sources of water; (v) capital costs  
21 and/or operating expenses to treat contaminated water supplies, including mobile and  
22 permanent GAC treatment facilities; (vi) deferral of depreciation and post in service  
23 AFUDC; and (vii) any other associated costs. The Company seeks authority to record all  
24 incurred costs as deferred debits in LPSCO Account No. 8600-2-0100-10-1910-0000  
25 (NARUC Account No. 186.2 – Other Deferred Debits) with express authorization to  
26 include those costs as capital costs in a future general rate case.



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26

and

LIBERTY UTILITIES

Todd C. Wiley  
Assistant General Counsel  
12725 W. Indian School Road, Suite D-101  
Avondale, AZ 85392

Attorneys for Liberty Utilities  
(Litchfield Park Water & Sewer) Corp.

An original and 15 copies of the  
foregoing was hand-delivered this  
23rd day of June 2016, to:

Docket Control  
Arizona Corporation Commission  
1200 West Washington  
Phoenix, AZ 85007

By: 

# **EXHIBIT A**



United States  
Environmental Protection  
Agency

Office of Water  
Mail Code 4304T

EPA 822-R-16-005  
May 2016

---

# **Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA)**

**Drinking Water Health Advisory  
for Perfluorooctanoic Acid (PFOA)**

Prepared by:

U.S. Environmental Protection Agency  
Office of Water (4304T)  
Health and Ecological Criteria Division  
Washington, DC 20460

EPA Document Number: 822-R-16-005  
May 2016

## ACKNOWLEDGMENTS

This document was prepared by the Health and Ecological Criteria Division, Office of Science and Technology, Office of Water of the U.S. Environmental Protection Agency (EPA). The Agency gratefully acknowledges the valuable contributions of EPA scientists Glinda Cooper, Ph.D.; Barbara Glenn, Ph.D.; Erin Hines, Ph.D.; Michael Wright, Sc.D.; John Wambaugh, Ph.D.; Thomas Speth, Ph.D.; and Daniel Hautman.

This Health Advisory was provided for review by and comments were received from staff in the following EPA program Offices:

- Office of Chemical Safety and Pollution Prevention
- Office of Children's Health Protection
- Office of General Counsel
- Office of Land and Emergency Response
- Office of Policy
- Office of Research and Development
- Office of Water

## CONTENTS

ACKNOWLEDGMENTS .....	3
ABBREVIATIONS AND ACRONYMS .....	7
EXECUTIVE SUMMARY .....	9
1.0 INTRODUCTION AND BACKGROUND .....	11
1.1 Safe Drinking Water Act.....	11
1.2 Current Advisories and Guidelines .....	12
1.3 Uses of PFOA.....	14
2.0 NATURE OF THE STRESSOR.....	15
2.1 Physical and Chemical Properties .....	15
2.2 Occurrence and Sources of Exposure.....	17
2.2.1 Surface Water and Ground Water.....	17
2.2.2 Drinking Water .....	18
2.2.3 Food .....	18
2.2.4 Ambient Air .....	21
2.2.5 Indoor Dust .....	22
2.2.6 Soils.....	22
2.2.7 Biosolids .....	23
2.2.8 Consumer Products .....	24
2.3 Environmental Fate .....	24
2.3.1 Mobility.....	24
2.3.2 Persistence.....	24
2.3.3 Bioaccumulation .....	25
2.4 Toxicokinetics .....	25
2.5 Human Biomonitoring Data .....	27
3.0 PROBLEM FORMULATION .....	28
3.1 Conceptual Model .....	28
3.1.1 Conceptual Model Diagram for Exposure via finished Drinking Water .....	29
3.1.2 Factors Considered in the Conceptual Model for PFOA .....	29
3.2 Analysis Plan .....	31
3.2.1 Health Advisory Guidelines.....	31
3.2.2 Establishing the Data Set .....	31
3.2.3 Approach for HA Calculation.....	32
3.2.4 Measures of Effect .....	33
3.2.5 Relative Source Contribution.....	34

4.0	EFFECTS ASSESSMENT .....	35
4.1	Noncancer Health Effects.....	35
4.1.1	Animal Toxicity Studies .....	35
4.1.2	Human Epidemiology Studies .....	39
4.1.3	Noncancer Mode of Action.....	42
4.2	Cancer.....	44
4.2.1	Animal Cancer Bioassays .....	44
4.2.2	Human Epidemiology Studies .....	45
4.2.3	Cancer Mode of Action.....	46
4.2.4	Weight of Evidence Classification.....	47
5.0	DOSE-RESPONSE ASSESSMENT .....	48
5.1	Uncertainty Factors .....	50
5.2	RfD Determination .....	51
6.0	HEALTH ADVISORY VALUES .....	53
6.1	Relative Source Contribution .....	53
6.2	Lifetime Health Advisory.....	54
7.0	QUANTIFICATION OF CANCER RISK .....	56
8.0	EFFECTS CHARACTERIZATION .....	57
8.1	Uncertainty and Variability .....	57
8.2	Use of Human Epidemiology Data .....	58
8.3	Consideration of Immunotoxicity .....	58
8.4	Effects on Mammary Gland Development.....	60
8.5	Alternative Exposure Scenarios .....	61
8.6	Relative Source Contribution Considerations .....	61
8.7	Sensitive Populations: Gender Differences.....	63
8.8	Sensitive Populations: Developmental Effects.....	63
9.0	ANALYTICAL METHODS .....	64
10.0	TREATMENT TECHNOLOGIES .....	65
11.0	REFERENCES .....	69
12.0	APPENDIX A-QUANTITATIVE CANCER ASSESSMENT MODELING.....	99

## TABLES

Table 1-1. State Guideline Values for PFOA .....	13
Table 1-2. International Guideline Values for PFOA.....	13
Table 2-1. Chemical and Physical Properties of PFOA.....	16
Table 5-1. Human Equivalent Doses Derived from the Modeled Animal Average Serum Values.....	49
Table 5-2. Candidate RfDs Derived from the HEDs from the Pharmacokinetic Model Average Serum Values.....	52

## FIGURES

Figure 2-1. Chemical Structures of PFOA and APFO.....	15
Figure 3-1. Conceptual Model for PFOA in Finished Drinking Water .....	28

## ABBREVIATIONS AND ACRONYMS

ALT	alanine aminotransferase
ALP	alkaline phosphatase
APFO	ammonium perfluorooctanoate
AST	aspartate aminotransferase
AUC	area under the curve
BAF	bioaccumulation factor
BCF	bioconcentration factor
BMDL	benchmark dose level
BMF	biomagnification factor
bw	body weight
CAR	constitutive androstane receptor
CCK	cholecystokinin
CCL	Contaminant Candidate List
COPD	chronic obstructive airways disease
CWA	Clean Water Act
DWEL	drinking water equivalent level
DWI	drinking water intake
EPA	U.S. Environmental Protection Agency
FXR	farnesoid X receptor
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HA	Health Advisory
HDL	high-density lipoprotein
HED	human equivalent dose
HESD	Health Effects Support Document
IgM	immunoglobulin M
IRIS	Integrated Risk Information System
K <sub>oc</sub>	organic carbon-water partitioning coefficient
K <sub>ow</sub>	octanol-water partition coefficient
LCT	Leydig cell tumor
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LDL	low-density lipoprotein
LOAEL	lowest observed adverse effect level
MOA	mode of action
MRL	minimum reporting level
ng/L	nanograms per liter
NHANES	National Health and Nutrition Examination Survey
NOAEL	no observed adverse effect level
PAC	powdered activated carbon
PACT	pancreatic acinar cell tumors
PBPK	physiologically based pharmacokinetic model
PFAS	perfluoroalkyl substance
PFC	perfluorinated compounds
PFOA	perfluorooctanoic acid
PFOS	perfluorooctanesulfonic acid

PTFE	polytetrafluoroethylene
pg/L	picograms per liter
PND	post-natal day
POD	point of departure
POE	point-of-entry
POU	point-of-use
PPAR $\alpha$	peroxisome proliferator activated receptor alpha
PWS	public water system
PXR	pregnane X receptor
REACH	Registration, Evaluation, Authorization, and Restriction of Chemicals
RfD	reference dose
RSC	relative source contribution
SDWA	Safe Drinking Water Act
SNUR	Significant New Use Rule
SRBC	sheep red blood cell
TMF	trophic magnification factor
TNSSS	Total National Sewage Sludge Survey
UCMR 3	third Unregulated Contaminant Monitoring Rule
UF	uncertainty factor
UV	ultraviolet

## EXECUTIVE SUMMARY

Perfluorooctanoic acid (PFOA) is a synthetic, fully fluorinated organic acid; it is used in a variety of consumer products and in the production of fluoropolymers, and it is generated as a degradation product of other perfluorinated compounds. Because of strong carbon-fluorine bonds, PFOA is stable to metabolic and environmental degradation. PFOA 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. Major U.S. manufacturers voluntarily agreed to phase out production of PFOA by the end of 2015. Exposure to PFOA 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. PFOA was detected in blood serum in 99% of the U.S. general population between 1999 and 2012; however, the levels of PFOA in blood have been decreasing since U.S. companies began to phase out production. Water resources contaminated by PFOA 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 PFOA of 0.07 micrograms per liter ( $\mu\text{g/L}$ ) based on a reference dose (RfD) derived from a developmental toxicity study in mice; the critical effects included reduced ossification in proximal phalanges and accelerated puberty in male pups following exposure during gestation and lactation. PFOA 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 PFOA as described in EPA's 2016 *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, which was revised following external peer review. Because the developing fetus and newborn are particularly sensitive to PFOA-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 PFOA, oral animal studies of short-term, subchronic, and chronic duration are available in multiple species including monkeys, rats and mice. These studies report developmental effects (survival, body weight changes, reduced ossification, delays in eye opening, altered puberty, and retarded mammary gland development), liver toxicity (hypertrophy, necrosis, and effects on the metabolism and deposition of dietary lipids), kidney toxicity (weight), immune effects, and cancer (liver, testicular, and pancreatic). Overall, the toxicity studies available for PFOA demonstrate that the developing fetus is particularly sensitive to PFOA-induced toxicity. Human epidemiology data report associations between PFOA exposure and high cholesterol, increased liver enzymes, decreased vaccination response, thyroid disorders, pregnancy-induced hypertension and preeclampsia, and cancer (testicular and kidney).

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, interspecies variability, and LOAEL to NOAEL extrapolation.

From a national perspective, the dominant source of human exposure to PFOA 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 PFOA 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 PFOA 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 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 2005), there is Suggestive Evidence of Carcinogenic Potential for PFOA. Epidemiology studies demonstrate an association of serum PFOA with kidney and testicular tumors among highly exposed members of the general population. Two chronic bioassays of PFOA support a positive finding for the ability of PFOA to be tumorigenic in one or more organs of rats, including the liver, testes, and pancreas. EPA estimated a cancer slope factor of 0.07 per milligram per kilogram-day (mg/kg-day)<sup>-1</sup> based on testicular tumors, and confirmed that the lifetime HA based on noncancer effects is protective of the cancer endpoint.

## 1.0 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.<sup>1</sup>

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., 1 day, 10 days, a lifetime). HAs 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.

Perfluorooctanoic acid (PFOA) is a manmade chemical in a large family of chemicals called perfluoroalkyl substances (PFASs) (Buck et al. 2011). PFOA has been used in a variety of consumer products and in the production of fluoropolymers, and is generated as a degradation product of other perfluorinated compounds. PFOA 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 Perfluorooctanoic Acid (PFOA)*, presents a guideline concentration for PFOA 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 PFOA as described in EPA's *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (USEPA 2016a). The HA value is not a legally enforceable federal standard and is subject to change as new information becomes available. 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). PFOA is included on the third CCL (USEPA 2009a) and on the draft fourth CCL (USEPA 2015a).

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 PFOA 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

---

<sup>1</sup> For more information see <http://water.epa.gov/drink/standards/hascience.cfm>.

monitoring data are still being compiled, but results to-date indicate that PFOA has been measured at or above the minimum reporting level (0.02 micrograms per liter [ $\mu\text{g/L}$ ]) by approximately 2% of PWSs nationwide. To-date, PFOA has been measured above the new lifetime HA level of 0.07  $\mu\text{g/L}$  by approximately 0.3% of PWSs. Approximately 1% of PWSs have reported data for which combined PFOA and PFOS results are above 0.07  $\mu\text{g/L}$ . 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 PFOA under the SDWA.

EPA developed a *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* and one for another PFAS, perfluorooctane sulfonate (also known as perfluorooctanesulfonic acid or PFOS), 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 PFOA (USEPA 2016a) 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 PFOA to assist federal, 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 Clean Water Act (CWA) for PFOA. In January 2009, EPA developed a provisional HA for PFOA in drinking water of 0.4 micrograms per liter ( $\mu\text{g/L}$ ). The provisional HA was developed to reflect an amount of PFOA that could cause adverse health effects in the short term (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 provides drinking water guideline values that were developed by states.

**Table 1-1. State Guideline Values for PFOA**

State	Guideline Value (µg/L)	Source
Delaware Department of Resources and Environmental Control	0.4	DNREC (2016)
Maine Department of Health and Human Services	0.1	Maine DHHS (2014)
Michigan Department of Environmental Quality	0.42	Michigan DEQ (2013)
Minnesota Department of Health	0.3	MDH (2009)
New Jersey Department of Environmental Protection	0.04	NJDEP (2014)
North Carolina Division of Water Quality	2	NCDEQ (2013)
Vermont Agency of Natural Resources	0.02	Vermont ANR (2016)

In 2013 the European Chemicals Agency adopted an agreement that identified PFOA as a “Substance of Very High Concern” because of its persistent, bioaccumulative, and toxic characteristics and placed it onto the Candidate List for Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) (Vierke et al. 2012). Once on the Candidate List, PFOA could be included in Annex XIV of the REACH regulation, which would effectively ban use in manufacturing and in the market.

PFOA also is being considered for listing under The Stockholm Convention on Persistent Organic Pollutants (Convention), a global treaty to protect human health and the environment from persistent organic pollutants. In October 2015, the Persistent Organic Pollutants Review Committee agreed that PFOA meets the screening criteria in Annex D of the Convention, the first of several steps toward listing of chemicals. Listing in various Annexes of the Convention obligates parties to abide by provisions set forth to prohibit, eliminate, or restrict production and use, as well as the import and export of persistent organic pollutants, except as allowed for by specific exemptions. Several international agencies have established guideline values for PFOA (Table 1-2).

**Table 1-2. International Guideline Values for PFOA**

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	5.0	Action levels: Tier 1: potential hazard Tier 2: > 0.3 Tier 3: > 5.0 Tier 4: > 45	UK Drinking Water Inspectorate (2009)
Danish Ministry of the Environment	0.3	Composite drinking water criteria are based on relative toxicity of PFOS, PFOA, and PFOSA	Danish Ministry of the Environment (2015)

Country/Agency	Guideline Value (µg/ L)		Source
	Health-based	Administrative	
Swedish National Food Agency	--	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 exceeds	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

### 1.3 Uses of PFOA

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

In 2006, EPA initiated the 2010/2015 PFOA Stewardship Program in which eight major companies committed to reduce facility emissions and product contents of PFOA and related chemicals on a global basis by 95% no later than 2010, and to work toward eliminating emissions and product content of these chemicals by 2015 (USEPA 2006). Although the 2010/2015 PFOA Stewardship Program has worked toward eliminating emissions and product content, there are still some ongoing uses that EPA is evaluating. Shorter-chain perfluoroalkyl-based products have been developed to replace these chemicals.

To complement the Stewardship Program, EPA developed Significant New Use Rules<sup>2</sup> (SNURs) to allow EPA to review any significant new uses of PFOA and many PFOA-related chemicals before they are commercialized in the United States. On October 22, 2013, EPA issued a final SNUR (published in the *Federal Register* [FR]; 78 FR 62443) requiring companies to provide notice of any new manufacturing or processing of long-chain perfluoroalkyl carboxylates for use in or on carpets (i.e., to impart soil, water, and stain resistance). Companies must now provide EPA with notice of their intent to manufacture (including import) any of these chemicals if they are used in carpets or to treat carpets. They must also notify EPA for these chemical substances if they intend to import carpets already containing these chemical substances. EPA subsequently proposed another SNUR on January 21, 2015, for PFOA and also for PFOA-related chemicals that have not yet been commercialized (80 FR 2885).

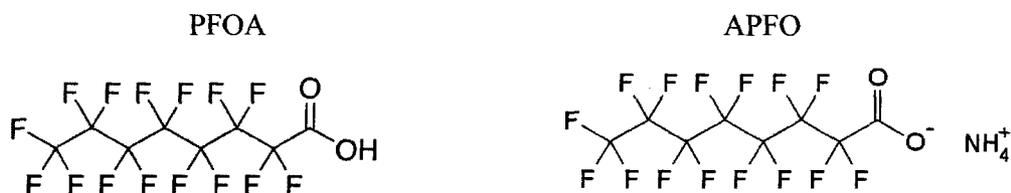
<sup>2</sup> For more information on EPA's SNURs visit <http://www.epa.gov/assessing-and-managing-chemicals-under-tsca/long-chain-perfluorinated-chemicals-pfcs>.

Given the limited ongoing uses of PFOA-related chemicals, releases to surface water and ground water from PFOA are expected to decline. Exposure to PFOA in the United States remains possible, however, because of its legacy uses, existing and legacy uses on imported goods, degradation of precursors, and extremely high persistence in the environment and in the human body.

## 2.0 NATURE OF THE STRESSOR

### 2.1 Physical and Chemical Properties

PFOA and its salts are fluorinated organic compounds and are part of the group of PFASs. PFOA is a completely fluorinated organic synthetic acid that was used in the United States primarily as an aqueous dispersion agent in the manufacture of fluoropolymers and in a variety of water-, oil-, and stain-repellant products. Ammonium perfluorooctanoate (APFO) is the ammonium salt of PFOA (Figure 2-1) which was a processing aid in the manufacture of certain fluoropolymers, especially as an emulsifier during the polymerization of tetrafluoroethylene to make polytetrafluoroethylene (e.g., Teflon™). Most of these primary uses have been voluntarily phased out in the United States as of 2015 (see section 1.3 above); however, limited U.S. uses and imports continue. Some sources of PFOA in the environment result from the atmospheric degradation or transformation and/or surface deposition of precursors, including related fluorinated chemicals (perfluorotelomer alcohols) (Wallington et al. 2006).



Source: SIAR 2008

**Figure 2-1. Chemical Structures of PFOA and APFO**

The structure of PFOA varies with the manufacturing process. PFOA can be either a linear or branched eight-carbon carboxylic acid with a partial negative charge on each fluorine and an acidic carboxylate functional group. Low concentrations of other perfluorocarboxylate chain lengths can also be present. It will tend to form micelles in aqueous solution and be attracted to surfaces that are characterized by positive charge.

In the environment, the acidic form ionizes in water to a PFOA anion, and the ammonium salt of PFOA rapidly dissociates. Physical and chemical properties and other reference information for PFOA are provided in Table 2-1. These properties help to define the behavior of PFOA in living systems and the environment. PFOA is a highly stable compound. It is a solid at room temperature with a low vapor pressure. The melting point for PFOA is identified as 50 to 60 degrees Celsius (°C); vapor pressures increase at temperatures near the melting point.

**Table 2-1. Chemical and Physical Properties of PFOA**

Property	Perfluorooctanoic Acid	Source
Chemical Abstracts Service Registry No. (CASRN <sup>a</sup> )	335-67-1	
Chemical Abstracts Index Name	2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctanoic acid	
Synonyms	PFOA; Pentadecafluoro-1-octanoic acid; Pentadecafluoro-n-octanoic acid; Octanoic acid, pentadecafluoro-; Perfluorocaprylic acid; Pentadecafluorooctanoic acid; Perfluoroheptanecarboxylic acid;	
Chemical Formula	C <sub>8</sub> HF <sub>15</sub> O <sub>2</sub>	
Molecular Weight (g/mol)	414.09	HSDB (2012); Lide (2007); SRC (2016)
Color/Physical State	White powder (ammonia salt)	HSDB (2012); Lewis (2004)
Boiling Point	192.4°C; Stable when bound	HSDB (2012); Lide (2007); SRC (2016)
Melting Point	54.3 °C	HSDB (2012); Lide (2007); SRC (2016)
Vapor Pressure	0.525 mm Hg at 25 °C (measured) 0.962 mm Hg at 59.25 °C (measured)	Hekster et al. (2003); HSDB (2012); SRC (2016) ATSDR (2015); Kaiser et al. (2005)
Henry's Law Constant	Not measureable	ATSDR (2015)
pKa	2.80	SRC (2016)
K <sub>oc</sub>	2.06	Higgins and Luthy (2006)
K <sub>ow</sub>	Not measurable	ATSDR (2015); EFSA (2008)
Solubility in Water	9.50 x 10 <sup>3</sup> mg/L at 25 °C (estimated)	ATSDR (2015); Hekster et al. (2003); HSDB (2012); Kauck and Diesslin (1951); SRC (2016)
Half-life in Water (25°C)	Stable	UNEP (2015)
Half-life in Air	Stable when bound	UNEP (2015)

*Notes:*

K<sub>ow</sub> = octanol-water partition co-efficient; K<sub>oc</sub> = organic carbon-water partitioning coefficient; g/mol = grams per mole  
<sup>a</sup>The CASRN given is for linear PFOA, but the toxicity studies are based on a mixture of linear and branched; thus, the RfD applies to the total linear and branched.

PFOA is a strong acid that is generally present in solution as perfluorooctanoate anion. It is water soluble and mobile in water, with an estimated log K<sub>oc</sub> of 2.06. PFOA 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. PFOA 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 PFOA in the arctic media and biota, including in polar bears, ocean-going birds, and fish found in remote areas (Lindstrom et al. 2011a; Smithwick et al. 2006). PFOA is present in ambient air and seawater globally (Ahrens et al. 2011; McMurdo et al. 2008; Yamashita et al. 2005; Young et al. 2007).

## 2.2 Occurrence and Sources of Exposure

PFOA and other PFASs have been discharged into the environment during use as processing aids for fluoropolymers, by degradation of precursors, including fluorotelomer-based polymers, and throughout the life cycle of products containing these compounds (i.e., from the point of product manufacture through its use and disposal) (Washington et al. 2009, 2015a, 2015b). PFOA and other PFASs are man-made chemicals, but because of their widespread use and chemical and physical properties (persistence and mobility) they have been transported into ground water, 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 PFOA are described below.

### 2.2.1 Surface Water and Ground Water

Water resources (i.e., surface water and ground water) are susceptible to contamination by PFOA released from manufacturing sites, industrial use, fire/crash training areas, and industrial or municipal waste sites where products are disposed of or applied. PFOA 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 stain-repellant fabrics (Renner 2009). Historically, land application of biosolids has been a source of PFOA and other PFASs in surface water or ground water (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 aqueous film forming foams used to combat aviation (or other hydrocarbon) fires release PFOA to the environment (Seow 2013; USEPA 2014b). Surface and ground water resources in close proximity to airports or other areas where these foams have been used can be contaminated (see Moody et al. 2002). PFOA was reported at concentrations as high as 105 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 PFOA concentrations of 11.3 µg/L at the confluence of Etobicoke Creek and Lake Ontario (Moody et al. 2002).

PFOA 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. PFOA has been reported in U.S. water bodies, including the Tennessee River (< 25–598 nanograms per liter [ng/L]), Mississippi River (< 1.0–125 ng/L), Lake Erie (21–47 ng/L), Lake Ontario (15–70 ng/L), and the Conasauga River (253–1,150 ng/L) and Altamaha River (3.0–3.1 ng/L) watersheds in Georgia (Boulanger et al. 2004; Hansen et al. 2002; Konwick et al. 2008; Nakayama et al. 2010). In another study, the 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 (USGS 2011); samples were collected in July and August 2010 from the Potomac River, the Patuxent River, and Saint Mary's Run. PFOA concentrations ranged from 3.6 to 20 ng/L in the Patuxent River; from 7.5 to 12 ng/L in the Potomac River; and from <2.0 to 47 ng/L in Saint Mary's Run.

Studies show that PFOA 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. PFOA 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, PFOA 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 PFOA in this survey was 0.02 µg/L. To-date, results for more than 36,000 samples have been reported by more than 4,800 PWSs for PFOA. The remainder of the results are expected to be reported by mid-2016. PFOA was measured at or above the MRL by approximately 2% of the PWSs. PFOA was reported above 0.07 µg/L by approximately 0.3% 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<sup>3</sup>) *National Drinking Water Database* includes PFOA analysis at 24 systems between 2004 and 2009 (EWG 2015). EWG obtained 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 PFOA; of these, five systems in Minnesota reported finding detectable levels. Four of the systems had average concentrations below 0.01 µg/L. One system had an average concentration of 0.09 µg/L and a maximum reported concentration of 0.25 µg/L.

PFOA detections in source water and drinking water are reported in several published studies. These studies frequently involve targeted local sampling; thus, the findings are not representative of national occurrence. For example, in New Jersey, monitoring of raw and finished water between 2006 and 2008 revealed concentrations as high as 0.14 µg/L in finished drinking water (NJDEP 2007; Post et al. 2009). In another study, PFOA concentrations in Little Hocking, Ohio, ranged from 1.5 and 7.2 µg/L in the municipal water distribution system and up to 14 µg/L in private wells between 2002 and 2005 (Emmett et al. 2006). A study in Minnesota reported PFOA concentrations up to 0.9 µg/L in municipal, noncommunity, and private wells between 2004 and 2008 (Goeden and Kelly 2006).

### 2.2.3 Food

PFOA ingestion from food is an important exposure source. PFOA was detected in a variety of food products including snack foods, vegetables, meat, dairy products, human breast milk, and fish, using data from Europe and North America as reported by Trudel et al. (2008). In North America, snack foods, fish and shellfish, and potatoes were the food items estimated to contribute the most to PFOA exposure, under intermediate and high-exposure conditions. In a survey that included multiple food types, PFOA was the second-most frequently detected PFAS

---

<sup>3</sup> For more information see <http://www.ewg.org>.

and was present at high concentrations relative to other related compounds (Hlouskova et al. 2013). In a 2011 assessment of exposure to Americans, Lorber and Egeghy (2011) concluded that food ingestion appears to be the primary route of exposure in adults, and dust and dietary ingestion is the major contributor for young children, under typical exposure conditions. Recent evidence shows that PFOA levels in food have been declining (Johansson et al. 2014).

Schechter et al. (2010) collected 10 samples of 31 commonly consumed foods from five grocery stores in Dallas, Texas, in 2008 and analyzed them for PFOA. 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 below the limit of detection, a value of zero was assigned. The estimated per capita daily estimate for exposure to PFOA was 60 nanograms per day (ng/day), or about 0.75 ng/day for an 80 kilogram (kg) adult. Based on a graphic presentation in the published paper, meat products (n = 8) accounted for about 40 ng/day with the remaining 30% equally distributed between fish (n = 7), vegetables (n = 7: three fat [olive oil, canola, margarine], one cereal, one apple, one potato, and one peanut butter sample), and dairy and egg products (n = 9).

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 PFASs exposure. PFOA was detected in roast beef, pizza, and microwave popcorn at 0.74 to 3.6 ng/g, wet weight. The average daily PFOA exposure was estimated at 70 ng.

Several studies are available from countries in Western Europe with diets that are comparable to those in 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 PFOA was 2.9 nanograms per kilogram of body weight (ng/kg) (232 ng/day for an 80 kg adult), with a 90<sup>th</sup> percentile intake of 672 ng/day. Haug et al. (2010) estimated exposures in Norway using a market basket approach comprised of 21 foods, three drinking water samples, one milk sample, and one tea sample. Total PFOA intake was estimated as 31 ng/day for the general Norwegian population. The highest levels were found in coffee, tea and cocoa (2.1 ng/day), root vegetables/potatoes (0.66 ng/day), tap water (0.54 ng/day), soft drinks (0.45 ng/day), and eggs (0.49 ng/day). Noorlander et al. (2011) estimated mean long-term daily intakes of 0.2 ng/kg (16 ng/day for an 80 kg adult) in the Netherlands using a pooled composite from foods purchased in retail chains with nationwide coverage; the 99<sup>th</sup> percentile value was 0.5 ng/kg (40 ng/day). Important sources were vegetables, fruits, and flour.

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 > 83% of the PFOA exposure in 6-month-old infants (Haug et al. 2011). Additional information on concentrations of PFOA in breast milk is provided in section 2.5.

PFOA has been detected in beef as a result of cattle ingesting contaminated feed. When cattle were exposed to feed contaminated with 13 ng PFOA/kg wet weight, PFOA accumulated in the liver (9 ng/kg) and in muscle (7 ng/kg) (Vestergren et al. 2013). The study also detected PFOA

in cow's milk at 6.7 ng/L. In addition, evidence suggests that livestock accumulate PFOA by grazing in fields where biosolids were applied (Renner 2009; Vestergren et al. 2013).

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). PFOA was not detected in river fish fillet samples, but it was detected in 12% of the Great Lakes samples. In the 2010 Great Lakes sampling, PFOA was detected in 19 out of 157 samples at a maximum concentration of 0.97 ng/g. The differences in PFOA detections between river and Great Lakes fish samples could be due to the availability of a more sensitive PFAS analytical method with lower detection limits when the Great Lakes study was initiated. Cooking of fish does not reduce the levels of PFOA in the fish (or the consumer's dietary exposure) (Bhavsar et al. 2014).

PFOA has been detected in wild caught and farmed fish, presumably because of bioaccumulation and/or trophic transfer. Bhavsar et al. (2014) found that PFOA concentrations were higher in wild-caught fish than farmed fish, and suggested that fish caught near contaminated sites could represent an important exposure source among recreational and subsistence fishers.

In a survey of French adult freshwater anglers, PFOA was a major contributor of total PFAS exposure from fish. Although some individuals had higher exposures, overall values for this population were close to those for the general population (Denys et al. 2014). In a study of French adults who consumed large amounts of seafood ( $n = 993$ ), mean lower bound exposure to PFOA was 1.16 ng/kg/day (92.8 ng/day for an 80 kg adult) compared to a lower bound of none in the general population ( $n = 1918$ ). The mean upper bound values were 2.06 and 0.74 ng/kg/day (164.5 to 59.2 ng/day), respectively, for the same highly exposed and general population groups (Yamada et al. 2014). In a sub-study that was restricted to 106 pregnant women, the upper bound mean was 1.52 ng/kg/day (121.6 ng/day) and the 95<sup>th</sup> percentile upper bound was 2.41 ng/kg/bw/day (192.8 ng/day).

PFOA can occur in plants grown in soils containing PFOA. For example, PFOA was taken up by corn when grown in biosolid-amended soil; however, the chemical remained in the roots and did not accumulate in edible parts of the plant (Krippner et al. 2014). PFOA accumulation in fruit crops tends to be lower than in shoot or root crops, presumably because there are more compartments through which PFOA would have to pass to reach the edible portion of the plant (Blaine et al. 2014).

PFOA was previously used in the manufacturing of several types of food packaging; in January 2016, the U.S. Food and Drug Administration (FDA) amended its 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 that comes in contact with aqueous and fatty foods (81 FR 5). PFOA is a breakdown product of the perfluorooctylethanol telomer alcohol used to make coatings for or additives in food contact paper where it adds a moisture or oil barrier to paper-type packaging, including microwave popcorn bags, fast food wrappers, candy wrappers, and pizza box liners (Begley et al. 2005). When used in this way, PFOA can migrate into foods from the packaging material. In a study conducted by FDA, Begley et al. (2005) was able to extract (4 micrograms per square decimeter [ $\mu\text{g}/\text{dm}^2$ ] paper) of PFOA into food oil before cooking and another  $7 \mu\text{g}/\text{dm}^2$  from paper after cooking. Based on these results, Begley et al. (2005) concluded that paper with treated coatings had a high potential for migration of fluorochemical to food.

Food can become contaminated with PFOA from preparation in nonstick cookware coated with polytetrafluoroethylene (PTFE) (Teflon™). PFOA is a processing aid in the manufacture of PTFE. Begley et al. (2005) also evaluated migration of PFOA to foods from cooking in Teflon™-lined cookware and found it to be much lower ( $0.03 \mu\text{g}/\text{dm}^2$  polymer) than migration from coated paper. In this study, new pans leached more compared to those that had been used before.

#### 2.2.4 Ambient Air

A number of PFASs are precursors of PFOA and degrade to PFOA in the environment via biotic and abiotic degradation. Some of these precursors are volatile and contribute to the formation of airborne PFOA. Indoor air sampling reportedly contains higher concentrations of these precursors than outdoor air (Vierke et al. 2012). Langer et al. (2010) reported detections of PFOA and precursors in indoor air samples from home residences and at stores that sold outdoor equipment, furniture, and carpet. Fraser et al. (2013) found that PFOA in serum was significantly correlated with air levels collected in offices, likely associated with carpeting, furniture, and paint.

PFOA can be emitted from nonstick cookware coated with PTFE. Schlummer et al. (2015) found that at typical cooking temperatures ( $< 230^\circ\text{C}$ ), perfluoroalkylcarboxylic acids (C4 to C12) dominated ( $4.75 \text{ ng per hour}$ ) by PFOA and perfluorobutanoic acid (PFBA) were released to the atmosphere; when pans were overheated PFBA and perfluoro-n-pentanoic acid (PFPeA) were dominant ( $> 260^\circ\text{C}$ ). Emissions were far greater at higher temperatures ( $12,190 \text{ ng per hour at } 370^\circ\text{C}$ ; Schlummer et al. 2015). Emissions are expected to decline with use of the product. The authors hypothesized that most of the emissions would end up in household dusts.

Based on its environmental fate properties, PFOA has low volatility. However, PFOA has been reported in ambient air, largely bound to particulate matter. It 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) and Antarctic (Del Vento et al. 2012). PFOA levels in outdoor air were measured in a variety of locations, most of which are countries outside the United States. Fromme et al. (2009) reported mean levels of 2 picograms per cubic meter ( $\text{pg}/\text{m}^3$ ) in particulate matter for eight samples collected in the summer in Albany, New York with a mean of  $3.2 \text{ pg}/\text{m}^3$

present in the gas phase. Mean air concentrations in Spain and England were 6.1 pg/m<sup>3</sup> and 3.5 pg/m<sup>3</sup>, respectively (Beser et al. 2011; Goosey and Harrad 2012). In a study conducted in China, airborne PFOA concentrations were similar (Liu et al. 2015). Areas near wastewater treatment plants, waste incinerators, and landfills can be point sources for PFOA in outdoor air (Ahrens et al. 2011). PFOA-derived telomer alcohols can also be present in air (Jogsten et al. 2012).

### 2.2.5 Indoor Dust

Because of its widespread use in carpets, upholstered furniture, and other textiles, PFOA 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 in legacy products and imported goods. As reported by Fraser et al. (2013), particulate matter from fabrics and carpeting are believed to be the source for the PFOA-containing dusts found in homes, offices, and automobiles.

A 2013 survey (Fraser et al. 2013) detected PFOA in samples of house dust (23.7 ng/g), office dust (32.0 ng/g), and vehicles (11.4 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 PFOA and 15 other PFASs in dust (Knobeloch et al. 2012). The median PFOA concentration was 44 ng/g. PFOA, PFOS and perfluorohexane sulfonate (PFHxS) accounted for about 70% of the total PFASs present in the dust. Lorber and Egeghy (2011) assessed Americans' PFOA exposure and concluded that ingestion of household dust and food are primary routes of PFOA exposure for 2-year-old children. For median exposed children, exposures were estimated to be 13 and 8 ng/d from dust and food, respectively. For highly exposed children (at the 95<sup>th</sup> percentile), PFOA exposure from dust was estimated to be three times that from food.

Jogsten et al. (2012) collected dust samples from 10 selected homes in Catalonia, Spain, and analyzed them for 20 PFASs. All samples contained PFOA; the levels ranged from 1.5 to 13.9 ng/g. An important outcome of this study was the identification of PFOA volatile telomer alcohol derivatives in the dust samples at concentrations of up to 1.3 ng/g. The 8:2 telomer alcohols degrade metabolically to PFOA once ingested. A study conducted in Belgium also found that PFOA was present in home (median: 0.7 ng/g dry weight) and office dust (median: 2.2 ng/g dry weight) (D'Hollander et al. 2010). The highest of the indoor dust concentrations of those sampled (114 ng/g) were found in homes in Germany (Xu et al. 2013).

### 2.2.6 Soils

PFOA persists in soils near manufacturing facilities and disposal sites (Xiao et al. 2015) and in areas, such as military bases, where firefighting foams containing PFOA were heavily used (Filipovic et al. 2015). Measured concentrations of PFOA in surface soils range from 8.0 ng/g (Xiao et al. 2015) to 287 ng/g (Filipovic et al. 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 PFOA had been used. In both cases, there was ground water contamination. Xiao et al. (2015) determined that levels of PFOA in soils increased with depth,

providing evidence for migration into ground water (see also section 2.2.1). Filipovic et al. (2015) found that PFOA concentrations in soil cores remained high more than 30 years after usage was discontinued.

Incidental ingestion of soils represents a potential exposure route for PFOA. Regional and geographic differences in soil characteristics can influence PFOA concentrations. Soil contamination tends to occur at manufacturing sites of producers and users, 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 PFOA 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 PFOA. 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 PFOA, PFOS 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 2011a; 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 PFASs from the TNSSS in five composite samples, which represented 94 wastewater treatment facilities from 32 U.S. states and the District of Columbia in 2001. PFOS was the most abundant PFC identified (mean  $403 \pm 127$   $\mu\text{g}/\text{kg}$  dry weight), followed by PFOA (mean  $34 \pm 22$   $\mu\text{g}/\text{kg}$  dry weight). Armstrong et al. (2016) collected biosolid samples every 2 months from a large municipal water recovery facility between 2005 and 2013. The highest mean PFOA concentration reported was  $23.5$   $\mu\text{g}/\text{kg}$  dry weight. Yoo et al. (2011) found PFOA and PFOS in plants (fescue, barley, bluegrass, and Bermuda grass) grown in soils amended with biosolids. Concentrations of PFOA ranged from 9.9 to 202.7  $\mu\text{g}/\text{kg}$ . 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., Stainmaster™, Zonyl™, Nuva™, Unidyne™, Baygard™) (Walters and Santillo 2006); these materials can be a particularly important exposure route for infants and children because of their hand-to-mouth behaviors.
- Cooking surfaces (e.g., Teflon™)
- Toothpaste, shampoos, cosmetics
- Polishes and waxes
- Electronics
- Flame repellants
- Paints, varnishes, sealants
- Lubricants/surfactants/emulsifiers (continuing use)
- Food containers and contact paper<sup>4</sup>
- Pesticide
- Aqueous film forming foams (continuing use; used for firefighting)
- Electronics
- Textiles (e.g., Gore-Tex™) and leather
- Plumbing tape
- Cleaning products

## 2.3 Environmental Fate

### 2.3.1 Mobility

PFOA is water soluble and has been found in surface water, ground water, 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 to the Arctic (Shoeib et al. 2006) and Antarctic (Del Vento et al. 2012). PFOA has a log  $K_{oc}$  of 2.06 and does not easily adsorb to sediments or aquifer materials; therefore, it tends to stay in the water column.

### 2.3.2 Persistence

PFOA is stable in the environment and resistant to hydrolysis, photolysis, volatilization, and biodegradation (see Table 2-1). No biodegradation or abiotic degradation processes have been found; the only dissipation mechanisms in water are dilution, advection, and sorption. Yamada et

---

<sup>4</sup> PFOA was used in some grease-proofing paper coatings or additives that can contribute to its presence in foods (Begley et al. 2005). However, in January 2016, FDA 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 (81 FR 5).

al. (2005) determined that typical municipal waste incinerators destroy PFOA on textiles and paper and do not release it into the atmosphere.

### 2.3.3 Bioaccumulation

Several criteria can be used to assess bioaccumulation, including octanol-water partition coefficient ( $K_{ow}$ ), bioconcentration factors (BCF), 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 PFOA, 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 PFOA (EFSA 2008; UNEP 2015). 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 PFOA in fish, wildlife, and humans.

Because of the physical-chemical properties of PFOA,  $K_{ow}$  cannot be reliably measured (Table 2-1; UNEP 2015; USEPA 2014b). 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, the validity of the use of such models is questionable (EFSA 2008; UNEP 2015). Available BCFs determined from lab studies have been reported and generally fall below traditional criteria used to assess bioaccumulation (e.g., Martin et al. 2003c). It is recognized, however, that BCFs determined by existing standard methods derived from lipid-partitioning are not an appropriate metric for assessing bioconcentration of PFOA (EFSA 2008; UNEP 2015). Although evidence of PFOA accumulation in many organisms has been documented, reported BAFs and BCFs for the chemical also fall below traditional criteria used to assess bioaccumulation potential (Loi et al. 2011; Martin et al. 2003a, 2003b; Morikawa et al. 2005; Quinete et al. 2009).

Field evidence of PFOA 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 2015). Trophic magnification has also been evaluated (Environment Canada and Health Canada, 2012; Houde et al. 2006; Kelly et al. 2009; Loi et al. 2011; Martin et al. 2004). Some field trophic studies revealed TMFs greater than 1, which indicates that PFOA accumulated and increased in concentration with increasing trophic level; other studies reported TMFs less than 1 for some food webs. The weight of evidence for trophic magnification was deemed sufficient to consider PFOA to be bioaccumulative by the Stockholm Convention Persistent Organic Pollutants Review Committee (UNEP 2015).

## 2.4 Toxicokinetics

Uptake and egress of PFOA from cells is largely regulated by transporters in cell membranes (Anzai et al. 2006; Cheng et al. 2006; Klaassen and Aleksunes 2010; Nakagawa et al. 2007, 2009; Weaver et al. 2009, 2010; Yang et al. 2010). PFOA is absorbed from the gastrointestinal tract as indicated by the serum measurements in humans and treated animals. In serum, it is electrostatically bound to albumin, occupying nine to 12 sites, and sometimes displaces other substances such as nutrients and pharmaceuticals that normally would occupy a site (MacManus-

Spencer et al. 2009; Salvalaglio et al. 2010; Wu et al. 2009a). Linear PFOA 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.

PFOA is distributed to tissues by a process requiring transporters. Accordingly, the tissue levels vary from organ to organ as demonstrated by Kemper (2003). The highest tissue concentrations are usually those in the liver. Liver accumulation in males is greater than that in females. Other tissues with a tendency to accumulate PFOA are the kidneys, lungs, heart, and muscle, plus the testes in males and uterus in females (Kemper, 2003). PFOA is not metabolized, thus any effects observed in laboratory toxicological studies are the result of parent compound, not metabolites.

Electrostatic interactions with proteins are an important toxicokinetic feature of PFOA. Studies demonstrate binding or interactions with receptors (e.g., peroxisome proliferator activated receptor alpha [PPAR $\alpha$ ], triiodothyronine [T3]), transport proteins and enzymes (Luebker et al. 2002; Weiss et al. 2009; L. Zhang et al. 2013). Saturable renal resorption of PFOA from the glomerular filtrate via transporters in the kidney tubules is a major contributor to the long half-life of this compound in humans (Nakagawa et al. 2007, 2009; Weaver et al. 2010; Yang et al. 2009, 2010). Branched-chain PFOAs are less likely to be resorbed than the linear molecules based on half-life information in humans (Y. Zhang et al. 2013). All toxicokinetic models for PFOA are built on the concept of saturable renal resorption first proposed by Andersen et al. (2006). Some PFOA is removed from the body with bile (Genuis et al. 2010), a process that also is transporter-dependent. Accordingly, the levels in fecal matter represent both unabsorbed material and material that is discharged to the intestines with bile.

During pregnancy, PFOA is present in the placenta and amniotic fluid in both animals (Fenton et al. 2009; Hinderliter et al. 2005) and humans (T. Zhang et al. 2013). Post-delivery, PFOA is transferred to offspring through lactation in a dose-related manner (Hinderliter et al. 2005, Fenton et al. 2009). Maternal serum levels decline as those in the pups increase. This also occurs in humans as demonstrated in the study by Mondal et al. (2014) of breastfeeding women and their infants in West Virginia and Ohio.

The half-life in humans for occupationally exposed workers (Olsen et al. 2007) was 3.8 years (95% CI [1.5, 9.1]). Bartell et al. (2010) determined an average half-life of 2.3 years based on a study of the decreases in human serum levels after treatment of drinking water for PFOA removal was instituted by the Lubeck Public Services District in West Virginia and the Little Hocking Water Association in Ohio. This is the value used for humans in this assessment because it applies to the general population and reflects humans whose exposure came primarily from their PWS. Half-lives are reported to be shorter in animals than for humans: 21 days (females) and 30 days (males) for monkeys (Butenhoff et al. 2004b); 11.5 days (males) and 3.4 hours (females) for Sprague-Dawley rats (Kemper 2003); 27.1 days (male) and 15.6 days (female) for CD-1 mice (Lau et al. 2006). Although the animal half-lives are shorter than humans, so, too, are their average lifetimes. In early life, the half-lives are nearly the same for both genders, but once the animals reach sexual maturity resorption increases in male rats, prolonging the half-lives (Hinderliter et al. 2006; Hundley et al. 2006). This change appears to be under the control of hormones in both males and females (Cheng et al. 2006; Kudo et al. 2002).

## 2.5 Human Biomonitoring Data

The Fourth National Report on Human Exposure to Environmental Chemicals from the Centers for Disease Control and Prevention (CDC 2009) included exposure data for PFOA from 2003 to 2004 collected by the National Health and Nutrition Examination Survey (NHANES). PFOA was detected in 99.7% of the general U.S. population. Since that time, CDC has issued several updates, the most recent of which was released in 2015 (CDC 2015). Taken together, the data suggest that PFOA concentrations in human serum in the U.S. generally declined between 1999 and 2012. The geometric mean PFOA concentration in human serum decreased from 5.2 to 2.1 µg/L, and the 95<sup>th</sup> percentile concentration decreased from 11.9 to 5.7 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 PFOA and PFOS in males and a slight increase in levels of PFOS with age (Calafat et al. 2007a, 2007b).

Precursors might also form PFOA in the body; this represents an important uncertainty in characterizing exposure as measured by blood serum. For example, Lorber and Egeghy (2011), indicated that the precursor fluorotelomer alcohols (FTOHs) and polyfluoroalkyl phosphoric acids (PAPs) would add to exposure but there is uncertainty as to the magnitude of the effect. The authors concluded that precursors “could very well contribute half or more of what is eventually measured as PFOA in the blood.”

Evidence shows that PFOA is distributed within the body and can be transferred from pregnant women to their unborn children and offspring. T. Zhang et al. (2013) collected serum and cord blood samples from 30 pregnant women in China. The maternal blood contained variable levels of 10 PFASs, eight acids, and two sulfonates. The mean maternal blood concentration for PFOA was 3.35 nanograms per milliliter (ng/mL). The mean was greater than the median, indicating a distribution skewed toward the higher concentrations. Compared to the mean PFOA blood levels in the pregnant women, the mean levels in cord blood (1.95 milligrams per milliliter [mg/mL]) was 47% of that in the mother’s blood.

PFOA has been detected in breast milk (Tao et al. 2008; Völkel et al. 2008) and cord blood (Apelberg et al. 2007; Monroy et al. 2008) at concentrations above the limit of quantification. Mondal et al. (2014) evaluated serum samples from breastfeeding women and their infants in West Virginia and Ohio. For each month of breastfeeding, maternal serum levels of PFOA were reduced by 3% (95% CI: 2%-5%) and infant serum levels increased by 6% (95% CI: 1%-10%). A publication from the French total diet study (Cariou et al. 2015) also examined human breast milk as an exposure route for infants using 61 mother-infant pairs. PFOA was detected in 77% of the breast milk samples, with a mean concentration of 0.041 ng/mL and a maximum concentration of 0.308 ng/mL. The regression coefficient for the association between the maternal serum concentration and the detected breast milk concentrations was 0.72 (n = 10).

### 3.0 PROBLEM FORMULATION

#### 3.1 Conceptual Model

The conceptual model provides useful information to characterize and communicate the potential health risks related to PFOA exposure from drinking water. The sources of PFOA, 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), and 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 PFOA are depicted in the conceptual diagram below (Figure 3-1).

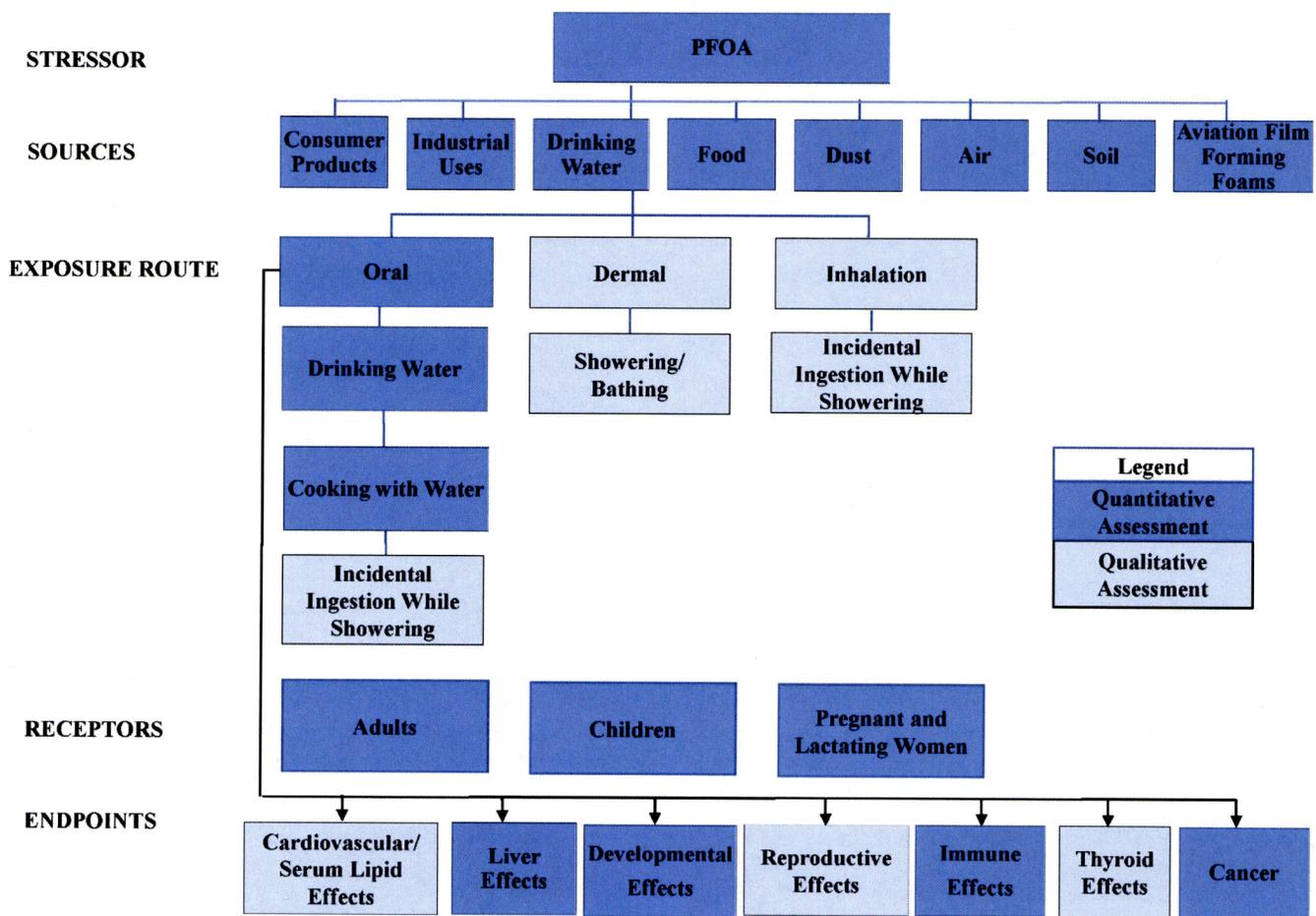


Figure 3-1. Conceptual Model for PFOA in Finished Drinking Water

### 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.

### 3.1.2 Factors Considered in the Conceptual Model for PFOA

*Stressors:* For this HA, the stressor is PFOA in drinking water from public water facilities or private wells.

*Sources:* Sources of PFOA include both ground and surface waters used for drinking. Multiple potentially important sources of PFOA 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 place 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 PFOA 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 PFOA 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 PFOA in humans and animals. Therefore, these routes of exposure are not quantitatively used in the derivation of the HA. PFOA has a low vapor pressure and is not expected to be present in air except as bound to particulate matter and in 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). PFOA 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 PFOA 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 PFOA exposure and high cholesterol, increased liver enzymes, decreased vaccination response, thyroid disorders, pregnancy-induced hypertension and preeclampsia, and cancer (testicular and kidney) (see section 4.1.2). These studies provide varying levels of support for the effects associated with PFOA exposure in the animals studies used for quantification of the HA. Cholesterol, liver enzymes, and thyroid effects were examined in numerous studies in different populations, but the pregnancy complications of hypertension and preeclampsia in women and testicular cancer in young men were only studied in a high-exposure community (located in the vicinity of a PFOA production plant in West Virginia; i.e., C8 Health Project). The C8 Science Panel assessed the links between PFOA and several diseases and concluded that a probable link existed between

PFOA and the observed kidney and testicular tumors among the population evaluated (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 PFOA 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 PFOA values come from PFOA derivatives or precursors that break down metabolically to PFOA. These compounds could originate from PFOA in diet and materials used in the home, which creates potential for confounding. In addition, 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 PFOA 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.<sup>5</sup>

For PFOA, oral animal studies of short-term, subchronic, and chronic duration are available in multiple species including monkeys, rats, and mice (see section 4.1.1). Adverse effects observed following exposure to PFOA include liver toxicity (hypertrophy, necrosis, and effects on the metabolism and deposition of dietary lipids), kidney toxicity, and developmental effects (survival, body weight changes, reduced ossification, altered puberty, and retarded mammary gland development), immune effects, and cancer. EPA quantitatively evaluated (i.e., modeled serum concentrations) for the liver, developmental, immune, and cancer 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 PFOA exposure. The liver also contains the highest levels of PFOA when analyzed after test animal sacrifice. The increases in liver weight and hypertrophy, however, also can be associated with activation of cellular PPAR $\alpha$  receptors, making it difficult to determine if this change is a reflection of PPAR $\alpha$  activation or an indication of PFOA toxicity. The PPAR $\alpha$  response is greater in rodents than it is in humans. EPA evaluated liver disease and liver function resulting from PFOA 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 were observed. Only the doses associated with the adverse effects were used for the quantification of risk.

---

<sup>5</sup> 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 reflect susceptible and/or more highly exposed populations.

- A 1-day HA is typically calculated for an infant (0 to 12 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 to 12 months or a 10-kg child), assuming a limited period of exposure of 1 to 2 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, 2005). 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 Perfluorooctanoic Acid (PFOA)* (USEPA 2016a) 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 for PFOA, EPA assembled available information on toxicokinetics, acute, short-term, subchronic and chronic toxicity along with developmental and reproductive toxicity, neurotoxicity, immunotoxicity, genotoxicity and cancer in humans and animals. For a more detailed description of the literature review search and strategy for inclusion and exclusion of studies, see the Forward and Appendix A of the HESD for PFOA.

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

- The data contribute substantially to the weight of evidence for any of the toxicity endpoints.
- 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 PFOA 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 U.S. EPA'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 could 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 PFOA 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 PFOA, 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.

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

Where:

HED<sub>NOAEL</sub> = The HED from the modeled average serum representing the highest of the given doses that lacked adverse effects (mg/kg/day).

HED<sub>LOAEL</sub> = 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.

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

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 an RSC described in USEPA (2000) and section 6.1.

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

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 for PFOA. These studies demonstrated dose-related effects on systemic and developmental endpoints in multiple species (monkeys, rats, mice) following exposure to PFOA for durations of 11 to 84 days; these are described in detail in the HESD for PFOA. 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 PFOA.

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 PFOA 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 PFOA 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 PFOA 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., PFOA) 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 exposure sources. In the case of PFOA, other potential sources include ambient air, foods, 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 PFOA by using the Exposure Decision Tree approach (USEPA 2000) (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 PFOA, 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:

- Adequacy of data available for each relevant exposure source and pathway.
- 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 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 2000).

## 4.0 EFFECTS ASSESSMENT

The database for PFOA includes a large number of laboratory animal toxicity studies, as well as numerous epidemiology studies. The most extensive epidemiology studies were conducted by the C8 Science Panel for a highly exposed population in West Virginia. These animal and human studies are described below and in greater detail in the HESD for PFOA (USEPA 2016a). 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 PFOA exposure to humans and health effects. In particular, effects on the liver enzymes indicative of liver effects, low birthweight, antibody response, and cancer in laboratory animals are supported by human epidemiology studies.

### 4.1 Noncancer Health Effects

#### 4.1.1 Animal Toxicity Studies

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*

Both rats and mice showed developmental toxicity based on low birth weights, skeletal effects (reduced ossification), altered onset of puberty (Butenhoff et al. 2004a; Lau et al. 2006; Wolf et al. 2007). Doses that elicited a response were higher in rats compared with those in mice. Meta-analyses were conducted to determine whether developmental exposure to PFOA was associated with fetal growth effects in animals (Koustas et al. 2014). Eight animal studies identified in the published literature met the criteria of the Navigation Guide systematic review methodology as developed and published by Woodruff and Sutton (2014) for inclusion in the analyses. The animal data sets included mouse gavage studies with maternal PFOA doses from 0.01 to 20 mg/kg/day. The results from the meta-analysis showed that a 1 mg/kg/day increase in PFOA dose was associated with a -0.023 g (95% CI [-0.029, -0.016]) difference in pup birth weight. The MOA for decreased pup body weight is not known, but receptor-activated changes in metabolism, hormonal perturbations, and impeded intercellular communication might play a role.

One animal neurological study (Johansson et al. 2009) showed effects on habituation and activity patterns in NMRI (Naval Medical Research Institute) mice treated on post-natal day (PND)10 with a single dose of PFOA and evaluated at 2 and 4 months of age (LOAEL = 0.58 mg/kg). The in vivo observations are supported by changes in the expression of a variety of neurologically active brain proteins in the treated pups (Johansson et al. 2009). The offspring of C57BL/6/Bkl dams fed diets that provided a dose of 0.3 mg PFOA/kg/day throughout gestation had detectable levels of PFOA in their brains at birth (Onishchenko et al. 2011). Behavioral assessments of the offspring starting at 5 weeks of age revealed sex-related differences in exploratory behavior patterns. In the social group setting, the PFOA-exposed males were more active and PFOA-exposed females were less active than their respective controls. The PFOA-exposed males also had increased activity counts compared to control males in circadian activity

experiments. The results of an *in vitro* study of hippocampal synaptic transmission and neurite growth in the presence of long chain perfluorinated compounds showed that 50 or 100 micromolar PFOA increased spontaneous synaptic current and had an equivocal impact on neurite growth (Liao et al. 2009a, 2009b). These data suggest a need for additional studies of the effects of PFASs, including PFOA, on the brain.

The developmental impacts of PFOA exposure ranged from delayed mammary gland development in pups (Albrecht et al. 2013; Macon et al. 2011; Tucker et al. 2015; White et al. 2009, 2011; Wolf et al. 2007) to delays in attaining developmental milestones (Lau et al. 2006; White et al. 2009; Wolf et al. 2007). The LOAEL for the mammary gland developmental effects in female offspring from dams given 0.01 mg/kg/day for 8 days from Macon et al. (2011) is of unknown biological significance. The same study showed no effects on offspring body weight at maternal doses up to 3 mg/kg/day for 17 days (Macon et al. 2011). Data from White et al. (2011) showed no significant effects on body weight gain in pups nursing from dams treated with 1 mg/kg/day, despite these dams having less fully developed mammary glands compared to controls. Similarly, no differences in response to a lactational challenge were seen in PFOA exposed dams with morphologically delayed mammary gland development (White et al. 2011).

#### *Immune Function*

Several animal studies demonstrate effects on the spleen and thymus as well as their cellular products (B lymphocytes and T-helper cells) in several strains of mice. Studies by Yang et al. (2000, 2001, 2002b) and DeWitt et al. (2008) were conducted using relatively high PFOA doses (~30 to 40 mg/kg/day). In each study, the PFOA-treated animals exhibited significant decreases in spleen and thymus weights as well as splenocyte and thymocyte populations at various stages of differentiation. Recovery usually occurred within several days of cessation of PFOA dosing. When the response of C57BL/6Tac PPAR $\alpha$  mice were compared to wild type of the same strain, the knockout mice showed no response with both spleen and thymus weights at 30 mg/kg/day, whereas there was a response in the wild-type strain (DeWitt et al. 2015), suggesting an impact of PPAR $\alpha$ . Both strains showed an increase in immunoglobulin M (IgM) in response to a sheep red blood cell (SRBC) injection. The 30 mg/kg/day dose was the LOAEL for the knockout mice and 7.5 mg/kg/day was the response level for the wild-type strain. Thus, the suppression of the immune system is not totally a PPAR $\alpha$ -related response.

DeWitt et al. (2008) used different functionality assays in their study in C57Bl/6 mice. The IgM response to SRBCs was suppressed by 20% when mice were immunized immediately after exposure to the initial dose of 30 mg PFOA/kg/day ceased. However, no significant increase occurred in the response to bovine serum albumin 4 days post-PFOA exposure, or in the immunoglobulin G (IgG) response to SRBC 15 days post-PFOA exposure. These results are indicative of recovery once PFOA exposures have ceased. DeWitt et al. (2008) followed their initial study of PFOA with one designed to examine the dose response for a 15-day drinking water exposure in a slightly different mouse strain, C57Bl/6N. The LOAEL was 3.75 mg/kg/day based on a significant decrease in IgM response, and the NOAEL was 1.88 mg/kg/day indicating the inability to respond to an immunological challenge.

### *Liver Disease and Liver Function*

Hepatocellular hypertrophy and an increased liver-to-body weight ratio are common findings in rodents, but are considered non-adverse if there is evidence for PPAR $\alpha$  activation. These effects are considered adverse if accompanied by necrosis, fibrosis, inflammation, and steatosis (Hall et al. 2012). Low-level necrotic cell damage was observed in the Palazzolo et al. (1993) rat study and in the Loveless et al. (2008) studies in CD rats and CD-1 mice. Palazzo et al. (1993) is an unpublished report that was later published as Perkins et al. (2004). The liver histopathology details of this study were only presented in Palazzolo et al. (1993). This study will be referred to throughout the rest of the document as Palazzolo et al. (1993)/Perkins et al. (2004). In this study there was a slight increase in coagulative necrosis at 1.94 and 6.5 mg/kg/day when compared to the control and lower dose (0.94 mg/kg/day). Some hepatocellular necrosis was also observed in conjunction with hepatocellular hypertrophy and increased liver weight at a dose of 3 mg/kg/day in F1 male rats from the Butenhoff et al. (2004a) two-generation study.

In general, effects on organs other than the liver tend to occur at doses higher than those that affect the liver. Lung effects including pulmonary congestion were observed in male Sprague-Dawley rats (LOAEL = 5 mg/kg/day) by Cui et al. (2009). Increased thickness and prominence of the adrenal zona glomerulosa and vacuolization in the cells of the adrenal cortex were observed in male rats fed 10 mg/kg/day for approximately 56 days (Butenhoff et al. 2004a).

### *Kidney Function*

Some studies have shown effects on the kidney of male rats at doses similar to those resulting in liver effects. Increases in absolute and relative-to-body kidney weights occurred in rats given 5 mg/kg/day (lowest dose tested) via gavage for 28 days (Cui et al. 2009). In a two-generation gavage study, F0 and F1 males had significantly increased absolute kidney weight at 1 and 3 mg/kg/day, but significantly decreased kidney weight at 30 mg/kg/day. Organ weight-to-terminal body weight ratios for the kidney were statistically significantly increased at  $\geq 1$  mg/kg/day. Kidney weight-to-brain weight ratios were significantly increased at 1, 3, and 10 mg/kg/day, but decreased at 30 mg/kg/day (Butenhoff et al. 2004a). In the high-dose group, absolute and relative kidney weight changes occurred in a pattern typically associated with decrements in body weight and are indicative of systemic toxicity. In the lower-dose groups, the consistently increased absolute and relative to body and brain weights suggest a cellular response, whereby the kidney tubular cells upregulate expression of transporter proteins to facilitate the PFOA excretion. This is adverse because it is a biomarker for systemic PFOA bioaccumulation. The differential expression of transporters in the kidney of male rats is under hormonal control with males having lower levels of export transporters compared to females (Kudo et al. 2002). No dose-related changes in kidney weight or histopathology were found in male rats at the end of 2 years with a dose of 14.2 mg/kg/day (Butenhoff et al. 2012).

### *Diabetes*

Hines et al. (2009) found no differences in glucose tolerance tests at 15–16 weeks and at 17 months of age in PFOA-exposed CD-1 mice, but did observe significantly increased serum leptin and insulin levels at 21 and 31 weeks of age suggesting that the insulin resistance mechanistic pathway could be affected by PFOA and a connection between PFOA and increased body weight. Leptin is a hormone secreted by adipose tissue that is associated with weight gain.

Conversely, Quist et al. (2015) found no dose-related impact on serum leptin in CD-1 pups on PND 91. Quist et al. (2015) found that when mice were on a high-fat diet and not fasted before serum collection and these were compared to the same mice that were fasted before serum collection, leptin increased, thereby suggesting that the leptin change could be temporary and dependent on the fat content of the diet and the timing of serum collection.

### *Thyroid*

Effects of PFOA on thyroid hormones in animals are not as well characterized as those of PFOS. Butenhoff et al. (2002) evaluated the toxicity of PFOA in a small number of male monkeys during 6 months of oral administration and reported that levels of total T3 and free T3 in circulation were reduced significantly in the 30/20 mg/kg/day treatment group, beginning at 5 weeks after initiation of treatment but accompanied by other signs of systemic toxicity. Recovery of T3 deficits was noted when PFOA returned to baseline 90 days later. Serum total thyroxine (T4), free T4, and thyroid-stimulating hormone (TSH) were not altered throughout the study. The preferential effects of PFOA on serum T3 and a lack of a TSH compensatory response are similar to those observed with PFOS, and are possibly a consequence of PFOA binding to the T3 receptor (Ren et al. 2015). None of the thyroid hormones were affected by PFOA in mature female rats (Butenhoff et al (2002), primarily because these animals were able to clear the chemical effectively (with half-life estimate of 2 to 4 hours, compared to that of 6 to 7 days for male rats). This suggests that the thyroid disrupting effects of PFOA are directly related to endogenous accumulation of the chemical and might be relevant to humans because of the long PFOA human half-life.

### *Fertility, Pregnancy, and Birth Outcomes*

Among animal studies there was no effect of PFOA on reproductive or fertility parameters in rats (Butenhoff et al. 2004a), but effects on male fertility were observed in mice given a dose of 5 mg/kg/day for 28 days prior to mating (Lu et al. 2015). A NOAEL of 2.5 mg/kg/day and a LOAEL of 5 mg/kg/day were reported for reduced sperm counts and changes in testicular morphology after a 14-day exposure by Liu et al. (2015); 2 mg/kg/day led to significantly increased serum estradiol and increased hepatic aromatase activity in the same study. Gender differences in dose response are likely related to half-life differences of hours for the female rat and days-to-weeks for the female mouse.

### *Serum Lipids*

Information on serum lipids from animal studies has received less attention than in the human population because decreases in triglycerides, cholesterol, and lipoprotein complexes are an expected consequence of PPAR $\alpha$  activation in rodents. PFOA is an activator of the PPAR $\alpha$  nuclear receptor in both humans and animals, but activation in humans does not increase the cellular levels of peroxisomes to the same extent it does in rodents. The PPAR $\alpha$  response in animals tends to lower rather than raise serum cholesterol and associated lipid levels. PFOA is known to activate the PPAR pathway by increasing transcription of mitochondrial and peroxisomal lipid metabolism, sterol, and bile acid biosynthesis and retinol metabolism genes. However, based on transcriptional activation of many genes in PPAR $\alpha$  null mice, the effects of PFOA involve more than activation of PPAR. Also activated are the constitutive androstane receptor (CAR), farnesoid X receptor (FXR), and pregnane X receptor (PXR).

Cholesterol and/or triglycerides were monitored in few animal studies. Nakamura et al. (2009) found that mice with a normal PPAR $\alpha$  receptor had significantly increased levels of cholesterol and triglycerides in liver, but not plasma, at a LOAEL of 0.3 mg/kg/day. However, no differences were observed in serum or liver cholesterol or triglycerides between PFOA-treated mice with a humanized PPAR $\alpha$  receptor or PPAR $\alpha$  null mice (NOAEL = 0.3 mg/kg/day) and their respective controls. A study by Minata et al. (2010) used higher doses and found that total cholesterol was significantly decreased and total triglycerides significantly increased in wild-type mice. In the PPAR $\alpha$  null mice, total triglycerides were significantly increased at all doses.

In animal studies, serum levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) were significantly increased indicative of apoptosis or necrosis of liver cells (Butenhoff et al. 2012; Minata et al. 2010; Son et al. 2008). Increased levels of ALT were observed at a LOAEL of 2.65 mg/kg/day in ICR mice by Son et al. (2008). Yahia et al. (2010) reported significantly increased ALT, gamma-glutamyl transferase (GGT), AST, and alkaline phosphatase (ALP) in PFOA-exposed (10 mg/kg) pregnant ICR mice. Total protein, albumin, and globulin were significantly decreased in the same mice.

#### 4.1.2 Human Epidemiology Studies

Numerous epidemiology studies evaluating large cohorts of highly exposed occupational and general populations have examined the association of PFOA exposure to a variety of health endpoints. Health outcomes assessed include blood lipid and clinical chemistry profiles; reproductive parameters; thyroid effects; diabetes; immune function; birth, fetal, and developmental growth measures; and cancer. Members of the general population living in the vicinity of the West Virginia DuPont Washington Works PFOA production plant in Parkersburg, West Virginia, are the focus of an ongoing study titled the C8 Health Project. Releases from the Washington Works plant, where PFOA was used as a processing aid in the manufacture of fluoropolymers, contaminated the ground water from six water districts near the plant, resulting in exposures to the general population. The C8 Health Project is the largest study evaluating human exposure and health endpoints for PFOA; the study included more than 65,000 people in Mid-Ohio Valley communities who were exposed to PFOA for longer than 1 year.

As part of the C8 Health Project, a panel of expert epidemiologists reviewed the epidemiological and other data available in 2011 and 2012 to assess probable links between PFOA exposure and disease.<sup>6</sup> The C8 Science Panel concluded that a probable link existed between PFOA exposure and the following conditions: high cholesterol, thyroid disease, pregnancy-induced hypertension, ulcerative colitis, and kidney and testicular cancer. The C8 Science Panel did not find a probable link between PFOA exposure and multiple other conditions, including other autoimmune diseases (rheumatoid arthritis, lupus, Type I diabetes, Crohn's disease, multiple sclerosis), Type II diabetes, high blood pressure, coronary artery disease, infectious disease, liver disease, Parkinson's disease, osteoarthritis, neurodevelopmental disorders in children (attention deficit hyperactivity disorder, learning disabilities), chronic kidney disease, stroke, asthma or chronic obstructive airways disease (COPD), and birth defects,

---

<sup>6</sup> For more information see [http://www.c8sciencepanel.org/prob\\_link.html](http://www.c8sciencepanel.org/prob_link.html).

miscarriage or stillbirth, preterm birth or low birth weight, and other types of cancer. The summary below focuses on the endpoints highlighted as “probable links” by the C8 Science panel, and on other epidemiology studies published after the 2011–2012 reports.

### *Serum Lipids*

The association between PFOA and serum lipids has been examined in several studies in different populations. Cross-sectional and longitudinal studies in occupational settings (Costa et al. 2009; Olsen et al. 2000, 2003; Olsen and Zobel, 2007; Sakr et al. 2007a, 2007b; Steenland et al. 2015) and in the high-exposure community (the C8 Health Project study population) (Fitz-Simon et al. 2013; Frisbee et al. 2010; Steenland et al. 2009; Winquist and Steenland 2014a) generally observed positive associations between serum PFOA and total cholesterol in adults and children (ages 1 to < 18 years); most of these effect estimates were statistically significant. Although exceptions to this pattern are present (i.e., some of the analyses examining incidence of self-reported high cholesterol based on medication use in Winquist and Steenland, 2014a, and in Steenland et al. 2015), the results are relatively consistent and robust. Similar associations were seen in analyses of low-density lipoprotein (LDL), but were not seen with high-density lipoprotein (HDL). The range of exposure in occupational studies is large (means varying between 0.4 and > 12 micrograms per milliliter [ $\mu\text{g}/\text{mL}$ ]), and the mean serum levels in the C8 population studies were around 0.08  $\mu\text{g}/\text{mL}$ . Positive associations between serum PFOA and total cholesterol (i.e., increasing lipid level with increasing PFOA) were observed in most of the general population studies at mean exposure levels of 0.002 to 0.007  $\mu\text{g}/\text{mL}$  (Eriksen et al. 2013; Fisher et al. 2013; Geiger et al. 2014; Nelson et al. 2010; Starling et al. 2014). The interpretation of these general population results is limited, however, by the moderately strong correlations (Spearman  $r > 0.6$ ) and similarity in results seen for PFOS and PFOA.

### *Liver Disease and Liver Function*

Few studies pertaining to the relation between PFOA and liver disease are available. The C8 Health Project did not observe associations with hepatitis, fatty liver disease, or other types of liver disease. In the studies of PFOA exposure and liver enzymes (measure in serum), positive associations were seen. The results of the occupational studies provide evidence of an association with increases in serum AST, ALT, and GGT, with the most consistent results seen for ALT. The associations were not large, and the associations could depend on the co-variates in the models, such as body mass index, use of lipid lowering medications, and triglycerides (Costa et al. 2009; Olsen et al 2000, 2003; Olsen and Zobel, 2007; Sakr et al. 2007a, 2007b).

Two population-based studies of highly exposed C8 area residents evaluated associations with liver enzymes, and the larger of the two studies reported associations of increasing serum ln ALT and ln GGT levels with increasing serum PFOA concentrations (Emmett et al. 2006; Gallo et al. 2012). A cross-sectional analysis of data from NHANES, representative of the U.S. national population, also found associations with ln PFOA concentration with increasing serum ALT and ln GGT levels. Serum bilirubin was inversely associated with serum PFOA in the occupational studies. A U-shaped exposure-response pattern for serum bilirubin was observed among the participants in the C8 Health Project which might explain the inverse associations reported for occupational cohorts. Overall, an association of serum PFOA concentration with elevations in serum levels of ALT and GGT was consistently observed in occupational, highly

exposed residential communities, and the U.S. general population. The associations are not large in magnitude, but indicate the potential to affect liver cells.

### *Immune Function*

Three studies examined associations between maternal and/or child serum PFOA levels and vaccine response (measured by antibody levels) in children (Grandjean et al. 2012; Granum et al. 2013) and adults (Looker et al. 2014). The study in adults was part of the high-exposure community C8 Health Project; a reduced antibody response to one of the three influenza strains tested after receiving the flu vaccine was seen with increasing levels of serum PFOA. The studies in children were conducted in general populations in Norway and in the Faroe Islands. As observed in the animal studies, decreased vaccine response in relation to PFOA levels was seen in these studies, but similar results also were seen with other correlated PFASs (e.g., PFOS).

### *Thyroid*

Three studies reported an increased risk of thyroid disease in women or girls, but not men (Lopez-Espinosa et al. 2012; Melzer et al. 2010; Winquist and Steenland, 2014b). A fourth study also reported a trend of elevated TSH and decreased T4 (hypothyroidism) in pregnant women testing positive for hypothyroid autoimmune disease (Webster et al. 2014). Similarly, the C8 Panel concluded there was strong evidence to link PFOA exposure to thyroid disease in its population. Hypothyroxinemia (decreased free thyroxine (FT4) without concomitant elevation of TSH) was measured in one study of pregnant women showing null findings for hypothyroxinemia incidence versus controls; hypothyroxinemia is not typically studied in the clinic as TSH and T4 concomitantly inversely shift with thyroid disease. Looking at thyroid hormone levels, some studies found changes in thyroid hormone levels associated with PFOA (de Cock et al. 2014; Shrestha et al. 2015; Webster et al. 2014; Wen et al. 2013.); others found null effects of PFOA in association with thyroid hormones. Generally null associations were found in other studies on the general population, pregnant women, and patients in association with thyroid hormone levels or one portion of the thyroid panel was outside of control range. Across multiple studies, thyroid hormone concentrations have mixed evidence (associations and null findings) in association with PFOA concentrations. Increased risk for thyroid disease in women appears to be associated with PFOA serum concentration; evidence is weaker or null in men.

### *Diabetes*

No associations were observed between serum PFOA levels and type II diabetes incidence rate in general or worker populations with mean serum PFOA up to 0.0913–0.113  $\mu\text{g}/\text{mL}$  (MacNeil et al. 2009; Steenland et al. 2015). PFOA was not associated with measures of metabolic syndrome in adolescents or adults (Lin et al. 2009). However, one study found an increased risk for developing gestational diabetes in women with mean serum PFOA (measured at preconception) of 0.00394  $\mu\text{g}/\text{mL}$  (Zhang et al. 2015).

### *Fertility, Pregnancy, and Birth Outcomes*

The association between PFOA and birth weight has been examined in numerous studies (see section 4.1.1.7 in USEPA 2016a). Most studies measured PFOA in the general population using

maternal blood samples taken in the second or third trimester or in cord blood samples. One study was able to collect samples earlier in the pregnancy (4–14 weeks) (Fei et al. 2007), and another study in the high-exposure community (the C8 Health Project population) modeled exposure based on data on residential history and environmental data (Savitz et al. 2012). Two meta-analyses of these studies have been conducted (Johnson et al. 2014; Verner et al. 2015), with similar results: mean birthweight reduction of 19 g (95% CI [-30, -9]) per each one unit (ng/mL) increase in maternal or cord serum PFOA levels in Johnson et al. (2014), and a mean birthweight reduction of 15 g (95% CI [-22, -8]) based on seven of these nine studies in Verner et al. (2015). It has been suggested that low glomerular filtration rate (GFR) can affect birth weight (Morken et al 2014). Verner et al (2015) conducted a meta-analysis based on physiologically based pharmacokinetic model (PBPK) simulations and found that some of the association reported between PFOA and birth weight is attributable to GFR and that the actual association may be closer to a 7 gram reduction (95% CI [-8, -6]). Verner et al. (2015) showed that in individuals with low GFR there are increased levels of serum PFOA and lower birth weights. Although some uncertainty exists in the interpretation of the observed association between PFOA and birth weight given the potential impact of low GFR, the available information indicate that the association between PFOA exposure and birth weight cannot be ruled out. In humans with low GFR (which includes women with pregnancy-induced hypertension or preeclampsia) the impact on body weight is likely due to a combination of the low GFR and the serum PFOA.

Two studies examined development of puberty in girls in relation to prenatal exposure to PFOA as measured through maternal or cord blood samples in follow-up of pregnancy cohorts conducted in England (Christensen et al. 2011) and in Denmark (Kristensen et al. 2013). The results of these two studies are conflicting, with no association (or a possible indication of an earlier menarche seen with higher PFOA) in Christensen et al. (2011), and a later menarche seen with higher PFOA in Kristensen et al. (2013). Another study examined PFOA exposure measured concurrently with the assessment of pubertal status (Lopez-Espinosa et al. 2011). An association between later age at menarche and higher PFOA levels was observed, but the interpretation of this finding is complicated by the potential effect of puberty on the exposure biomarker levels (i.e., reverse causality). Menstruation is a route of excretion for albumin-bound PFOA; thus, the beginning of menstruation will remove serum PFOA when the menstruation periods begin during puberty and its cessation at menarche will decrease the loss of PFOA in blood and allow serum levels to increase.

Limited data suggest a correlation between higher PFOA levels ( $>0.02$   $\mu\text{g/mL}$ ) in women and decreases in fecundity and fertility (Fei et al. 2009; Vélez et al. 2015), but there are no clear effects of PFOA on male fertility endpoints ( $0.0035$ – $0.005$   $\mu\text{g/mL}$ ; Joensen et al. 2009, 2013).

#### **4.1.3 Noncancer Mode of Action**

No published cohesive MOA exists that accounts for the varied toxicological properties of PFOA. 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 with areas of positive charge, especially proteins (MacManus-Spencer et al. 2009; Salvalaglio et al. 2010; Wu et al. 2009b; L. Zhang et al. 2013).
- Displacement of endogenous/exogenous substances normally bound to serum albumin such as fatty acids, bile acids, pharmaceuticals, and T3 (Fasano et al. 2005; Qin et al. 2010; Wu et al. 2009a).
- Renal resorption (Andersen et al. 2006) and biliary excretion that are dependent on 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 related to fatty acid metabolism and lipid transport (Nakamura et al. 2009; Rosen et al. 2007, 2009a, 2009b; Takacs and Abbott 2007).
- Interference with intercellular communication (Upham et al. 1998, 2009).

The renal resorption and biliary competition between natural substrates and PFAS contribute to ambiguity in some of the epidemiology study outcomes where serum levels of endogenous or dietary-transported substrates are altered because of preferential removal or resorption of the PFOA, or the PFOA serum level increases because of the preferred excretion of the natural material. Physiological status also has an impact on the epidemiology results given that blood loss through menstruation is an excretory pathway for serum-albumin-bound PFOA. Thus, serum levels will be lower in girls after puberty than before, and will increase in women after menopause. In pregnant women, increased blood volume as well as cessation of monthly menstrual blood flow route also influences serum levels.

The outcome from studies of antibodies or immunoglobulins can be confounded by PFOA protein binding depending on the impact of morphological changes caused by PFOA binding on the sensitivity of the assay. Interaction of PFOA and other PFASs (Ren et al. 2015) with the T3 receptor has the potential to influence cellular uptake of T3. Binding to thyroid hormone transport protein or transthyretin (TTR) can displace T4 increasing the unbound level in serum (Weiss et al. 2009).

There are no cohesive studies designed to identify modes of action for the liver weight and hypertrophy endpoints represented in the animal studies. Both effects are clearly, in part, an outcome of PPAR $\alpha$  activation. They become adverse when accompanied by inflammation, fibrosis, steatosis, or necrosis (Hall et al. 2012) as seen in Palazzolo et al. (1993)/Perkins et al. (2004), Loveless et al. (2008), and Butenhoff et al. (2004a).

The MOA for decreased pup body weight observed in the animal studies is unknown (Butenhoff et al. 2004a; White et al. 2009; Wolf et al. 2007). The observed effects on birth weight in animals are supported by evidence of an association between PFOA and low birth weight in humans (Johnson et al. 2014). Receptor-activated changes in metabolism, hormonal perturbations, and impeded intercellular communication could play a role in this effect. It has been suggested that GFR can affect birth weight (Morken et al 2014). Verner et al (2015) conducted a meta-analysis based on PBPK simulations and found that some of the association reported between PFOA and birth weight could be partially attributable to low GFR and that the actual association might be closer to a 7 gram reduction (95% CI [-8, -6]). However, the study

authors demonstrated that individuals with low GFR have increased levels of serum PFOA and lower birth weights. Although some uncertainty exists in the interpretation of the observed association between PFOA and birth weight given the potential impact of low GFR, the available information indicate that the association between PFOA exposure and birth weight cannot be ruled out. In humans with low GFR (which includes women with pregnancy-induced hypertension or preeclampsia) the impact on body weight is likely due to a combination of the low GFR and the serum PFOA.

Women with hypertension during pregnancy are a susceptible population that could have an increased risk for having a low birth weight baby.

There also is a lack of data relative to the MOA for immunological effects of PFOA as seen in animal studies. Some of the responses are PPAR $\alpha$  linked (increased spleen and thymus weights) but not all as demonstrated by DeWitt et al. (2015). Effects on serum immunoglobulins observed in humans could be a reflection of analytical method interference as a result of PFOA binding to the immunoglobulin (Kerstner-Wood et al. 2003).

PFOA is associated with delayed breast tissue development (reduced ductal branching and numbers of terminal endbuds) in CD-1 mice (Albrecht et al. 2013; Macon et al. 2011; Tucker et al. 2015; White et al. 2009); however, no functional impacts on the ability of the dams to provide nourishment were observed based on the weight increases in the pups reared by the impacted dams (Macon et al. 2011; White et al. 2011). CD-1 mice seem to be more sensitive for this effect than other mice strains evaluated (Tucker et al. 2015). No mechanistic studies exist that inform the MOA for the mammary gland development effects.

Quist et al. (2015) found that the level of dietary fat in an animal diet is an important variable that influences liver lipid levels. At PFOA doses < 0.3 mg/kg/day, the LDL and total serum cholesterol levels in the fasted and nonfasted high-fat diet animals were greater than in the untreated Purina controls. Tan et al. (2013) found that the fat content of the diet was an important variable in determining the impact of PFOA (5 mg/kg/day) on liver and serum lipids. Intake of a high-fat diet plus PFOA increased liver triglycerides and serum free fatty acids as compared to a regular fat diet plus PFOA, but it had no impact on liver cholesterol concentrations. Serum cholesterol was not monitored. A high-fat diet predisposes animals and possibly humans to hepatic steatosis.

## **4.2 Cancer**

### **4.2.1 Animal Cancer Bioassays**

The only animal carcinogenicity studies available for PFOA indicate that exposure can lead to liver adenomas (Biegel et al. 2001), Leydig cell adenomas (Biegel et al. 2001; Butenhoff et al. 2012), and pancreatic acinar cell tumors (PACT) (Biegel et al. 2001) in male Sprague-Dawley rats. In the Butenhoff et al. (2012) study there was an increase in liver carcinomas at the high dose (14.2 mg/kg/day) in the males compared to controls (6% versus 10%). For the females receiving 16.1 mg/kg/day (i.e., the high dose) the tumor incidence compared to controls was 0% versus 2%. The increase in liver tumors did not show a direct relationship to dose in the male rats and was not statistically significantly elevated in either males or females at the high dose when

compared to controls (Butenhoff et al. 2012). Liver adenomas were observed in the Biegel et al. (2001) study at an incidence of 10/76 (13%) at 20 mg/kg/day. The incidence in the control group was 2/80 (3%).

Butenhoff et al. (2012) also observed increased incidence of testicular Leydig cell tumors (LCTs) in rats. At the 1-year sacrifice, testicular masses were found in 7/50 (14%) high-dose and 2/50 (4%) low-dose rats, but not in any of the controls. A significant increase ( $p < 0.05$ ) in the incidence of testicular (Leydig) cell adenomas was also observed in the high-dose male rats at the end of the study. The LCT incidence in the control, low-, and high-dose groups was 0/50 (0%), 2/50 (4%), and 7/50 (14%), respectively. Biegel et al. (2001) observed a significant increase in the incidence of Leydig cell adenomas in the treated rats (11%, 8/76) when compared to the pair-fed control rats (3%, 2/78) supporting the observations from the Butenhoff et al. (2012) study. The LCTs in the Butenhoff et al. (2012) study were accompanied by statistically significant testicular vascular mineralization and by Leydig cell hyperplasia in the Biegel et al. (2001) study.

PACTs were only observed in the Biegel et al. (2001) study, with an incidence of 11% at 20 mg/kg/day compared to controls. Although no PACTs were observed by Butenhoff et al. (2012), pancreatic acinar hyperplasia was observed at 1.3 and 14.2 mg/kg/day at incidences of 6% and 2%, respectively. Re-examination of the pancreatic lesions in Butenhoff et al. (2012) and Biegel et al. (2001) resulted in the conclusion that the high dose increased the incidence of proliferative acinar cell lesions in both studies. Some lesions in the Biegel et al. (2001) study had progressed to adenomas but not those in the Butenhoff et al. (2012) study.

The initial findings from the Butenhoff et al. (2012) study were equivocal for mammary fibroadenomas in female rats. However, a re-examination of the tissues by a pathology working group (PWG) found no statistically significant differences in the incidence of fibroadenomas or other neoplasms of the mammary gland between control and treated animals (Hardisty et al. 2010). The PWG used the diagnostic criteria and nomenclature of the Society of Toxicological Pathologists for the re-examination.

#### **4.2.2 Human Epidemiology Studies**

Evidence of carcinogenic effects of PFOA in epidemiology studies is based on studies of kidney and testicular cancer. These cancers have relatively high survival rates (2005–2011 5-year survival rates are 73% and 95%, respectively, for kidney and testicular cancer, based on NCI Surveillance, Epidemiology and End Results data); therefore, studies that examine population cancer incidence are particularly useful for these types of cancers. For testicular cancer, the high-exposure community studies also have the advantage of including the age period of greatest risk, as the median age at diagnosis is 33 years. The two occupational cohorts in Minnesota and West Virginia (most recently updated, respectively, in Raleigh et al. 2014 and Steenland and Woskie, 2012) do not support an increased risk of these cancers, but each of these is limited by a small number of observed cases (six kidney cancer deaths, 16 incident kidney cancer cases, and five incidence testicular cancer cases in Raleigh et al. [2014]; 12 kidney cancer deaths and one testicular cancer death in Steenland and Woskie [2012]). Two studies involving members of the C8 Health Project showed a positive association between PFOA levels (mean at enrolment 0.024  $\mu\text{g/mL}$ ) and kidney and testicular cancers (Barry et al. 2013; Vieira et al. 2013);

some of the cases included in these studies overlap. None of the general population studies examined kidney or testicular cancer, but no associations were found in the general population between mean serum PFOA levels up to 0.0866 µg/mL and colorectal, breast, prostate, bladder, and liver cancer (Bonfeld-Jørgensen et al. 2014; Eriksen et al. 2009; Hardell et al. 2014; Innes et al. 2014).

#### 4.2.3 Cancer Mode of Action

The mode of carcinogenic action of PFOA is not clearly understood. Some researchers have concluded from the available data that the liver tumors observed in the cancer bioassays can be attributed mostly to the impact of PFOA on peroxisome proliferation based on a hypothesized lower sensitivity of humans to this MOA (Klaunig et al. 2003, 2012). Some data support the hypothesis that PPAR $\alpha$  agonism MOA could be responsible for observed liver tumors in animals. Rosen et al. (2008a, 2008b) examined transcript profiles in the livers of wild-type and PPAR $\alpha$ -null mice dosed with PFOA for up to 7 days. This study showed that animal responses were consistent with PPAR $\alpha$  agonism, but evidence also shows PPAR $\gamma$  agonism (down-regulation of cholesterol synthesis) and activation of CAR and PXR-related genes (Martin et al. 2007). There is evidence that PFOA is a potent peroxisome proliferator inducing peroxisome formation in the livers of rats and mice (Elcombe et al. 2010; Minata et al. 2010; Pastoor et al. 1987; Wolf et al. 2008; Yang et al. 2001). Beyond activation of PPAR $\alpha$ , few studies have evaluated whether additional steps (i.e., cell proliferation and apoptosis) are in the hypothesized PPAR $\alpha$  agonism MOA (Elcombe et al. 2010; Minata et al. 2010; Wolf et al. 2008). For example, no studies were identified that focused specifically on preneoplastic foci and clonal expansion of altered cells after PPAR activation.

The proposed MOA for testicular LCTs is linked to decreased serum testosterone levels and signaling of the hypothalamus to produce gonadotropin releasing hormone (GnRH), a signaling agent for the pituitary to release luteinizing hormone which upregulates testosterone production in Leydig cells. Administering PFOA to adult male rats by gavage for 14 days was shown to decrease testosterone levels and increase serum estradiol levels (Cook et al. 1992). These endocrine changes correlated with its potency to induce LCTs in rats and were hypothesized to play a role in the PFOA-induction of LCTs (Biegel et al. 2001). Support for PPAR $\alpha$ -mediated inhibition of testosterone production is found in Li et al. (2011). However, some researchers have proposed that data are not currently sufficient to demonstrate that the other key steps in the postulated MOA are present in PFOA-treated animals following exposures that lead to tumor formation (Klaunig et al. 2012).

Two hypothetical MOAs have been proposed for PACTs (Klaunig et al. 2003, 2012; Obourn et al. 1997). In one case, growth factors such as cholecystokinin (CCK) and/or gastrin activate a feedback loop resulting in proliferation of the secretory pancreatic acinar cells leading to tumors. The other proposed MOA suggests that increased serum testosterone supports the growth of acinar cell preneoplastic foci.

Li et al. (2011) found that serum testosterone levels were decreased, not increased, in wild-type, PPAR $\alpha$ - null and mice with humanized PPAR $\alpha$ . Biegel et al. (2001) found no change in serum testosterone in their bioassay. Obourn et al. (1997) studied the impact of PFOA on CCK and trypsin using *in vitro* assays and found that PFOA was not an agonist for the cholecystokinin

agonism receptor receptor that activated CCK release. Plummer et al. (2007) reported on gene expression changes induced in pancreatic acinar cells isolated from Sprague-Dawley rats fed diets containing 300 parts per million (~20 mg/kg/day) PFOA for 28 days. Expression of genes regulated by PPAR $\alpha$ ,  $\gamma$ ,  $\delta$  in pancreatic acinar cells was directly opposite of the expression of those same genes in liver tissue. At the present time, data are insufficient to demonstrate a MOA that can account for the PACTs identified in the chronic study by Biegel et al. (2001).

The mutagenicity data on PFOA are largely negative, although some evidence shows clastogenicity in the presence of microsomal activation and at cytotoxic concentrations (Murli 1996a, 1996b). PFOA's clastogenic effects are likely the result of an indirect mechanism, given the chemical and physical properties of PFOA (i.e., it is not metabolized, it binds to cellular proteins, and it carries a net negative electrostatic surface charge). PFOA has the potential to interfere with the process of DNA replication because of its protein-binding properties and the fact that histone proteins, spermine, and spermidine carry a net positive surface charge. Involvement of reactive oxygen species (ROS) in the MOA as a result of PFOA alone is unlikely because of its metabolic stability. Conditions leading to ROS would be a function of metabolic responses perturbed by PFOA, rather than PFOA alone.

A compound that is not metabolized will not be able to covalently alter the structure of DNA or intercalate because of electrostatic repulsion between the aromatic base pi bond electrons and the partial negative charges on the PFOA fluoride atoms. Because of its protein-binding properties, PFOA could affect one or more of the proteins involved in the process of DNA replication or cell division (cytoskeletal proteins), however, no mechanistic studies were identified that examined the biochemical effects of PFOA on DNA replication or cell division. No data support this as a MOA for clastogenic effects.

#### 4.2.4 Weight of Evidence Classification

Under EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2005) there is Suggestive Evidence of Carcinogenic Potential of PFOA in humans. The bioassay findings for Leydig cell testicular tumors in rats, combined with the C-8 Panel finding of a probable link to testicular and renal tumors among the members of the C8 Health Project, support this conclusion.

In June 2014, 20 experts met at the International Agency for Research on Cancer (IARC) in Lyon, France, to assess the carcinogenicity of perfluorooctanoic acid (PFOA), among other chemicals. Although the assessments have not yet been published (they are expected to be published in volume 110 of the IARC monographs), the expert findings from this meeting are available in a peer-reviewed publication (Benbrahim-Tallaa et al. 2014), and their determination is on the IARC website. The working group classified PFOA as *possibly carcinogenic to humans* (*Group 2B*) and considered the evidence regarding mechanisms of PFOA-associated carcinogenesis to be moderate. This assessment did not lead to a change in the overall classification of PFOA by IARC.

## 5.0 DOSE-RESPONSE ASSESSMENT

As an initial step in the dose-response assessment, EPA identified a suite of animal studies with NOAELs and/or LOAELs that identified them as potential candidates for development of the RfD for PFOA. These studies included short-term, subchronic, and chronic exposures, including developmental and reproductive toxicity studies. The available studies evaluated endpoints including liver effects (weight changes with histopathology), body weight changes in adults and offspring, reproductive outcomes such as fertility, developmental effects (altered puberty, survival, and developmental delays such as eye opening), and immune effects. The candidate studies were selected based on their NOAEL and/or LOAEL values, a duration of 11 to 91 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 deriving 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 PFOA intakes.

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 statistical analysis 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.

The average serum concentrations were converted into an oral equivalent dose by recognizing that clearance from the body equals dose to the body. Clearance can be calculated if the rate of elimination (derived from half-life) and the volume of distribution are both known. EPA used the Bartell et al. (2010) calculated human half-life of 2.3 years (general population) with the Thompson et al. (2010) volume of distribution ( $V_d$ ) of 0.17 L/kg body weight (bw) to determine a clearance of  $1.4 \times 10^{-4}$  L/kg bw/day by the following equation:

$$CL = V_d \times (\ln 2 \div t_{1/2}) = 0.17 \text{ L/kg bw} \times (0.693 \div 839.5 \text{ days}) = 0.00014 \text{ L/kg bw/day}$$

Where:

$$V_d = 0.17 \text{ L/kg}$$

$$\ln 2 = 0.693$$

$$t_{1/2} = 839.5 \text{ days} (2.3 \text{ years} \times 365 \text{ days/year} = 839.5 \text{ days})$$

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 bw/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.

Table 5-1 provides 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.

**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 mg/L	HED mg/kg/d	LOAEL mg/kg/d	LOAEL (Av serum) mg/L	HED mg/kg/d
DeWitt et al. (2008): mice; ↓ IgM response to SRBC	15	1.88	38.2	0.0053	3.75	61.9	0.0087
Lau et al. (2006): mice decreased ↓ pup ossification (m, f), accelerated male puberty	17	None	-	-	1	38.0	0.0053
Palazzolo et al. (1993); Perkins et al. (2004): rats; ↑liver weight/necrosis	91	0.64	31.6	0.0044	1.94	77.4	0.0108
Wolf et al. (2007): mice; GD 1–17 ↓Pup body weight	17	None	-	-	3	77.9	0.0109
Wolf et al. (2007): mice; GD 7–17 ↓Pup body weight <sup>1</sup>	11	None	-	-	5	87.9	0.0123
Butenhoff et al. (2004a): ↓ relative body weight/↑ relative kidney weight and ↑kidney: brain weight ratio in F0 and F1 at sacrifice	84	None	-	-	1	45.9	0.0064

*Notes:*

Significance  $p < 0.05$  or  $p < 0.01$

m = male; f = female; SRBC = sheep red blood cell; IgM = immunoglobulin M; GD = gestation day

<sup>1</sup> serum from pups on PND 22

The external doses in each of the studies varied. The NOAELs ranged from 0.64 to 1.88 mg/kg/day. The corresponding average serum values ranged from 1.6 mg/L (rat) to 38.2 mg/L (mouse). At the LOAEL, the average serum values range from 38 µg/mL (mouse) to 87.6 µg/mL (monkey) at doses estimated to represent about 56% to 96 % of steady state. At the low end of the range the effects of concern are observed in neonates (low birth weight, delays in developmental endpoints, with increased kidney weight at sacrifice later in life).

Much of the variability in the average serum levels for the LOAELs was due to differences in the doses used in the individual studies. For example, two of the modeled endpoints (Wolf et al. 2007) identified low birth weights in mouse pups as the critical effect, but had a single external dose that was 3 to 5 times higher than the low dose from the Lau et al. (2006) mouse study (1 mg/kg/day).

Among the studies conducted in mice, dose was a more important variable in determining serum level and percent of steady state than duration of exposure. This is a characteristic of the nonlinear toxicokinetics exhibited by PFOA. The half-life for doses that exceed the resorption capacity of the kidney are shorter than lower doses that can be resorbed and thereby persist in serum over a longer exposure duration. For example, in Wolf et al. (2007), an 11-day dose of 5 mg/kg/day resulted in an average serum of 88 mg/L (82% of concentration at steady state or  $C_{ss}$ ) whereas a 1 mg/kg/day dose for 17 days resulted in an average serum of 38 mg/L (56% of  $C_{ss}$ ). In rats, dosed at 1 mg/kg/day, over two generations (84 days), an average serum of 45.9 mg/L at 87% of steady state was determined (Butenhoff et al. 2004a). A 91-day exposure (Palazzolo et al. 1993/Perkins et al. 2004) to 1.94 mg/kg/day resulted in a serum value of 77 mg/kg/day and was 91% of steady state. The endpoints in Butenhoff et al. (2004a) are effects on body weight and relative kidney weight in the adult F0 and F1 rats, while the endpoint for Palazzolo et al. (1993)/Perkins et al. (2004) was systemic increased liver weight with lower-level necrosis.

Assuming that MOA and susceptibility to toxicity do not vary and that pharmacokinetics alone explains variation, it is reasonable to expect similar concentrations to cause similar effects in humans and are more important than both dose and duration once steady state is attained.

## 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 (toxicokinetic genetic, life stage, health status) and extrinsic (life style) factors that can influence the response to dose. 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 is applied to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability). The 3-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 toxicokinetic differences between animals and humans.

An uncertainty factor for LOAEL to NOAEL extrapolation ( $UF_L$ ) of 10 is applied to all PODs other than the Palazzolo et al. (1993)/Perkins et al. (2004) and DeWitt et al. (2008) studies to account for use of a LOAEL for the POD. The POD for the Palazzolo et al. (1993)/Perkins et al. (2004) and DeWitt et al. (2008) studies are NOAELs for the effect identified as critical.

An uncertainty factor for extrapolation from a subchronic to a chronic exposure duration ( $UF_s$ ) of 1 is applied because the PODs are based on average serum concentrations and determined to represent >80% of steady state for each study (81–91%), except for the Lau et al. (2006) developmental study (56%). The Lau et al. (2006) developmental HED was not adjusted

for lifetime exposures because the average serum values associated with the developmental studies are more protective than those for the longer-term studies of systemic toxicity. A UF<sub>s</sub> of 10 was applied to the DeWitt et al. (2008) study serum derived HED reflecting (74%) of steady state because the data suggest that longer term exposures to the same dose have the potential to increase serum values beyond the levels indicated by the 15-day study. In addition, the NOAEL for immunological effects (0.94 mg/kg/day) was a LOAEL for effects on liver weight in the absence of histological evaluation on both days 16 and 31 following a 15-day exposure (DeWitt et al. 2008). Thus, there is a potential that lifetime exposures at steady state can affect the liver and increase the risk for tissue damage.

A database uncertainty factor (UF<sub>D</sub>) of 1 was applied to account for deficiencies in the database for PFOA. There are extensive human data from epidemiological data from the general population as well as worker cohorts. The epidemiology data provide strong support for the identification of hazards observed following exposure to PFOA in the laboratory animal studies and human relevance. However, uncertainties in the use of the available epidemiology data precluded their use at this time in the quantification of the effect level for derivation of the drinking water HA. In animals, acute, short term, subchronic and chronic studies, including a long term cancer study, are available. In addition, several developmental studies and a two-generation reproductive toxicity study evaluating exposure of pregnant dams and offspring to PFOA are available.

## 5.2 RfD Determination

Table 5-2 provides the calculations for candidate 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, and Table 5-2 illustrates the array of candidate RfD outcomes. Each POD is affected by the doses used in the subject study, the endpoints monitored, and the animal species/gender studied. Thus, the array of outcomes, combined with knowledge of the individual study characteristics helps to inform selection of an RfD that will be protective for humans. Other than DeWitt et al. (2008) and Lau et al. (2006), all of the selected studies had serum levels that had reached > 80% of C<sub>ss</sub>. It is important to note the relatively narrow range of RfDs across the multiple endpoints and study durations evaluated.

Using the pharmacokinetic model of Wambaugh et al. (2013), average serum PFOA concentrations were derived from 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 0.00015 mg/kg/day across multiple endpoints. The RfD of 0.00002 mg/kg/day calculated from HED average serum values from Lau et al. (2006) was selected. This RfD is derived from reduced ossification of the proximal phalanges (forelimb and hindlimb) and accelerated puberty in male pups (4 days earlier than controls) as the critical effects. The POD for the derivation of the RfD for PFOA is the HED of 0.0053 mg/kg/day that corresponds to a LOAEL that represents approximately 60% of steady-state concentration. An UF of 300 (10 UF<sub>H</sub>, 3 UF<sub>A</sub>, and 10 UF<sub>L</sub>) was applied to the HED LOAEL to derive an RfD of 0.00002 mg/kg/day.

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

POD	HED POD mg/kg/day	UF <sub>H</sub>	UF <sub>A</sub>	UF <sub>L</sub>	UF <sub>S</sub>	UF <sub>D</sub>	UF <sub>total</sub>	Candidate RfD mg/kg/day
PK-HED <sub>NOAEL</sub> Palazzolo et al. (1993)/Perkins et al. (2004) rats; ↑liver weight/necrosis	0.0044	10	3	-	-	-	30	0.00015
PK-HED <sub>LOAEL</sub> Wolf et al. (2007) GD1-17 mice; ↓Pup body weight	0.0109	10	3	10	-	-	300	0.00004
PK-HED <sub>LOAEL</sub> Wolf et al. (2007) GD 7-17 mice; ↓Pup body weight (serum from pups on PND 22)	0.0123	10	3	10	-	-	300	0.00004
PK-HED <sub>NOAEL</sub> DeWitt et al. (2008) mice; ↓ IgM response to SRBC	0.0053	10	3	-	10	-	300	0.00002
PK-HED <sub>LOAEL</sub> Lau et al. (2006) mice decreased ↓ pup ossification (m, f), accelerated male puberty	0.0053	10	3	10	-	-	300	0.00002
PK-HED <sub>LOAEL</sub> Butenhoff et al. (2004a) ↓ relative body weight/↑ relative kidney weight and ↑kidney: brain weight ratio in F0 and F1 at sacrifice	0.0064	10	3	10	-	-	300	0.00002

*Notes:*

PK-HED = pharmacokinetic human equivalent dose; NOAEL = no observed adverse effect level; LOAEL = lowest observed adverse effect level; GD = gestation day; IgM = immunoglobulin M; m = male; f = female; SRBC = sheep red blood cell; UF<sub>H</sub> = intraindividual uncertainty factor; UF<sub>A</sub> = interspecies uncertainty factor; UF<sub>S</sub> = subchronic to chronic uncertainty factor; UF<sub>L</sub> = LOAEL to NOAEL uncertainty factor; UF<sub>D</sub> = incomplete database uncertainty factor; UF<sub>total</sub> = total (multiplied) uncertainty factor

Decreased pup body weights also were observed in studies conducted by Wolf et al. (2007), White et al. (2009), and Lu et al. (2015) using mice receiving external doses within the same order of magnitude (1, 3, and 5 mg/kg/day respectively) as those chosen for the RfD. The selected RfD from the reproductive and developmental studies is supported by the longer term RfD for effects on the response of the immune system to external challenges as observed following the short-term exposures to mature mice and the effects on kidney weight observed at the time of sacrifice in the F0 and F1 adult males that provided the serum in the Butenhoff et al. (2004a) study (DeWitt et al. 2008).

Support for the selected RfD also is provided by other key studies with NOAELs and LOAELs similar to those used for quantification, but lacking serum data that could be used for modeling. There were effects on liver weight and hepatic hypertrophy in the Perkins et al. (2004) and DeWitt et al. (2008) studies that were modeled but not considered in the derivation of the

RfD because of a lack of data to demonstrate adversity as determined by the Hall et al. (2012) criteria at the dose causing the liver effects but not the effects identified as critical. The LOAEL for evidence of hepatic necrosis and other signs of tissue damage in the F1 male rat pups from the Butenhoff et al. (2004a) study was 3 mg/kg/day; the NOAEL was 1 mg/kg/day. In the Loveless et al. (2008) study, the LOAEL for increased relative liver weight accompanied by focal liver necrosis in male rats was 10 mg/kg/day and the NOAEL was 1 mg/kg/day, while in male mice, the LOAEL for the same effect was 1 mg/kg/day and the NOAEL was 0.3 mg/kg/day following a 29-day exposure. In the study by Tan et al. (2013), the degree of damage to the liver at 5 mg/kg/day became more severe with increased necrosis, inflammation, and steatosis when animals were given a high-fat diet. The HED modeled from the average serum value in mice for the LOAEL (3 mg/L) from Wolf et al. (2007) and White et al. (2009) was 0.0110 mg/kg/day, about twice that for the rats in the Lau et al. (2006) study (0.0053 mg/kg/day). Both studies lacked a NOAEL. Each of these data sets support LOAELs for the critical study by Lau et al. (2006) selected for RfD derivation and, as a consequence, the HED derived from modeled average serum values.

## **6.0 HEALTH ADVISORY VALUES**

### **6.1 Relative Source Contribution**

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

Food is a significant source of exposure to PFOA: It has been detected in a variety of foods including snack foods, vegetables, meat, dairy products, human breast milk, and fish. 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 PFOA from drinking water, consumption of plants grown in contaminated soil, and through particulate matter in air; fish from contaminated water ways; and packaging materials.

PFOA has been detected in finished drinking water samples collected by EPA and others. PFOA is not regulated under the SDWA and was included in EPA's UCMR 3. PFOA was detected at a small number of PWSs (0.9%) through this monitoring program. Therefore, there is potential exposure to PFOA from drinking water ingestion.

The vapor pressure of PFOA indicates that volatilization is low; however, PFOA can be released into the atmosphere from industrial and municipal waste incinerators and adsorb to airborne particulates. It can be transported long distances through the atmosphere and has been detected globally at low concentrations. Inhalation of PFOA is possible, and 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 telomer alcohols that metabolically degrade to PFOA. Given the widespread commercial and industrial use of PFOA and its physical properties, air is a potential source of exposure to it and the C8:2 telomer alcohol precursors.

PFOA also has 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 for PFOA, there are many are potential sources. Following EPA's Exposure Decision Tree in its 2000 methodology (USEPA 2000), 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 PFOA.

## 6.2 Lifetime Health Advisory

Based on the consistency of the responses across the chronic studies and those for reproductive and developmental endpoints, and with recognition of the use of developmental toxicity as the most sensitive endpoint, 0.00002 mg/kg/day was selected as the RfD for PFOA. This value is based on the HED for developmental effects (reduced ossification in male and female pups and accelerated puberty in male pups) from the Lau et al. (2006) 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 values derived from the two-generation study by Butenhoff et al. (2004a) for effects on adult body weight plus relative liver and kidney weights in F0 and F1 male rats is the same as the value based on the developmental effects observed by Lau et al (2006). The candidate RfD from the DeWitt et al. (2008) study for suppression of the immunological response to a challenge is the same as that from Lau et al. (2006).

Due to the potential increased susceptibility during the time period of pregnancy and lactation, EPA used drinking water intake and body weight parameters for lactating women in the calculation of a lifetime HA for this target population during this potential critical time period. EPA used the rate of 54 mL/kg-day representing the consumers only estimate of combined direct and indirect community water ingestion at the 90<sup>th</sup> percentile for lactating women (see Table 3-81 in USEPA 2011b). Comparing the pregnant woman and the lactating woman, the lactating woman is the more protective scenario given her increased water intake rate for her body weight needed to support milk production. Additionally, human studies demonstrate that PFOA is transferred from mother to infant via cord blood and breast milk. A recent study showed that breast milk contributed > 83% of the PFOA 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 as well as of the general population. Thus, the protection conferred by the lifetime HA is broadly protective of public health.

The lifetime HA for PFOA is calculated as follows:

A DWEL is derived from the RfD and assumes that 100% of the exposure comes from drinking water.

$$DWEL = \frac{RfD \times bw}{DWI}$$

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

Where:

RfD = 0.00002 mg/kg/day; based on the LOAEL for reduced ossification of the proximal phalanges (forelimb and hindlimb) in male and female pups and accelerated (4 days earlier than controls) puberty in male pups of dams exposed to PFOA by gavage on gestation days 1 to 17 and sacrificed at weaning (Lau et al. 2006).

DWI/bw = 0.054 L/kg-day; 90<sup>th</sup> 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:

$$\begin{aligned} \text{Lifetime HA} &= DWEL \times RSC \\ &= 0.00037 \text{ mg/L} \times 0.2 \\ &= 0.000074 \text{ mg/L (rounded to 0.00007 mg/L)} \\ &= 0.07 \text{ } \mu\text{g/L} \end{aligned}$$

The lifetime HA for PFOA is based on effects (reduced ossification in male and female pups and accelerated puberty in male pups) 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 can 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 at various stages in development, a single exposure at a critical time in development can produce an adverse effect (USEPA 1991). Additionally, PFOA 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 PFOA 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  $\mu\text{g/L}$  also applies to short-term exposure scenarios (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 serum antibodies in humans. Among the animal studies, there are common effects on the liver, neonate development, and responses to immunological challenges. Both compounds also were associated with tumors in long-term animal studies. The effects that serve as the basis for the RfDs for both PFOA and PFOS are developmental endpoints (reduced ossification and accelerated puberty in males for PFOA and decreased pup birth weight for PFOS (USEPA 2016a, 2016b). Because the RfDs for both PFOA

and PFOS are based on similar developmental effects and are numerically identical, where 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).

## 7.0 QUANTIFICATION OF CANCER RISK

The evidence for the carcinogenicity of PFOA is considered suggestive because only one species has been evaluated, and the tumor responses (liver, testicular Leydig cell, and pancreatic acinar cell tumors) occurred primarily in males. Dose-response data are only available for the LCTs in one study. The dose-response data on LCTs from the (Butenhoff et al. (2012) studies were modeled to provide a perspective on the magnitude of the potential cancer risk as it compares with the level of protection provided by the RfD.

Under EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2005), when there is Suggestive Evidence for Carcinogenic Potential for a chemical, a dose-response assessment would generally not be attempted. The guidelines state that, when the evidence includes a well-conducted study, quantitative analyses could be useful for some purposes—for example, by providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. The data from the Butenhoff et al. (2012) study are adequate to support a quantitative cancer dose-response assessment for PFOA's testicular tumors. The epidemiology studies demonstrate an association of serum PFOA with kidney and testicular tumors among highly exposed members of the general population. Thus, EPA concluded that a quantitative analysis could be useful by providing a sense of the magnitude of potential carcinogenic risk.

The dose-response data for LCTs in rats was analyzed using the multistage cancer model for a dichotomous data set to predict the dose at which a 4% increase in tumor incidence would occur (see appendix A). A benchmark response of 4% was chosen as the low end of the observed response range within the study results. The resulting benchmark dose level (BMDL<sub>04</sub>) was 1.99 mg/kg/day, which yields a HED of 0.58 mg/kg/day and a slope factor of 0.07 (mg/kg/day)<sup>-1</sup>. The cancer slope factor was calculated to determine if a lifetime HA derived from the RfD would be protective for the cancer endpoint. As a comparative analysis, the concentration of PFOA in drinking water that would have a one-in-1-million chance of an increased cancer risk was calculated using the oral slope factor for testicular tumors, assuming a default adult body weight of 80 kg (mean weight for adults ages 21 and older) (Table 8.1 in USEPA 2011b) and a default drinking water intake rate of 2.5 L/day (consumers only estimate of combined direct and indirect community water ingestion at the 90<sup>th</sup> percentile for adults ages 21 and older) (Table 3-33 in USEPA 2011b). The resultant 0.5 µg/L value is greater than the lifetime HA (0.07 µg/L) based on noncancer effects (see section 6.22.2.), indicating that the HA derived based on the developmental endpoint is protective for the cancer endpoint.

$$10^{-6} \text{ cancer risk} = \frac{0.000001 \times 80 \text{ kg}}{(0.07 \text{ mg/kg/day} \times 2.5 \text{ L/d})} = 0.00046 \text{ mg/L rounded to } 0.5 \text{ µg/L}$$

## 8.0 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 PFOA identified 20 short- or long-term studies that provided dose-response information and were considered during the quantitative assessment of risk (USEPA 2016a). The range of external dose NOAELs among the 20 studies is 0–30 mg/kg/day for females and 7.5 mg/kg/day for males. The LOAELs range from zero to 30 mg/kg/day for females and zero to 14.2 mg/kg/day for males (USEPA 2016a). 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 chosen for use in the derivation of the RfD. The external dose range for the NOAELs in the modeled studies is 0–1.88 mg/kg/day and the LOAEL range is 1–5 mg/kg/day (USEPA 2016a). 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 the PFOA hazard and the selection of reduced ossification, and accelerated male puberty as the critical effects with lifetime implications at a LOAEL dose (1 mg/kg/day) from the low end of the narrow range of values evaluated.

The intrinsic uncertainties in the risk 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. The central tendency estimates are derived from small numbers of genetically, relatively similar animals representing one or more strains of 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 the use 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. Studies of systemic toxicity monitor an array of endpoints that are 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-term 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 LOAEL from developmental study in mice with application of an uncertainty factor of 300 to cover extrapolation from a LOAEL to a NOAEL, variability in the human population, and differences in the ways humans and rodents respond to the PFOA that reaches their tissues (Lau et al. 2006). The selected RfD is based on the developmental effects in neonates to provide protection to both the sensitive life stages and the general population. The RfD is supported by the outcomes from two other studies based on different endpoints, Butenhoff et al. (2004a) and DeWitt et al. (2008), with RfDs for systemic effects on liver, kidney and the immune system. These data increase the confidence in the RfD.

## 8.2 Use of Human Epidemiology Data

The human epidemiology studies provide evidence of an association between PFOA exposure and health effects in humans, and is another line of evidence supporting this assessment. The human data demonstrate an association between PFOA exposure and endpoints, including effects on serum lipids, antibody responses, fetal growth and development, and the liver. They provide support for identification of hazards of PFOA exposure. The associations observed for serum lipids, and reproductive parameters and immunotoxicity are the strongest. For many endpoints, however, the results are inconsistent. Although the human studies collectively support the conclusion that PFOA 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 and C8 study data indicate that serum levels in the general population are declining. Because epidemiology data are a reflection of the serum concentration at the time the sample was collected, there is no way to determine if levels were previously higher and had decreased. All of the C8 study serum samples were collected after the PFOA peak exposures had presumably passed. The half-life measurement for the general population of the Little Hocking area was derived from declining serum concentrations over time, demonstrating that serum levels among that population were not constant (Bartell et al. 2010).

Some of the human exposure that results in serum PFOA can come from telomer alcohol PFOA derivatives that break down metabolically to PFOA (Gebbink et al. 2015; Jogsten et al. 2012). The derivatives do not originate from PFOA in drinking water; they usually originate from diet and materials used in the home. Thus, there is added uncertainty in the observed epidemiological associations between serum PFOA and health effects.

Although the epidemiology studies provide valuable associations between exposure to PFOA 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 adjust for other potential toxicants as confounding factors, their presence constitutes a level of uncertainty that is usually absent in the animal studies.

The database for PFOA includes extensive human data from epidemiology studies of 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 also are 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 effect of PFOA on the immune system. However, there are uncertainties related to MOA and the level, duration, and/or

timing of exposure that are not yet clearly delineated. As a result, EPA used the animal data rather than the human data to quantify the dose response for immunotoxicity for PFOA.

Taken together, available human studies do not provide consistent evidence of a significant association between PFOA exposure and serological vaccine responses in general (Grandjean et al. 2012; Granum et al. 2013; Looker et al. 2014). Within each study, 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 PFOA 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 or 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 PFOA, some epidemiology 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 (Emmett et al. 2006; Grandjean et al. 2012; Looker et al. 2014). 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, cited in Chang et al. 2016). The only way to determine whether a given value outside a reference range is truly abnormal is to associate it with a clinical abnormality; this has not been done in most epidemiology studies of immune biomarkers.

Although Grandjean et al. (2012) found fairly consistent, albeit mostly statistically nonsignificant, intrastudy associations between childhood serum PFOA 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 PFOA levels prior to ascertaining vaccine response (Grandjean et al. 2012; Granum et al. 2013), and 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 PFOA concentrations, but several significant associations between higher PFOA 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 PFOA 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 immune-related, health condition in humans. The majority of the studies reviewed by the authors are included in EPA's HESDs for PFOA and PFOS (USEPA 2016a, 2016b). The authors identified numerous weaknesses in study designs, including lack of validation of self-reported medical conditions, basing conclusions on significant associations without considering statistical significance, inadequate consideration of confounding factors, bias, and the role of chance being responsible for outcomes. After application of 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."

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

#### **8.4 Effects on Mammary Gland Development**

Several studies in mice have examined postnatal mammary gland development in female mice. A qualitative/quantitative assessment found delayed mammary gland development of female CD-1 mouse pups following maternal doses  $\geq 0.01$  mg PFOA/kg in Macon et al. (2011) and Tucker et al. (2015). Macon et al. (2011) also found significant differences from controls in quantitative measures of longitudinal and lateral growth and numbers of terminal end buds at 1 mg/kg/day. However, Albrecht et al. (2013) found no significant differences in the average length of mammary gland ducts and the average number of terminal end buds per mammary gland per litter in female pups of PPAR $\alpha$  wild type, PPAR $\alpha$ -null, or hPPAR $\alpha$  sv/129 following a maternal dose of 3 mg/kg using an approach to scoring that lacked a qualitative component adjustment such as that used by Macon et al. (2011) in identifying the 0.01 mg/kg/day dose as a LOAEL.

The approach to scoring mammary gland development was not consistent across studies and little information was provided on the qualitative components of the scores. This makes comparisons across studies difficult. Statistical significance was attained at higher dose levels for the quantitative portion of the Macon et al. (2011) scoring protocol than for the qualitative component of the score. Tucker et al. (2015) found that CD-1 mice were considerably more sensitive to effects on mammary gland development (LOAEL 0.01 mg/kg/day) than C57BL/6 mice (NOAEL 0.1 mg/kg/day). Scoring was conducted using the Macon et al. (2011) approach.

White et al. (2011) used doses of 0 or 1 mg PFOA/kg/day for F0 dams throughout gestation with and without the addition of drinking water containing 5-ppb PFOA beginning on gestation day 7 and continuing the contaminated drinking water during the production of two more generations; no persistent significant differences were found in the body weights of the pups in the F1 and F2 generations for the pups receiving 1 mg/kg/day, indicating a poor correlation between mammary duct branching patterns and the ability to support pup growth during lactation. The 5-mg/kg/day dose did affect body weight. Albrecht et al. (2013) also found no

significant impacts on pup body weight in their one-generation assay at a dose of 3 mg/kg/day. Despite the diminished ductal network assessed in the qualitative mammary gland developmental score of the dams in White et al. (2011), milk production was sufficient to nourish growth in the exposed pups as reflected in the body weight measurements compared to controls at the 1-mg/kg/day dose. The MOA for PFOA-induced delayed mammary gland development is unknown and requires further investigation.

## 8.5 Alternative Exposure Scenarios

EPA is issuing a lifetime HA for PFOA 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 90<sup>th</sup> percentile for lactating women (see Table 3-81 in USEPA [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 USEPA[2011b]).

PFOA 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 PFOA 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 PFOA is also protective of adverse health effects in the adult general population (e.g., testicular and kidney cancer, liver damage, immune effects).

## 8.6 Relative Source Contribution Considerations

EPA used the Exposure Decision Tree methodology to derive the RSC for this HA (USEPA 2000). Findings from studies on populations in the United States, Canada, and Western Europe support the conclusion that diet is the major contributor to total PFOA 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 exposure to total PFASs, with a negligible contribution from drinking water, based on samples collected from two cities in Canada.
- Lorber and Egeghy (2011) used models to estimate exposures for adults and 2-year-olds. The data and analysis identify dietary ingestion as the major contributor to adult intake of PFOA, and dust and diet for young children in different media. The authors estimated

PFOA exposure from drinking water at 17 ng/day or approximately 24% of total intake for both adults and children. As background concentrations of PFOA in water increase, drinking water represents a greater source of total dietary intake.

- Gebbink et al. (2015) estimated the relative contributions of the major exposure media to total direct and indirect PFOA exposures under assumptions of low (5<sup>th</sup> percentile), intermediate (median values), and high (95<sup>th</sup> percentile) exposures. The authors used a scenario-based risk assessment modeling approach with data collected in 2007 to estimate the relative contributions of diet, dust, water, and air to total exposures. Only data for samples collected in North America, Europe, Korea, and Japan were included in the evaluation. The authors point out that both the blood serum concentrations and the temporal trends of PFASs in the United States, Europe, and Japan are similar. The data for direct and indirect contributors to serum PFOA are presented graphically in the published paper. They are consistent with the following exposure patterns for the combination of direct and indirect (precursor) exposures in adults:
  - Low-exposure scenario: diet (~50%) > air (~25%) > dust (~15%) > water (~10%);
  - Intermediate-exposure scenario: diet (~45%) > dust (~35%) > water (~10%) ≈ air (~10%); and
  - High-exposure scenario: dust (~65%) > diet (~20%) > water (10%) > air (~5%).

As the environmental level increases, so does the contribution of precursors to total exposure, increasing from about 15% to 30% to 60% as the exposure increases from low to high.

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 often in Europe 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 PFOA and its precursors, it is difficult to assess current relative exposures to the general population.

Additionally, there is a lack of data on other routes of exposure:

- 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 PFOA in water that becomes incorporated in solid foods during home preparation and cooking or that is present in commercial beverages.
- Transformation of PFOA precursors that decay or are metabolized to PFOA is a route that is rarely evaluated in dietary studies yet can contribute to total exposure. Air and dust can be vehicles for derivatives that metabolically degrade to PFOA.

Given these uncertainties, EPA used the Exposure Decision Tree methodology, described in section 6.1, to estimate an RSC of 20% for drinking water for the general population.

## 8.7 Sensitive Populations: Gender Differences

Some animal species have gender differences that affect toxicity of PFOA. Sexually mature female rats excreted almost all of a 10-mg/kg dose of PFOA within 48 hours compared to only 19% excreted by male rats. Male hamsters excrete PFOA faster than female hamsters, and female rabbits excrete PFOA slightly faster than male rabbits. Male and female mice excrete PFOA at approximately the same rate (Hundley et al. 2006). Studies of the transporters involved in the toxicokinetics of PFOA demonstrate that they are differentially affected by the presence of male and female sex hormones (Cheng et al. 2006; Kudo et al. 2002). As studied in rats (Kudo et al. 2002), the male sex hormones increased half-life (decreased excretion) of PFOA while the female hormones were associated with shorter half-lives (increased excretion). The gender differences in toxicokinetics in mice are not as pronounced as those in rats. Work by Cheng et al. (2006) and Cheng and Klaassen (2009) demonstrated that the hormones affected transporters in the liver and kidney, protecting the females and increasing the sensitivity for males. Results of the NHANES data on PFOA suggest that in humans, serum levels are lower in females (Calafat et al. 2007a, 2007b; Jain 2014); both menstruation and lactation are excretory routes in females and shorten the half-life of PFOA during associated life phases.

In studies where both male and female rats were used, the males were more sensitive to toxicity than the females (Butenhoff et al. 2004a). Mice displayed similar sensitivities following PFOA exposure (Kennedy 1987). In the monkey studies, the number of animals per gender per dose group was too small to reveal a difference related to gender.

Unfortunately, much work remains to be done to determine whether the gender difference seen in rats is relevant to humans. Similarities are possible because the long half-life in humans suggests that they might be more like the male rat than the female rat. The broad range of half-lives in human epidemiology studies suggests a variability in human transport capabilities resulting from the isomeric composition of the PFOA and genetic variations in transporter structures and consequently in function (Y. Zhang et al. 2013, 2014). Genetic variation in human transporters are identified in a review by Zaïr et al. (2008).

## 8.8 Sensitive Populations: Developmental Effects

PFOA-exposure during development in rats and mice resulted in increased resorptions (mouse), increased fetal skeletal variation (rats, mouse), decreased neonatal survival (rat, mouse), decreased postnatal body weight (mouse), delayed eye opening and body hair growth (rat, mouse), delayed vaginal opening (mouse), accelerated preputial separation (mouse), and delayed mammary gland development (mouse) (Butenhoff et al. 2004a; Lau et al. 2006; Macon et al. 2011; Tucker et al. 2015; White et al. 2007, 2009, 2011; Wolf et al. 2007). Some effects were seen as low-dose exposures such as the ossification delays and accelerated puberty in male mice exposed via their dams to a dose of 1 mg/kg/day during gestation (Lau et al. 2006), the mammary gland effects (0.01 mg/kg/day) (Macon et al. 2011), and the postnatal effects on body weight in pups exposed to PFOA during gestation and lactation to doses of 3 or 5 mg/kg/day (White et al. 2009; Wolf et al. 2007). Only the low birth weight receives support from the epidemiology studies. The other effects generally lack correlates among the effects evaluated by the studies.

In the Wolf et al. (2007) study, pup postnatal body weights were lower than controls for all exposure durations during the last 10 days of gestation evaluated. The authors found that the magnitude of the body weight effect was directly related to the days of exposure (i.e., 3, 5, 7, or 10); the longer the exposure, the greater the body weight deficit in the male and female pups during the PND 2–22 time period. In male but not female pups, the exposure duration deficits in body weight persisted up to PND 92. The difference in the male rat response over the PND 29–92 period likely reflects their longer half-life than females.

Both gestational and lactational exposures contribute to the impact of PFOA on body weight during early life as illustrated by cross-fostering control unexposed female pups with those dosed with PFOA. Three cross-fostering combinations were evaluated by White et al (2009): control pups nursed by exposed dams, exposed pups nursed by control dams, and exposed pups nursed by exposed dams. Two doses were evaluated: 3 and 5 mg/kg/day. The PND 1–10 body weight data were only provided for the 5-mg/kg/day dose. PFOA exposures significantly reduced pup body weights and increased liver weights. The body weight deficits compared to control were greatest for the gestation and lactation exposure combination and lowest for the lactation-only group.

Diet can influence the risk associated with PFOA exposures. Animal studies demonstrate an increased risk for liver steatosis in animals on a high-fat diet and possibly for insulin resistance (Hines et al. 2009; Quist et al. 2015; Tan et al. 2013). The epidemiology data are not supportive of a correlation with insulin resistance, but the observations of elevated serum triglycerides, especially among a highly exposed population, could be viewed as a risk factor for steatosis. Most of the epidemiology studies did not evaluate dietary factors as part of the study design for either birth weight or serum lipids (e.g., cholesterol, triglycerides, LDL).

## 9.0 ANALYTICAL METHODS

EPA developed a liquid chromatography/tandem mass spectrometry (LC/MS/MS) analytical method—Method 537—to monitor drinking water for 14 select perfluorinated alkyl acids that include PFOA (USEPA 2009b). Accuracy and precision data were generated for PFOA, PFOS, and the other 12 PFASs in reagent water, finished ground water, and finished surface water. This method identifies a single laboratory lowest concentration minimum reporting level or quantitation limit for PFOA at 5.1 ng/L (0.0051 µg/L) and for PFOS at 6.5 ng/L (0.0065 µg/L). The method-published detection limit for PFOA is 1.7 ng/L (0.0017 µg/L).

In this method, PFAS standards, extracts, and samples should not come into contact with any glass containers or pipettes because PFASs 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 PTFE products, liquid chromatograph solvent lines, methanol, aluminum foil, and solid phase extraction (SPE) sample transfer lines. These materials need to be routinely demonstrated to be free of interferences per the guidelines for laboratory reagent blanks described in the method. In summary, the method procedure involves passing a preserved 250-mL water sample (fortified with an extraction surrogate) 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. *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 2009b) is available for download at <http://www.epa.gov/nerlcwww/ordmeth.htm>.

## 10.0 TREATMENT TECHNOLOGIES

As mentioned above, PFOA is an organic compound in which the carbon-hydrogen bonds are replaced by carbon-fluorine bonds. This influences the chemical characteristics of both molecules 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, making it exceedingly resistant to biodegradation, hydrolysis, oxidation, and photolysis. Also, because PFOA is a dissolved contaminant that is resistant to oxidation to an insoluble form, treatment processes that are designed for particulate control such as conventional treatment will not be effective. This leaves adsorption, ion exchange resins, and high-pressure membranes as the technologies that can be effective. The following subsections discuss the effectiveness of commonly used drinking water technologies in rough order of applicability for PFOA and PFOS removal. Additional information can be found on EPA's Drinking Water Treatability Database (USEPA 2015b) at <https://iaspub.epa.gov/tdb/pages/general/home.do>.

To varying degrees of applicability, the technologies discussed 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 treat the water as it enters the building or house, and POU systems treat the water where used, such as a kitchen or bathroom sink. Although the cost of treatment varies with scale, the following general discussion on the relative effectiveness of each technology applies regardless of scale. One reference below specifically addresses POU systems (MDH 2008).

### *Activated Carbon Adsorption*

Activated carbon is applied in either powdered or granular form. Either can be effective; however, because PFOA and PFOS have 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. Although some studies have shown limited PFOA and PFOS removal in plants using PAC (Quiñones and Snyder 2009), in general, PAC can be an effective treatment strategy for the removal of PFOA and PFOS given the correct choice of carbon type, high enough carbon doses, and adequate contact time (Dudley et al. 2015; Hansen et al. 2010).

### *Granular Activated Carbon*

Granular activated carbon 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 PFOA and PFOS have moderate adsorbability, a post-filter adsorber with a deeper bed is considered a safer approach. In general, granular activated carbon 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 2008; Shivakoti et al. 2010; Takagi et al. 2008).

### *Membrane Technologies*

There are many types of membrane technologies. They can be broadly classified as either low-pressure or high-pressure systems. This distinction also corresponds to the general effectiveness of removing PFOA and PFOS with low-pressure membranes being 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 through which water and dissolved contaminants can easily flow, leaving behind larger particulate matter that includes turbidity and microbiological agents. Low-pressure membranes have been found to be ineffective for PFOA and 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. However, as with conventional treatment, low-pressure membranes can be effective if they are used in conjunction with PAC. The PAC will adsorb the PFOA and PFOS, and the low-pressure membrane will remove the spent PAC. Care should be taken in the design of the system, including the choice of the PAC as mentioned above (Dudley et al. 2015).

#### *High-pressure Membranes*

High-pressure systems have a much tighter pore structure, relying on water diffusing 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 PFOA and PFOS

(Appleman et al. 2013, 2014; MDH 2008; Quiñones and Snyder 2009; Tang et al. 2006, 2007; Thompson et al. 2011).

### *Ion Exchange Resin Treatment*

There are two broad categories of ion exchange resins: cationic and anionic. Cationic exchange resins are effective for removing positively charged contaminants. Anion exchange resins are effective for negatively charged contaminants. Because PFOA and PFOS are negatively charged in drinking waters, cation-exchange resins will not be effective, and therefore, have not been studied. There have been studies that 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 PFOA and PFOS removal (Appleman et al. 2014; Carter and Farrell 2010; Chularueangaksorn et al. 2013; Dudley et al. 2015), although the design of the system including regeneration effectiveness is important. Special consideration should be given to dealing with the regenerate brine waste, and if frequent regenerations are needed, to the amount of operator effort and expertise required.

### *Oxidation / Disinfection*

Oxidation/disinfection processes can transform certain contaminants into different molecules, which ideally have less toxicity. It also 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. Due to the strength of the carbon-fluorine bond, all drinking water oxidants or disinfectants have been shown to be ineffective in reacting PFOA or 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; 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 also is true for advanced oxidation processes (AOPs) that use the nonselective hydroxyl radical as an oxidative agent. There are many ways of producing hydroxyl radicals, usually 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 PFOA and 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, it is expected that both aerobic and anaerobic biological treatment processes (e.g., biofiltration, bioreactors) are expected to be ineffective for PFOA and PFOS removal. A number of researchers have found this to be the case (Kwon et al. 2014; Saez et al. 2008; Thompson et al. 2011). Some results have shown that specific microbes could have the ability to break the carbon-to-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: 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 and microbiological agents). Dissolved contaminants, however, will not be removed by conventional treatment. The exception is when the contaminants are first 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 PFOA and PFOS to oxidation to an insoluble form and their moderately high solubility, conventional treatment is not expected to be effective in their removal, even in enhanced coagulation conditions. Numerous studies have confirmed this statement (Appleman et al. 2014; Loos et al. 2007; Quiñones 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 PAC (see above). The PAC will adsorb the PFOA and 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 the system, including the choice of the PAC (Dudley et al. 2015).

## 11.0 REFERENCES

- AACC (American Association for Clinical Chemistry). 2015. *Reference Ranges and What They Mean. Lab Tests Online*. Accessed May 2016.  
<https://labtestsonline.org/understanding/features/ref-ranges/start/6>.
- Abbott, B.D., C.J. Wolf, J.E. Schmid, K.P. Das, R.D. Zehr, L.Helfant, S. Nakayama, A.B. Lindstrom, M.J. Styrnar, and C. Lau. 2007. Perfluorooctanoic acid-induced developmental toxicity in the mouse is dependent on expression of peroxisome proliferator-activated receptor- $\alpha$ . *Toxicological Science* 98:571–581.
- Ahrens, L., M. Shoeb, 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.
- Albrecht, P.P., N.E. Torsell, P. Krishnan, D.J. Ehresman, S.R. Frame, S.-C. Chang, J.L. Butenhoff, G.L. Kennedy, F.J. Gonzalez, and J.M. Peters. 2013. A species difference in the peroxisome proliferator-activated receptor  $\alpha$ -dependent response to the developmental effects of perfluorooctanoic acid. *Toxicological Science* 131: 568–582.
- Andersen, M.E., H.J. Clewell, III, Y-M. Tan, J.L. Butenhoff, and G.W. Olsen. 2006. Pharmacokinetic modeling of saturable, renal resorptions of perfluoroalkylacids in monkeys-probing the determinants of long plasma half-lives. *Toxicology* 227:156–164.
- Anzai, N., Y. Kanai, and H. Endou. 2006. Organic anion transporter family: Current knowledge. *Journal of Pharmacological Science* 100:411–426.
- Apelberg, B.J., L.R. Goldman, A.M. Calafat, J.B. Herbstman, Z. Kuklenyik, J. Heidler, L.L. Needham, R.U. Halden, and F.R. Witter. 2007. Determinants of fetal exposure to polyfluoroalkyl compounds in Baltimore, Maryland. *Environmental Science & Technology* 41:3891–3897.
- Appleman, T.D., E.R.V. 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. Quiñones, B.J. Vanderford, C. Kolstad, J.C. Zeigler-Holady, and E.R.V. Dickenson. 2014. Treatment of Poly- and Perfluoroalkyl Substances in U.S. Full-Scale Water Treatment Systems. *Water Research* 51: 246–55.
- 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.
- 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](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>.
- Barry, V., A. Winqvist, and K. Steenland. 2013. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environmental Health Perspectives* 121:1313–1318.
- Bartell, S., A. Calafat, C. Lyu, K. Kato, P.B. Ryan, and K. Steenland. 2010. Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. *Environmental Health Perspectives* 118:222–228.
- Beesoon, S., and J.W. Martin. 2015. Isomer-specific binding affinity of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) to serum proteins. *Environmental Science & Technology* 49(9):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 and Contaminants* 22(10):1023–1031.
- Benbrahim-Tallaa, L., B. Laubry-Secretan, D. Loomis, K.Z. Guyton, Y. Grosse, F. El Ghissassi, V. Bouvard, N. Guha, H. Mattock, and K. Straif, on behalf of the International Agency for Research on Cancer Monograph Working Group. 2014. Carcinogenicity of perfluorooctanoic acid, tetrafluoroethylene, dichloromethane, 1,2-dichloropropane, and 1,3-propane sultone. *Lancet Oncology* 15(9):924–925.
- 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* 43:1513–1522.
- 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. Bronson, and S. A. Tittlemier. 2014. Cooking fish is not effective in reducing exposure to perfluoroalkyl and polyfluoroalkyl substances. *Environmental International* 66:107–114.
- Biegel, L.B., M.E. Hurtt, S. R. Frame, J.C. O'Connor, and J.C. Cook. 2001. Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicological Science* 60:44–55.
- 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, 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.
- 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.J. van Leeuwen. 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. *Integrated Environmental Management and Assessment* 7(4):513–541.
- Butenhoff, J., G. Costa, C. Elcombe, D. Farrar, K. Hansen, H. Iwai, R. Jung, G. Kennedy Jr., P. Lieder, G. Olsen, and P. Thomford. 2002. Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicological Science* 69:244–257.
- Butenhoff, J.L., G.L. Kennedy, Jr., S.R. Frame, J.C. O'Connor, and R.G. York. 2004a. The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology* 196:95–116.
- Butenhoff, J.L., G.L. Kennedy, P.M. Hinderliter, P.H. Lieder, R. Jung, K.J. Hansen, G.S. Gorman, P.E. Noker, and P.J. Thomford. 2004b. Pharmacokinetics of perfluorooctanoate in Cynomolgus monkeys. *Toxicological Science* 82:394–406.
- Butenhoff, J.L., G.L. Kennedy, Jr., S.C. Chang, and G.W. Olsen. 2012. Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. *Toxicology* 298:1–13.
- Calafat, A.M., L.Y. Wong, Z. Kuklennyik, J.A. Reidy, and L.L. Needham. 2007a. 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.
- Calafat, A.M., Z. Kuklennyik, J.A. Reidy, S.P. Caudill, J.S. Tully, and L.L. Needham. 2007b. Serum concentrations of 11 polyfluoroalkyl compounds in the US population: data from the National Health and Nutrition Examination Survey (NHANES) 1999–2000. *Environmental Science & Technology* 41(7):2237–2242.
- Cariou, R., B. Veyrand, A. Yamada, A. 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.

- CDC (Centers for Disease Control and Prevention). 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/>.
- CDC (Centers for Disease Control and Prevention). 2015. *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, February*. Department of Health and Human Services, Centers for Disease Control and Prevention. Accessed May 2016. <http://www.cdc.gov/exposurereport/>.
- 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):279–331.
- Cheng, X., J. Maher, H. Lu, and C.D. Klaassen. 2006. Endocrine regulation of gender-divergent mouse organic anion-transporting polypeptide (Oatp) expression. *Molecular Pharmacology* 70:1291–1297.
- Cheng, X., and C.D. Klaassen. 2008. Critical role of PPAR- $\alpha$  in perfluorooctanoic acid– and perfluorodecanoic acid–induced downregulation of Oatp uptake transporters in mouse livers. *Toxicological Sciences* 106(1):37–45.
- Cheng, X., and C.D. Klaassen. 2009. Tissue distribution, ontogeny, and hormonal regulation of xenobiotic transporters in mouse kidneys. *Drug Metabolism and Disposition* 37:2178–2185.
- Christensen, K.Y., M. Maisonet, C. Rubin, A. Holmes, A.M. Calafat, K. Kato, W.D. Flanders, J. Heron, M.A. McGeehin, and M. Marcus. 2011. Exposure to polyfluoroalkyl chemicals during pregnancy is not associated with offspring age at menarche in a contemporary British cohort. *Environment International* 37(1):129–135.
- Chularueangaksorn, P., S. Tanaka, S. Fujii, and C. Kunacheva. 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.
- Clegg, L.X., E.J. Feuer, D.N. Midthune, M.P. Fay, and B.F. Hankey. 2002. Impact of reporting delay and reporting error on cancer incidence rates and trends. *Journal of the National Cancer Institute* 94(20):1537–1545.
- Cook, J.C., S.M. Murray, S.R. Frame, and M.E. Hurtt. 1992. Induction of Leydig cell adenomas by ammonium perfluorooctanoate: A possible endocrine-related mechanism. *Toxicology and Applied Pharmacology* 113: 209–217.
- Costa G., S. Sartori, and D. Consonni. 2009. Thirty years of medical surveillance in perfluorooctanoic acid production workers. *Journal of Occupational and Environmental Medicine* 51:364–372.

- 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.
- D'eon, J.C., and S. A. Mabury. 2011. Is indirect exposure a significant contributor to the burden of perfluorinated acids observed in humans? *Environmental Science & Technology* 45(19):7974–7984.
- D'Hollander, W., L. Roosens, A. Covaci, C. Cornelis, H. Reynders, K. Van Campenhout, P. de Voogt, and L. Vervoets. 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.
- de Cock, M., M.R. de Boer, M. Lamoree, J. Legler, and M. van de Bor. 2014. Prenatal exposure to endocrine disrupting chemicals in relation to thyroid hormone levels in infants – a Dutch prospective cohort study. *Environmental Health* 13(1):1–10.
- Del Vento, S., C. Halsall, R. Gioia, K. Jones, and J. Dachs. 2012. Volatile per- and polyfluoroalkyl compounds in the remote atmosphere of the western Antarctic Peninsula: an indirect source of perfluoroalkyl acids to Antarctic waters? *Atmospheric Pollution Research* 3(4):450–455.
- 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.
- DeWitt, J.C., C.B. Copeland, M.J. Strynar, and R.W. Luebke. 2008. Perfluorooctanoic acid-induced immunomodulation in adult C57BL/6J or C57BL/6N female mice. *Environmental Health Perspectives* 116:644–650.
- DeWitt, J.C., W.C. Williams, J. Creech, and R.W. Luebke. 2015. Suppression of antigen-specific antibody responses in mice exposed to perfluorooctanoic acid: Role of PPAR $\alpha$  and T- and B-cell targeting. *Journal of Immunotoxicology* 13(1):38–45.
- 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>.

- 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.
- EFSA (European Food Safety Authority). 2008. Opinion of the scientific panel on contaminants in the food chain on perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) and their salts. *EFSA Journal* 653:1–131.
- 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.
- Elcombe, C.R., B.M. Elcombe, J.R. Foster, D.G. Farrar, R. Jung, S.C. Chang, G.L. Kennedy, and J.L. Butenhoff. 2010. Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats following dietary exposure to ammonium perfluorooctanoate occurs through increased activation of the xenosensor nuclear receptors PPAR $\alpha$  and CAR/PXR. *Archives of Toxicology* 84(10):787–798.
- Emmett, E.A., H. Zhang, F.S. Shofer, D. Freeman, N.V. Rodway, C. Desai, and L.M. Shaw. 2006. Community Exposure to Perfluorooctanoate: Relationships between Serum Concentrations and Certain Health Parameters. *Journal of Occupational Medicine* 48:771–779.
- Environment Canada and Health Canada. 2012. *Screening Assessment Report, Perfluorooctanoic Acid, its Salts, and its Precursors*. Accessed May 2016. [https://www.ec.gc.ca/ese-ees/370AB133-3972-454F-A03A-F18890B58277/PFOA\\_EN.pdf](https://www.ec.gc.ca/ese-ees/370AB133-3972-454F-A03A-F18890B58277/PFOA_EN.pdf).
- Eriksen, K.T., M. Sørensen, J.K. McLaughlin, L. Lipworth, A. Tjønneland, K. Overvad, and O. Raaschou-Nielsen. 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.
- EWG (Environmental Working Group). 2015. *National Drinking Water Database*. Accessed May 2016. <http://www.ewg.org/tap-water/chemical-contI6:J7aminants/Perfluorooctanoic-Acid-PFOA/E207/>.
- Fasano, W.J., G.L. Kennedy, B. Szostek, D.G. Farrar, R.J. Ward, L. Haroun, and P.M. Hinderliter. 2005. Penetration of ammonium perfluorooctanoate through rat and human skin in vitro. *Drug and Chemical Toxicology* 28(1):79–90.
- 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, L. Lipworth, and J. Olsen. 2009. Maternal levels of perfluorinated chemicals and subfecundity. *Human Reproduction* 24:1200–1205.
- Fenton, S.E., J.L. Reiner, S.F. Nakayama, A.D. Delinsky, J.P. Stanko, E.P. Hines, S.S. White, A.B. Lindstrom, M.J. Strynar, and S.-S.E. Petropoulou. 2009. Analysis of PFOA in dosed CD-1 mice. Part 2: Disposition of PFOA in tissues and fluids from pregnant and lactating mice and their pups. *Reproductive Toxicology* 27(3):365–372.
- Filipovic, M., A. Woldegiorgis, K. Norstrom, M. Bibi, M. Lindberg, and A.H. Osteras. 2015. Historical usage of aqueous film forming foam: A case study of the widespread distribution of perfluoroalkyl acids from a military airport to groundwater, lakes, soils and fish. *Chemosphere* 129:39–45.
- 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.
- Fitz-Simon, N., T. Fletcher, M.I. Luster, K. Steenland, A.M. Calafat, K. Kato, and B. Armstrong. 2013. Reductions in serum lipids with a 4-year decline in serum perfluorooctanoic acid and perfluorooctanesulfonic acid. *Epidemiology* 24(4):569–576.
- 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., O. Midasch, D. Twardella, J. Angerer, S. Boehmer, and B. Liebl. 2007. Occurrence of perfluorinated substances in an adult German population in southern Bavaria. *International Archives of Occupational and Environmental Health* 80(4):313–319.
- 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.
- Gallo, V., G. Leonardi, B. Genser, M.J. Lopez-Espinosa, S.J. Frisbee, L. Karlsson, A.M. Ducatman, and T. Fletcher. 2012. Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. *Environmental Health Perspectives* 120:655–660.
- 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.

- Geiger, S.D., J. Xiao, A. Ducatman, S. Frisbee, K. Innes, and A. Shankar. 2014. The association between PFOA, PFOS and serum lipid levels in adolescents. *Chemosphere* 98:78–83.
- Genuis, S.J., D. Birkholz, M. Ralitsch, and N. Thibault. 2010. Human detoxification of perfluorinated compounds. *Public Health* 124:367–375.
- 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>.
- Gobas, F.A.P.C., 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, MN, 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.
- 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.
- 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. Borreson, M. Schlabach, and G. Cornelissen. 2010. Sorption of perfluorinated compounds from contaminated water to activated carbon. *Journal of Soils and Sediments* 10:179–185.

- Hardell, E., A. Kärman, B. van Bavel, J. Bao, 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.
- Hardisty, J.F., G.A. Willson, W.R. Brown, E.E. McConnell, S.R. Frame, D.W. Gaylor, G.L. Kennedy, and J.L. Butenhoff. 2010. Pathology Working Group review and evaluation of proliferative lesions of mammary gland tissues in female rats fed ammonium perfluorooctanoate (APFO) in the diet for 2 years. *Drug and Chemical Toxicology* 33(2):131–137.
- Haug, L.S., S. Salihovic, I.E. Jogsten, C. Thomsen, B. van Bavel, G. Lindstrom, and G. Becher. 2010. Levels in food and beverages and daily intake of perfluorinated compounds in Norway. *Chemosphere* 80:1137–1143.
- 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.
- Hekster, F.M., R.W. Laane, and P. de Voogt. 2003. Environmental and toxicity effects of perfluoroalkylated substances. *Reviews of Environmental Contamination and Toxicology* 179:99–121.
- Higgins C., and R. Luthy. 2006. Sorption of Perfluorinated Surfactants on Sediments. *Environmental Science & Technology* 40(23):7251–7256.
- Hill, A.B. 1965. The environment and disease: Association or causation? In *Proceedings of the Royal Society of Medicine* 58(5):295–300.
- Hinderliter, P.M. 2004. Ammonium perfluorooctanoate: Age effect on the PFOA plasma concentration in post-weaning rats following oral gavage. E.I. du Pont de Nemours and Company. Laboratory Project ID: Dupont-15302. December 2, 2004.
- Hinderliter, P.M., E. Mylchreest, S.A. Gannon, J.L. Butenhoff, and G.L. Kennedy, Jr. 2005. Perfluorooctanoate: Placental and lactational transport pharmacokinetics in rats. *Toxicology* 211:139–148.
- Hinderliter, P.M., X. Han, G.L. Kennedy, Jr., and J.L. Butenhoff. 2006. Age effect on perfluorooctanoate (PFOA) plasma concentration in post-weaning rats following oral gavage with ammonium perfluorooctanoate (APFO). *Toxicology* 225:195–203.
- Hines, E.P., S.S. White, J.P. Stanko, E.A. Gibbs-Flournoy, C. Lau, and S.E. Fenton. 2009. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. *Molecular and Cellular Endocrinology* 304:97–105.
- Hlouskova, V., P. Hradkova, J. Poustka, B. Gianfranco, S.P. De Filipps, W. D'Hollander, L. Bervoets, D. Herzke, S. Huber, P. de Voogt, and J. Pulkrabova. 2013. Occurrence of perfluoroalkyl substances (PFAS) in various food items of animal origin collected in four European countries. *Food Additives and Contaminants: Part A* 30(11):1918–1932.

- Hori, H., E. Hayakawa, H. Einaga, S. Kutsuna, K. Koike, T. Ibusuki, H. Kiatagawa, and R. Arakawa. 2004. Decomposition of environmentally persistent perfluorooctanoic acid in water by photochemical approaches. *Environmental Science & Technology* 38:22:6118.
- Houde, M., T.A. Bujas, J. Small, R.S. Wells, P.A. Fair, G.D. Bossart, K.R. Solomon, and D.C. Muir. 2006. Biomagnification of perfluoroalkyl compounds in the bottlenose dolphin (*Tursiops truncatus*) food web. *Environmental Science & Technology* 40(13):4138–4144.
- HSDB (Hazardous Substances Data Bank). 2012. *Perfluorooctanoic acid*. Accessed May 2016. <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+7137>.
- Hundley, S.G., A.M. Sarrif, and G.L. Kennedy, Jr. 2006. Absorption, distribution, and excretion of ammonium perfluorooctanoate (APFO) after oral administration to various species. *Drug and Chemical Toxicology* 29(2):137–145.
- 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.
- Jain, R.B. 2014. Contribution of diet and other factors to the levels of selected polyfluorinated compounds: Data from NHANES 2003-2008. *International Journal of Hygiene and Environmental Health* 217:52–61.
- Joensen, U.N., R. Bossi, H. Leffers, A.A. Jensen, N.E. Skakkebæk, and N. Jørgensen. 2009. Do perfluoroalkyl compounds impair human semen quality? *Environmental Health Perspectives* 117: 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, N., P. Eriksson, and H. Viberg. 2009. Neonatal exposure to PFOS and PFOA in mice results in changes in proteins which are important for neuronal growth and synaptogenesis in the developing brain. *Toxicological Science* 108: 412–418.
- 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.
- Johnson, P.I., P. Sutton, D.S. Atchley, E. Koustas, J. Lam, S. Sen, K.A. Robinson, D.A. Axelrad, and T.J. Woodruff. 2014. The Navigation Guide – evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environmental Health Perspectives* 122:1028–1039.

- Kaiser, M.A., B.S. Larsen, C-P.C. Kao, and R.C. Buck. 2005. Vapor pressures of perfluoro-octanoic, -nonanoic, -decanoic, undecanoic, and dodecanoic acids. *Journal of Chemical and Engineering Data* 50(6):1841–1843.
- Kauck, E.A., and A.R. Diesslin. 1951. Some Properties of Perfluorocarboxylic Acids. *Industrial and Engineering Chemical Research* 43(10):2332–2334.
- Kelly, B.C., M.G. Ikonomou, J.D. Blair, B. Surrige, D. Hoover, R. Grace, and F.A.P.C. Gobas. 2009. Perfluoroalkyl contaminants in an Arctic Marine Food Web: Trophic Magnification and Wildlife Exposure. *Environmental Science & Technology* 43:4037–4043.
- Kemper, R.A. 2003. Perfluorooctanoic acid: Toxicokinetics in the rat. Laboratory Project ID: Dupont-7473. Haskell Laboratory for Health and Environmental Sciences, E.I. du Pont de Nemours and Company. April 2, 2003. U.S. Environmental Protection Agency Administrative Record 226-1499.
- Kennedy, G.L. 1987. Increase in mouse liver weight following feeding of ammonium perfluorooctanoate and related fluorochemicals. *Toxicology Letters* 39(2):295–300.
- 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.
- Kirk-Othmer. 1994. Encyclopedia of Chemical Technology. 4th ed. Volumes 1: New York, NY. John Wiley and Sons, 1991-Present. V11:551.
- Klaassen, C.D., and L.M. Aleksunes. 2010. Xenobiotic, bile acid, and cholesterol transporters: Function and regulation. *Pharmacology Review* 62:1–96.
- Klaunig, J.E., M.A. Babich, L.P. Baetcke, J.C. Cook, J.C. Corton, R.M. David, J.G. DeLuca, D.Y. Lai, R.H. McKee, J.M. Peters, R.A. Roberts, and P.A. Fenner-Crisp. 2003. PPAR $\alpha$  agonist-induced rodent tumors: modes of action and human relevance. *Critical Reviews in Toxicology* 33: 655–780.
- Klaunig, J.E., B.A. Hocevar, and L.M. Kamendulis. 2012. Mode of action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and human relevance. *Reproductive Toxicology* 33:410–418.
- Knobeloch, L., P. Imm, and H. Anderson. 2012. Perfluoroalkyl chemicals in vacuum cleaner dust from 39 Wisconsin homes. *Chemosphere* 88:779–783.
- 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.

- Koustaş, E., J. Lam, P. Sutton, P.I. Johnson, D.S. Atchley, S. Sen, K.A. Robinson, D.A. Axelrad, and T.J. Woodruff. 2014. The Navigation Guide – evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. *Environmental Health Perspectives* 122:1015–1027.
- 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.
- Kristensen, S.L., C.H. Ramlau-Hansen, E. Ernst, S.F. Olsen, J.P. Bonde, A. Vested, T.I. Halldorsson, G. Becher, L.S. Haug, and G. Toft. 2013. Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction. *Human Reproduction* 0:1–12.
- Kudo, N., M. Katakura, Y. Sato, and Y. Kawashima. 2002. Sex hormone-regulated renal transport of perfluorooctanoic acid. *Chemico-Biological Interactions* 139:301–316.
- 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.
- Lange F.T., C. Schmidt, and H.J. Brauch. 2006. Perfluoroalkyl Carboxylates and Sulfonates, Rhine Water Works, The Netherlands, Association of River Waterworks – RIWA. Accessed May 2016. [http://www.riwa-rijn.org/wp-content/uploads/2015/05/137\\_ptfe\\_report.pdf](http://www.riwa-rijn.org/wp-content/uploads/2015/05/137_ptfe_report.pdf).
- 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 Science* 74:382–392.
- Lau, C., J.R. Thibodeaux, R.G. Hanson, M.G. Narotsky, J.M. Rogers, A.B. Lindstrom, and M.J. Strynar. 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. *Toxicological Science* 90:510–518.
- Lewis, R.J., Sr., ed. 2004. *Sax's Dangerous Properties of Industrial Materials*. 11th ed. Wiley-Interscience, Wiley & Sons, Inc., Hoboken, N.J V3:2860.
- Li, X., S. Chen, X. Quan, and Y. Zhang. 2011. Enhanced adsorption of PFOA and PFOS on multiwalled carbon nanotubes under electrochemical assistance. *Environmental Science & Technology* 45(19):8498–8505.
- Liao, C., T. Wang, L. Cui, Q. Zhou, S. Duan, and G. Jiang. 2009a. 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.

- Liao, C., T. Wang, L. Cui, Q. Zhou, S. Duan, and G. Jiang. 2009b. Supporting Information: Changes in synaptic transmission, calcium current, and neurite growth by perfluorinated compounds are dependent on the chain length and functional group. *Environmental Science & Technology*.
- Lide, D.R. 2007. *CRC Handbook of Chemistry and Physics*. 88th ed. CRC Press, Taylor & Francis, Boca Raton, FL. 3–412.
- Lin, C-Y., Y-C Lin, P-C Chen, and L-Y Lin. 2009. Association among serum perfluoroalkyl chemicals, glucose homeostasis, and metabolic syndrome in adolescents and adults. *Diabetes Care* 32:702–707.
- 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. Nakayama, 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.
- 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, 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, 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>.
- Loi, E.I., L.W. Yeung, S. Taniyasu, P.K.S. Lam, K. Kannan, and N. Yamashita. 2011. Trophic magnification of poly- and perfluorinated compounds in a subtropical food web. *Environmental Science & Technology* 45(13):5506–5513.
- Looker, C., M.I. Luster, A.M. Calafat, V.J. Johnson, G.R. Burlison, F.G. Burlison, and T. Fletcher. 2014. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *Toxicological Science* 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. Armstrong, 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*.
- Lopez-Espinosa, M.-J., D. Mondal, B. Armstrong, M.S. Bloom, and T. Fletcher. 2012. Thyroid function and perfluoroalkyl acids in children living near a chemical plant. *Environmental Health Perspectives* 120:1036–1041.
- Lorber, M., and P.P. Egeghy. 2011. Simple intake and pharmacokinetic modeling to characterize exposure of Americans to perfluorooctanoic acid, PFOA. *Environmental Science & Technology* 45:8006–8014.
- Loveless, S.E., D. Hoban, G. Sykes, S.R. Frame, and N.E. Everds. 2008. Evaluation of the immune system in rats and mice administered linear ammonium perfluorooctanoate. *Toxicological Science* 105:86–96.
- Lu, Y., B. Luo, J. Li, and J. Dai. 2015. Perfluorooctanoic acid disrupts the blood-testes barrier and activates TNF $\alpha$ /p38 MAPK signaling pathway in vivo and in vitro. *Archives of Toxicology* 90(4):971–983.
- 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.
- MacNeil, J., N.K. Steenland, A. Shankar, and A. Ducatman. 2009. A cross-sectional analysis of type II diabetes in a community with exposure to perfluorooctanoic acid (PFOA). *Environmental Research* 109: 997–1003.
- Macon, M.B., L.R. Villanueva, K. Tatum-gibbs, R.D. Zehr, M.J. Strynar, J.P. Stanko, S.S. White, L. Helfant, and S.E. Fenton. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low dose developmental effects and internal dosimetry. *Toxicological Science* 122(1):135–145.
- MacManus-Spencer, L.A., M.L. Tse, P.C. Hebert, H.N. Bischel, and R.G. Luthy. 2010. Binding of perfluorocarboxylates to serum albumin: a comparison of analytical methods. *Analytical Chemistry* 82(3):974–981.
- Maine DHHS (Department of Health and Human Services). 2014. *Maximum Exposure Guideline for Perfluorooctanoic Acid in Drinking Water*. CAS Registry Number (Free Acid): 335-67-1. Augusta, ME: Environmental and Occupational Health Program. Accessed May 2016. <https://www1.maine.gov/dhhs/mecdc/environmental-health/eohp/wells/documents/pfoameg.pdf>.
- Martin, J.W., S.A. Mabury, K.R. Solomon, and D.C. Muir. 2003a. Bioconcentration and tissue distribution of perfluorinated acids in rainbow trout (*Oncorhynchus mykiss*). *Environmental Toxicology and Chemistry* 22(1):196–204.

- Martin, J.W., S.A. Mabury, K.R. Solomon, and D.C. Muir. 2003b. Dietary accumulation of perfluorinated acids in juvenile rainbow trout (*Oncorhynchus mykiss*). *Environmental Toxicology and Chemistry* 22(1):189–195.
- Martin, J.W., S.A. Mabury, K.R. Solomon, and D.C. Muir. 2003c. Progress toward understanding the bioaccumulation of perfluorinated alkyl acids. *Environmental Toxicology and Chemistry* 32(11):2421–2423.
- Martin, J.W., M.M. Smithwick, B.M. Braune, P.F. Hoekstra, D.C.G. 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 predicts toxicity and categorizes chemicals based on mechanisms of toxicity. *Toxicological Science* 97:595–613.
- McLaughlin, C., S. Blake, T. Hall, M. Harman, R. Kanda, J. Foster, and P. Rumsby. 2011. Perfluorooctane sulphonate in raw and drinking water sources in the United Kingdom. *Water and Environment Journal* 25:1:13.
- McMurdo, C.J., D.A. Ellis, E. Webster, J. Butler, R.D. Christensen, and L.K. Reid. 2008. Aerosol enrichment of the surfactant PFO and mediation of the water– air transport of gaseous PFOA. *Environmental Science & Technology* 42(11):3969–3974.
- MDH (Minnesota Department of Health). 2008. *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/pfoa.pdf>.
- 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 NHANES study. *Environmental Health Perspectives* 118: 686–692.
- Michigan DEQ (Department of Environmental Quality). 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](http://www.michigan.gov/documents/deq/wrd-swas-rule57_372470_7.pdf).
- Minata, M., K.H. Harada, A. Kärman, T. Hitomi, M. Hirose, F.J. Gonzales, and A. Koizumi. 2010. Role of peroxisome proliferator-activated receptor- $\alpha$  in hepatobiliary injury induced by ammonium perfluorooctanoate in mouse liver. *Industrial Health* 48:96–107.

- 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* 122:187–192.
- Monroy, R., K. Morrison, K. Two, S. Atkinson, C. Kubwabo, B. Steward, and W.G, 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.C. 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 perfluorinated surfactants in groundwater at a fire-training area at Wurtsmith Air Force Base, Michigan, USA. *Journal of Environmental Monitoring* 5:341–345.
- Morikawa, A., N. Kamei, K. Harada, K. Inoue, T. Yoshinaga, N. Saito, and A. Koizumi. 2005. The bioconcentration factor of perfluorooctane sulfonate is significantly larger than that of perfluorooctanoate in wild turtles (*Trachemys scripta elegans* and *Chinemys reevesii*): an Ai river ecological study in Japan. *Ecotoxicology and Environmental Safety* 65(1):14–21.
- Morken, N.-H., G.S. Travlos, R.E. Wilson, M. Eggesbø, and M.P. Longnecker. 2014. Maternal glomerular filtration rate in pregnancy and fetal size. *PLOS One* 9:e101897.
- Murli, H. 1996a. *Mutagenicity test on T-6342 measuring chromosomal aberrations in human whole blood lymphocytes with a confirmatory assay with multiple harvests*. Corning-Hazelton, Inc., Vienna, VA. Study No. 17073-0-449CO, November 1, 1996. U.S. Environmental Protection Agency Administrative Record 226-0433.
- Murli, H. 1996b. *Mutagenicity test on T-6564 measuring chromosomal aberrations in Chinese Hamster Ovary (CHO) cells with a confirmatory assay with multiple harvests*. Corning Hazleton Inc., Vienna, VA. Study No. 17750-0-437CO, September 16, 1996. U.S. Environmental Protection Agency Administrative Record 226-0431.
- Nakagawa, H., T. Hirata, T. Terada, P. Jutabha, D. Miura, K.H. Harada, K. Inoue, N. Anzai, H. Endou, K. Inui, Y. Kanai, and A. Koizumi. 2007. Roles of organic anion transporters in the renal excretion of perfluorooctanoic acid. *Basic and Clinical Pharmacology and Toxicology* 103:1–8.
- Nakagawa, H., T. Terada, K.H. Harada, T. Hitomi, K. Inoue, K. Inui, and A. Koizumi. 2009. Human organic anion transporter hOAT4 is a transporter of perfluorooctanoic acid. *Basic and Clinical Pharmacology and Toxicology* 105:136–138.

- Nakamura, F., Y. Ito, Y. Yanagiba, D.H. Ramdhan, Y. Kono, H. Naito, Y. Hayashi, Y. Li, T. Aoyam, F.J. Gonzalez, and T. Nakajima. 2009. Microgram-order ammonium perfluorooctanoate may activate mouse peroxisome proliferator-activated receptor  $\alpha$ , but not human PPAR $\alpha$ . *Toxicology* 9: 27–33.
- 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.
- NCDEQ (North Carolina Department of Environmental Quality). 2013. *Interim Maximum Allowable Concentration for Perfluorooctanoic Acid (PFOA) in Groundwater*. April 2013. Accessed May 2016. [https://ncdenr.s3.amazonaws.com/s3fs-public/documents/files/IMAC%20table\\_5-22-13.pdf](https://ncdenr.s3.amazonaws.com/s3fs-public/documents/files/IMAC%20table_5-22-13.pdf).
- 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 U.S. population. *Environmental Health Perspectives* 118:197–202.
- NJDEP (New Jersey Department of Environmental Protection). 2007. *Determination of Perfluorooctanoic Acid (PFOA) in Aqueous Samples: Final Report*. January 2007. NJDEP, Division of Water Supply.
- NJDEP (New Jersey Department of Environmental Protection). 2014. *Occurrence of Perfluorinated Chemicals in Untreated New Jersey Drinking Water Sources: Final Report*. April 2014, NJDEP Division of Water Supply & Geoscience. Accessed May 2016. <http://www.nj.gov/dep/watersupply/pdf/pfc-study.pdf>.
- 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.
- Obourn, J.D., S.R. Frame, R.H. Bell, Jr., D.S. Longnecker, G.S. Elliott, and J.C. Cook. 1997. Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. *Toxicology and Applied Pharmacology* 145: 425–436.
- 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., J.M. Burris, M.M. Burlew, and J.H. Mandel. 2000. Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. *Drug and Chemical Toxicology* 23:603–620.

- Olsen, G.W., M.M. Burlew, J.M. Burris, and J.H. Mandel. 2001. *A Cross-Sectional Analysis Of Serum Perfluorooctanesulfonate (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*. 3M Company. Final Report. October 11, 2001. U.S. Environmental Protection Agency Administrative Record 226-1087.
- Olsen, G.W., 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., and L.R. Zobel. 2007. Assessment of lipid, hepatic, and thyroid parameters with serum perfluorooctanoate (PFOA) concentrations in fluorochemical workers. *International Archives of Occupational and Environmental Health* 81:231–246.
- 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 Perspective* 115:1298–1305.
- Onishchenko, N., C. Fischer, W.N.W. Ibrahim, S. Negri, S. Spulbur, S. Cottica, and S. Ceccatelli. 2011. Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. *Neurotoxicity Research* 19:452–461.
- Palazzolo, M.J. 1993. *Thirteen-Week Dietary Toxicity Study With T-5180, Ammonium Perfluorooctanoate (CAS No. 3825-26-1) In Male Rats*. Final Report. Laboratory Project Identification HWI 6329-100. Hazleton Wisconsin, Inc. U.S. Environmental Protection Agency Administrative Record 226-0449.
- Pastoor, T.P., K.P. Lee, M.A. Perri, and P.J. Gillies. 1987. Biochemical and morphological studies of ammonium perfluorooctanoate-induced hepatomegaly and peroxisome proliferation. *Experimental and Molecular Pathology* 47(1):98–109.
- Perkins, R., J. Butenhoff, G. Kennedy, and M. Palazzolo. 2004. 13-Week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. *Drug and Chemical Toxicology* 27: 361–378.
- Plummer, S.M., D.G. Farrar, and C.R. Elcombe. 2007. Comparison of gene expression changes in whole pancreas with isolated pancreatic acinar cells of rats fed diets containing Wyeth-14,643 or ammonium perfluorooctanoate. *Toxicology* 240: 171–172.
- Post, G.B., J.B. Louis, K.R. Cooper, B.J. Boros-Russo, and R.L. Lippincott. 2009. Occurrence and potential significance of perfluorooctanoic acid (pfoa) detected in New Jersey public drinking water systems. *Environmental Science & Technology* 43(12):4547–4554.
- Qin, P., R. Liu, X. Pan, X. Fang, and Y. Mou. 2010. Impact of carbon chain length on binding of perfluoroalkyl acids to bovine serum albumin determined by spectroscopic methods. *Journal of Agricultural and Food Chemistry* 58(9):5561–5567.

- Quinete, N., Q. Wu, T. Zhang, S.H. Yun, I. Moreira, and K. Kannan. 2009. Specific profiles of perfluorinated compounds in surface and drinking waters and accumulation in mussels, fish, and dolphins from southeastern Brazil. *Chemosphere* 77(6):863–869.
- 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.
- Quist, E.M., A.J. Filgo, C.A. Cummings, G.E. Kissling, and M.J. Hoenerhoff. 2015. Hepatic mitochondrial alteration in CD-1 mice associated with prenatal exposures to low doses of perfluorooctanoic acid (PFOA). *Toxicologic Pathways* 41:546–557.
- Raleigh, K.K., B.H. Alexander, G.W. Olsen, G. Ramachandran, S.Z. Morey, T.R. Church, P.W. Logan, L.L.F. Scott, and E.M. Allen. 2014. Mortality and cancer incidence in ammonium perfluorooctanoate production workers. *Occupational Environmental Medicine* 0:1–7.
- 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. 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.
- Rosen, M.B., J.R. Thibodeaux, C.R. Wood, R.D. Zehr, J.E. Schmid, and C. Lau. 2007. Gene expression profiling in the lung and liver of PFOA-exposed mouse fetuses. *Toxicology* 239:15–33.
- Rosen, M.B., B.A. Abbott, D.C. Wolf, J.C. Corton, C.R. Wood, J.E. Schmid, K.P. Das, R.D. Zehr, E.T. Blair, and C. Lau. 2008a. Gene profiling in the livers of wild-type and PPAR $\alpha$ -null mice exposed to perfluorooctanoic acid. *Toxicological Pathology* 36:592–607.
- Rosen, M.B., J.S. Lee, H. Ren, B. Vallanat, J. Liu, M.P. Waalkes, B.D. Abbott, C. Lau, and J.C. Corton. 2008b. Toxicogenomic dissection of the perfluorooctanoic acid transcript profile in mouse liver: evidence for the involvement of nuclear receptors PPAR $\alpha$  and CAR. *Toxicological Science* 103: 46–56.
- Rosen, M.B., C. Lau, and J.C. Corton. 2009a. Does exposure to perfluoroalkyl acids present a risk to human health? *Toxicological Sciences* 111(1):1–3.
- Rosen, M.B., J.E. Schmid, K.P. Das, C.R. Wood, R.D. Zehr, and C. Lau. 2009b. Gene expression profiling in the liver and lung of perfluorooctane sulfonate-exposed mouse fetuses: comparison to changes induced by exposure to perfluorooctanoic acid. *Reproductive Toxicology* 27(3):278–288.

- Saez, 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* 15:472–477.
- Sakr, C.J., R.C. Leonard, K.H. Kreckmann, M.D. Slade, and M.R. Cullen. 2007a. Longitudinal study of serum lipids and liver enzymes in workers with occupational exposure to ammonium perfluorooctanoate. *Journal of Occupational and Environmental Medicine* 49: 872–879.
- Sakr, C.J., K.H. Kreckmann, J.W. Green, P.J. Gillies, J.L. Reynolds, and R.C. Leonard. 2007b. Cross-sectional study of lipids related to a serum biomarker of exposure (ammonium perfluorooctanoate or APFO) as part of a general health survey in a cohort of occupationally exposed workers. *Journal of Occupational and Environmental Medicine* 49:1086–1096.
- Salvalaglio, M., I. Muscionico, and C. Cavallotti. 2010. Determination of energies and sites of binding of PFOA and PFOS to human serum albumin. *Journal of Physical Chemistry B* 114:14860–14874.
- Savitz, D.A., C.R. Stein, S.M. Bartell, B. Elston, J. Gong, H.M. Shin, and G.A. Wellenius. 2012. Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community. *Epidemiology* 23:386–92.
- Schechter, A., J. Colacino, D. Haffner, K. Patel, M. Opel, O. Pöpke, and L. Birnbaum. 2010. Perfluorinated compounds, polychlorinated biphenyls, and organochlorine pesticide contamination in composite food samples from Dallas, Texas, USA. *Environmental Health Perspectives* 118(6):796.
- Schlummer, M., C. Sölch, T Meisel, M. Still, L. Gruber, and G. Wolz. 2015. Emission of perfluoroalkyl carboxylic acids (PFCA) from heated surfaces made of polytetrafluoroethylene (PTFE) applied in food contact materials and consumer products. *Chemosphere* 129:46–53.
- 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.
- 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](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).
- Shivakoti, B.R., 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.
- Shrestha, S., M.S. Bloom, R. Yucel, R.F. Seegal, Q. Wu, K. Kannan, R. Rej, and E.F. Fitzgerald. 2015. Perfluoroalkyl substances and thyroid function in older adults. *Environmental International* 75:206–214
- SIAR (SIDS Initial Assessment Profile). 2008. *Final SIDS Assessment Report: PFOA*. Organization for Economic Cooperation and Development. Paris, France. April 16-18. Accessed May 2016. <http://webnet.oecd.org/HPV/UI/handler.axd?id=1f391916-96ba-46f6-a7ce-c96712da3b7e>.
- 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.G. 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.
- Son, H-Y., A-H Kim, H-I. Shin, H-I. Bae, and J-H. Yang. 2008. Perfluorooctanoic acid-induced hepatic toxicity following 21-day oral exposure in mice. *Archives of Toxicology* 82:239–246.
- 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. *The Science of the Total Environment* 499:185–195.
- Starling, A.P., S.M. Engel, K.W. Whitworth, D.B. Richardson, A.M. Stuebe, J.L. Daniels, L.S. Haug, M. Eggesbø, G. Becher, A. Sabaredzovic, C. Thomsen, R.E. Wilson, G.S. Travlos, J.A. Hoppin, D.D. Baird, and M.P. Longnecker. 2014. Perfluoroalkyl substances and lipid concentrations in plasma during pregnancy among women in the Norwegian Mother and Child Cohort Study. *Environment International* 62:104–112.
- 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* 170:1269–1278.
- Steenland, K., and S. Woskie. 2012. Cohort mortality study of workers exposed to perfluorooctanoic acid. *American Journal of Epidemiology* 176:909–917.
- Steenland, K., L. Zhao, and A. Winquist. 2015. A cohort incidence study of workers exposed to perfluorooctanoic acid (PFOA). *Occupational and Environmental Medicine* 0:1–8.
- Takacs, M.L., and B.D. Abbott. 2007. Activation of mouse and human peroxisome proliferator-activated receptors ( $\alpha$ ,  $\beta/\delta$ ,  $\gamma$ ) by perfluorooctanoic acid and perfluorooctane sulfonate. *Toxicological Science* 95:108–117.

- Takagi, S., F. Adachi, K. Miyano, Y. Koizumi, H. Tanaka, M. Mimura, I. Watanabe, S. Tanabe, and K. Kannan. 2008. Perfluorooctane sulfonate and perfluorooctanoate in raw and treated tap water from Osaka, Japan. *Chemosphere* 72:1409.
- Tan, X., G. Xie, X. Sun, Q. Li, W. Zhong, P. Oiao, X. Sun, W. Jai, and Z. Zhou. 2013. High fat diet feeding exaggerates perfluorooctanoic acid-induced liver injury in mice via modulating multiple metabolic pathways. *PLOS One* 8(4):e61409.
- 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.
- 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. Thesis. Air Force Institute of Technology, Wright-Patterson Air Force Base, Ohio.
- Thompson, J., M. Lorber, L.-M.L. Toms, K. Kato, A.M. Calafat, and J.F. Mueller. 2010. Use of simple pharmacokinetic modeling to characterize exposure of Australians to perfluorooctanoic acid and perfluorooctane sulfonic acid. *Environment International* 36:390–397.
- Thompson, J., G. Eaglesham, J. Reungoat, Y. Poussade, M. Bartkowiak, 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.
- Tittlemier, S.A., K. Pepper, C. Seymour, J. Moisey, R. Bronson, X.L. Cao, and R.W. Dabeka. 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.
- 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 & Technology* 5(1):1–8.
- Trudel, D., L. Horowitz, M. Wormuth, M. Scheringer, I.T. Cousins, and K. Hungerbühler. 2008. Estimating Consumer Exposure to PFOS and PFOA. *Risk Analysis* 28:251–269.

- Tucker, D.E., M.B. Macon, M.J. Strynar, S. Dragnino, E. Andersen, and S.E. Fenton. 2015. The mammary gland is a sensitive pubertal target in CD-1 and C57BL/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. *Reproductive Toxicology* 54:26–36.
- UK (United Kingdom) Drinking Water Inspectorate. 2009. *Guidance on the Water Supply (Water Quality) Regulations 2001 specific to PFOS (perfluorooctane sulphonate) and PFOA (perfluorooctanoic acid) concentrations in drinking water*. Accessed May 2016. [http://www.dwi.gov.uk/stakeholders/information-letters/2009/10\\_2009annex.pdf](http://www.dwi.gov.uk/stakeholders/information-letters/2009/10_2009annex.pdf).
- UNEP (United Nations Environmental Program). 2015. *Proposal to list pentadecafluorooctanoic acid (CAS No: 335-67-1, PFOA, perfluorooctanoic acid), its salts and PFOA-related compounds in Annexes A, B and/or C to the Stockholm Convention on Persistent Organic Pollutants*.
- 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 Advisory: Pesticides*. Lewis Publishers, Chelsea, MI. ISBN: 978-0-87371-235-4.
- USEPA (U.S. Environmental Protection Agency). 2000. *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 Water, Office of Science and Technology, Washington, DC. Accessed May 2016. [http://www.nj.gov/drbc/library/documents/EPA\\_human-health-criteria2000.pdf](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, Washington, DC. Accessed May 2016. <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>.
- USEPA (U.S. Environmental Protection Agency). 2005. Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency. *Federal Register* 70(66):17765–18717.
- USEPA (U.S. Environmental Protection Agency). 2006. Letter to Charles O. Holliday, Jr., Chairman and Chief Executive Officer of Dupont, inviting participation in the PFOA Stewardship Program. Accessed May 2016. <https://www.epa.gov/sites/production/files/2015-10/documents/dupont.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](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. *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, Office of Research and Development, National Exposure Research Laboratory, Cincinnati, OH. Accessed May 2016. [https://cfpub.epa.gov/si/si\\_public\\_file\\_download.cfm?p\\_download\\_id=525468](https://cfpub.epa.gov/si/si_public_file_download.cfm?p_download_id=525468).
- USEPA (United States Environmental Protection Agency). 2009c. *Provisional Health Advisories for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS)*. Office of Water. US Environmental Protection Agency. Washington, D.C. Accessed May 2016. [http://www.epa.gov/waterscience/criteria/drinking/pha-PFOA\\_PFOS.pdf](http://www.epa.gov/waterscience/criteria/drinking/pha-PFOA_PFOS.pdf).
- 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](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, Office of the Science Advisor, 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 – Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA) (Fact Sheet)*. EPA 505-F-14-001. U.S. Environmental Protection Agency, Solid Waste and Emergency Response. Accessed May 2016. <http://nepis.epa.gov/Exe/ZyPDF.cgi/P100LTG6.PDF?Dockkey=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. *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). 2015c. *Perfluorooctanoic Acid (PFOA) and Fluorinated Telomers, Basic Information*. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. <http://www.epa.gov/oppt/pfoa/pubs/pfoainfo.html>.

- 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>.
- Upham, B.L., N.D. Deocampo, B. Wurl, and J.E. Trosko. 1998. Inhibition of gap junctional intercellular communication by perfluorinated fatty acids is dependent on the chain length of the fluorinated tail. *International Journal of Cancer* 78(4):491–495.
- Upham, B.L., J.S. Park, P. Babica, I. Sovadinova, A.M. Rummel, J.E. Trosko, A. Hirose, R. Hasegawa, J. Kanno, and K. Sai. 2009. Structure-activity-dependent regulation of cell communication by perfluorinated fatty acids using in vivo and in vitro model systems. *Environmental Health Perspectives* 117(4):545.
- Vélez, M.P., T.E. Arbuckle, and W.D. Fraser. 2015. Maternal exposure to perfluorinated chemicals and reduced fecundity: The MIREC study. *Human Reproduction* 30:701–709.
- Venkatesan, A.K., and R.U. Halden. 2013. National inventory of perfluoroalkyl substances in archived U.S. biosolids from the 2001 EPA National Sewage Sludge Survey. *Journal of Hazardous Materials* 252–253:413–418.
- Vermont ANR (Agency of Natural Resources). 2016. Summary of perfluorooctanoic acid (PFOA) drinking water contamination. March 10, 2016. Vermont Agency of Natural Resources, Department of Health. Accessed May 2016. <http://healthvermont.gov/enviro/pfoa.aspx>.
- Verner, M.A., A.E. Loccisano, N.H. Morken, M. Yoon, H. Wu, R. McDougall, M. Maisonet, M. Marcus, R. Kishi, C. Miyashita, M.H. Chen, W.S. Hsieh, M.E. Andersen, H.J. Clewell, III, and M.P. Longnecker. 2015. Associations of perfluoroalkyl substances (PFAS) with lower birth weight: An evaluation of potential confounding by glomerular filtration rate using a physiologically based pharmacokinetic model (PBPK). *Environmental Health Perspectives* 123:1317–1324.

- 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.
- Vieira, V.M., K. Hoffman, H.M. Shin, J.M. Weinberg, T.F. Webster, and T. Fletcher. 2013. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: A geographic analysis. *Environmental Health Perspectives* 121(3).
- Vierke, C., C. Staude, A. Biegel-Engler, W. Drost, and C. Schulte. 2012. Perfluorooctanoic acid (PFOA) — Main concerns and regulatory developments in Europe from an environmental point of view. *Environmental Sciences Europe* 24:16.
- 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.
- Wallington, T.J., M.D. Hurley, J. Xia, D.J. Wuebbles, S. Sillman, A. Ito, J.E. Penner, D.A. Ellis, J. Martin, S.A. Mabury, O.J. Nielsen, and M.P. Sulbaek Andersen. 2006. Formation of C7F15COOH (PFOA) and Other Perfluorocarboxylic Acids during the Atmospheric Oxidation of 8:2 Fluorotelomer Alcohol. *Environmental Science & Technology* 40:924–930.
- 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 Science* 136:308–327
- Washington, J.W., J.J. Ellington, T.M. Jenkins, J.J. Evans, H. Yoo, and S.C. Hafner. 2009. Degradability of an acrylate-linked, fluorotelomer polymer in soil. *Environmental Science & Technology* 43:6617–6623.
- 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.
- Washington, J.W., and T.M. Jenkins. 2015a. Abiotic hydrolysis of fluorotelomer polymers as a source of perfluorocarboxylates at the global scale. *Environmental Science & Technology* 49:14129–14135.

- Washington, J.W., T.M. Jenkins, K. Rankin, and J.E. Naile. 2015b. Decades-Scale Degradation of Commercial, Side-Chain, Fluorotelomer-based Polymers in Soils & Water. *Environmental Science & Technology* 49:915–923.
- Weaver, Y.M., D.J. Ehresman, J.L. Butanhoff, and B. Hagenbuch. 2009 (epub). Roles of renal organic anion transporters in transporting perfluorinated carboxylates with different chain lengths. *Toxicological Science* 113:305–314.
- Weaver, J.D., B.J. Ka, D.K. Morris, W. Thompson, and J.A. Tunge. 2010. Stereospecific decarboxylative allylation of sulfones. *Journal of the American Chemical Society* 132(35):12179–12181.
- 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.
- 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 Science* 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 U.S. adults: The National Health and Nutrition Examination survey 2007-2010. *The Journal of Clinical Endocrinology and Metabolism* 98(9):E1456–E1464.
- White, S.S., A.M. Calafat, A. Kuklennyik, L. Villanueva, R.D. Zehr, L. Helfant, M.J. Strynar, A.B. Lindstrom, J.R. Thibodeaux, C. Wood, and S.E. Fenton. 2007. Gestational PFOA exposure of mice is associated with altered mammary gland development in dams and female offspring. *Toxicological Science* 96:133–144.
- White, S.S., K. Kato, L.T. Jia, B.J. Basden, A.M. Calafat, E.P. Hines, J.P. Stanko, C.J. Wolf, B.D. Abbott, and S.E. Fenton. 2009. Effects of perfluorooctanoic acid on mouse mammary gland development and differentiation resulting from cross-foster and restricted gestational exposures. *Reproductive Toxicology* 27:289–298.
- White, S.S., J.P. Stanko, K. Kato, A.M. Calafat, E.P. Hines, and S.E. Fenton. 2011. Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. *Environmental Health Perspectives* 119(8):1070–1076.
- Winqvist, A., and K. Steenland. 2014a. Modeled PFOA exposure and coronary artery disease, hypertension, and high cholesterol in community and worker cohorts. *Environmental Health Perspectives* 122:1299–1305.
- Winqvist, A., and K. Steenland. 2014b. Perfluorooctanoic acid exposure and thyroid disease in community and worker cohorts. *Epidemiology* 25:255–264.

- Wolf, C.J., S.E. Fenton, J.E. Schmid, A.M. Calafat, Z. Kuklennyik, X.A. Bryant, J. Thibodeaux, K.P. Das, S.S. White, C.S. Lau, and B.D. Abbott. 2007. Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposure. *Toxicological Science* 95:462–473.
- 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 Science* 106:162–171.
- Woodruff, T.J., and P. Sutton. 2014. The Navigation Guide Systematic Review Methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environmental Health Perspectives* 122:1007–1014.
- Wu, L., H. Gao, N. Gao, F. Chen, and L. Chen. 2009a. Interaction of perfluorooctanoic acid with human serum albumin. *BMC Structural Biology* 9:31.
- Wu, J., H.M. Zhou, H.Z. Li, P.C. Zhang, and J. Jiang. 2009b. Impacts of hydrodynamic shear force on nucleation of flocculent sludge in anaerobic reactor. *Water Research* 43(12):3029–3036.
- 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 U.S. metropolitan area: Migration and implications for human exposure. *Water Research* 72:64–74.
- Xu, Z., S. Fiedler, G. Pfister, B. Henkelmann, C. Mosch, W. Volkel, H. Fromme, and K.W. Schramm. 2013. Human exposure to fluorotelomer alcohols, perfluorooctane sulfonate and perfluorooctanoate via house dust in Bavaria, Germany. *The Science of the Total Environment* 443:485–490.
- Yahia, D., M.A. El-Nasser, M. Abedel-Latif, C. Tsukuba, M. Yoshida, I. Sato, and S. Tsuda. 2010. Effects of perfluorooctanoic acid (PFOA) exposure to pregnant mice on reproduction. *Journal of Toxicological Science* 35: 527–533.
- Yamada, A., N. Bemrah, B. Veyrand, C. Pollono, M. Merlo, V. Desvignes, and J.P. Antignac. 2014. Dietary exposure to perfluoroalkyl acids of specific French adult sub-populations: high seafood consumers, high freshwater fish consumers and pregnant women. *Science of the Total Environment* 491:170–175.
- Yamada, T., P.H. Taylor, R.C. Buck, M.A. Kaiser, and R.J. Giraud. 2005. Thermal degradation of fluorotelomer treated articles and related materials. *Chemosphere* 61(7):974–84.
- 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.
- Yang, Q., Y. Xie, and W. Depierre. 2000. Effects of peroxisome proliferators in the thymus and spleen of mice. *Clinical and Experimental Immunology* 122:219–226.

- Yang, Q., Y. Xie, A.M. Ericksson, B.D. Nelson, and J.W. DePierre. 2001. Further evidence for the involvement of inhibition of cell proliferation and development in thymic and splenic atrophy induced by the peroxisome proliferator perfluorooctanoic acid in mice. *Biochemical Pharmacology* 62:1133–1140.
- Yang, Q., M. Abedi-Valugerdi, Y. Xie, X. Zhao, G. Molle, B.D. Nelson, and J.W. DePierre. 2002a. Potent suppression of the adaptive immune response in mice upon dietary exposure to the potent peroxisome proliferator, perfluorooctanoic acid. *International Immunopharmacology* 2:389–397.
- Yang, Q., Y. Xie, S.H.E. Alexson, B.D. Nelson, and J.W. DePierre. 2002b. Involvement of the peroxisome proliferator-activated receptor alpha in the immunomodulation caused by peroxisome proliferators in mice. *Biochemical Pharmacology* 63:1893–1900.
- Yang, C., Y.S. Tan, J.R. Harkema, and S.Z. Haslam. 2009. Differential effects of peripubertal exposure to perfluorooctanoic acid on mammary gland development in C57Bl/6 and Balb/c mouse strains. *Reproductive Toxicology* 27:299–306.
- Yang, C.-H., K.P. Glover, and X. Han. 2010. Characterization of cellular uptake of perfluorooctanoate via organic-anion transporting polypeptide 1A2, organic anion transporter 4, and urate transporter 1 for their potential roles in mediating human renal reabsorption of perfluorocarboxylates. *Toxicological Science* 117:294–302.
- Yoo, H., J.W. Washington, T.M. Jenkins, and J.J. Ellington. 2011. Quantitative determination of perfluorochemicals and fluorotelomer alcohols in plants from biosolid-amended fields using LC/MS/MS and GC/MS. *Environmental Science & Technology* 45(19):7985–7990.
- Young, C.J., 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.
- Zaïr, Z.M., J.J. Eloranta, B. Stieger, and G.A. Kullak-Ublick. 2008. Pharmacogenetics of OATP (SLC21/SLCO), OAT and OCT (SLC22) and PRPT (SLC15) transporters in the intestine, liver, and kidney. *Pharmacogenomics* 9:597–624.
- 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* 91:725–732.
- Zhang, L., X.-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, 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, Y., S. Beesoon, L. Zhu, and J.W. Martin. 2013. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. *Environmental Science & Technology* 47(18):10619–10627.
- 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. *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.

## 12.0 APPENDIX A-QUANTITATIVE CANCER ASSESSMENT MODELING

### Multistage Model for Leydig Cell Tumors

```
=====
Multistage Cancer Model. (Version: 1.9; Date: 05/26/2010)
Input Data File: C:/1Data/MyFiles/PFOA-PFOS/PFOA Docs/msc_Leydig_Opt.(d)
Gnuplot Plotting File: C:/1Data/MyFiles/PFOA-PFOS/PFOA Docs/msc_Leydig_Opt.plt
Thu May 09 11:59:27 2013
=====
```

BMDS\_Model\_Run

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{beta1} * \text{dose}^{1 - \text{beta2} * \text{dose}^2})]$$

The parameter betas are restricted to be positive

Dependent variable = Col2  
Independent variable = Col1

Total number of observations = 3  
Total number of records with missing values = 0  
Total number of parameters in model = 3  
Total number of specified parameters = 0  
**Degree of polynomial = 2**

Maximum number of iterations = 250  
Relative Function Convergence has been set to: 1e-008  
Parameter Convergence has been set to: 1e-008

#### Default Initial Parameter Values

Background = 0.0132945  
Beta(1) = 0.0097738  
Beta(2) = 0

#### Asymptotic Correlation Matrix of Parameter Estimates

( \*\*\* The model parameter(s) -Beta(2)  
have been estimated at a boundary point, or have been specified by  
the user,  
and do not appear in the correlation matrix )

	Background	Beta(1)
Background	1	-0.64
Beta(1)	-0.64	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0.00409839	*	*	*
Beta(1)	0.0116288	*	*	*
Beta(2)	0	*	*	*

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-28.6454	3			
Fitted model	-29.3468	2	1.40286	1	0.2362
Reduced model	-34.0451	1	10.7995	2	0.004518

AIC: 62.6936

Goodness of Fit

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0041	0.205	0.000	50	-0.454
1.3000	0.0190	0.952	2.000	50	1.084
14.2000	0.1557	7.784	7.000	50	-0.306

Chi<sup>2</sup> = 1.48 d.f. = 1 P-value = 0.2245

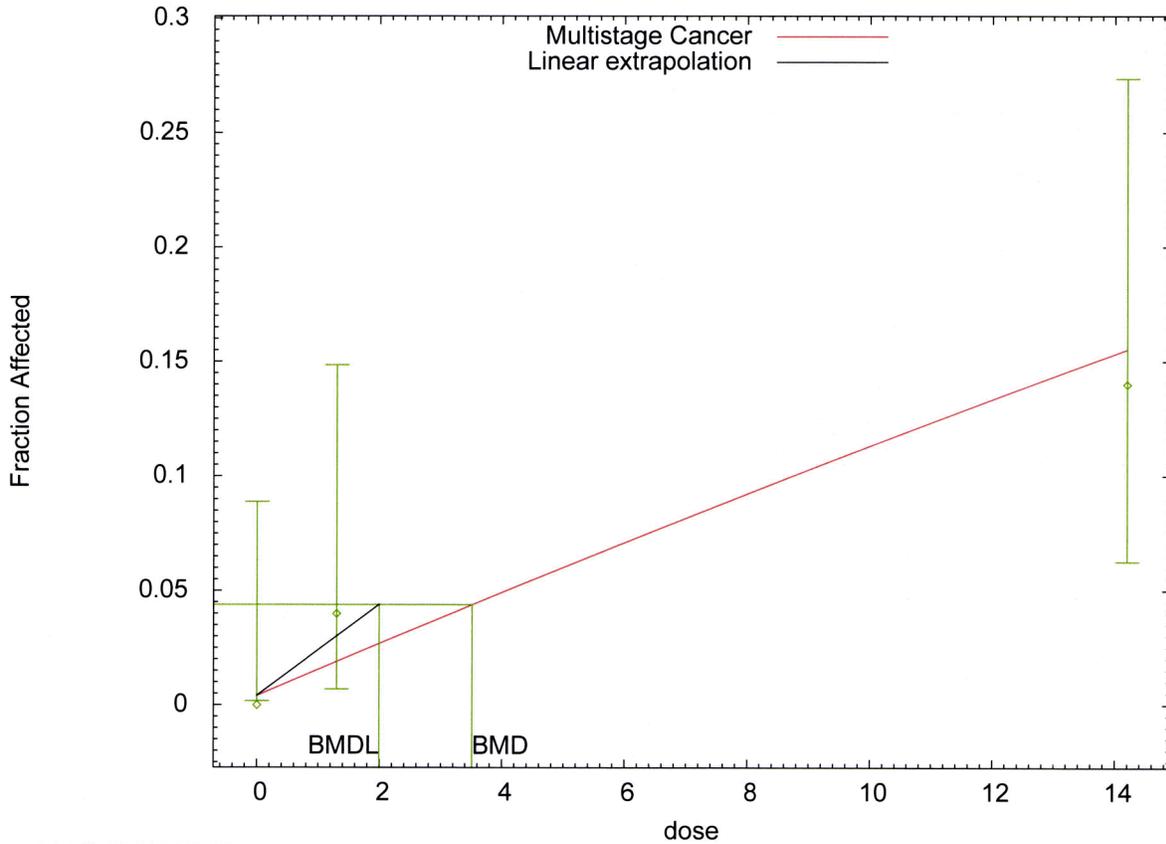
Benchmark Dose Computation

Specified effect = 0.04  
 Risk Type = Extra risk  
 Confidence level = 0.95  
 BMD = 3.51044  
 BMDL = 1.99346  
 BMDU = 10.7788

Taken together, (1.99346, 10.7788) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0200656

Multistage Cancer Model with 0.95 Confidence Level



11:59 05/09 2013

```

=====
Multistage Cancer Model. (Version: 1.9; Date: 05/26/2010)
Input Data File: C:/1Data/MyFiles/PFOA-PFOS/PFOA Docs/msc_Leydig_Opt.(d)
Gnuplot Plotting File: C:/1Data/MyFiles/PFOA-PFOS/PFOA Docs/msc_Leydig_Opt.plt
Thu May 09 12:05:42 2013
=====
    
```

BMDS\_Model\_Run

The form of the probability function is:

$$P[\text{response}] = \text{background} + (1-\text{background}) * [1-\text{EXP}(-\text{beta}1 * \text{dose}^1)]$$

The parameter betas are restricted to be positive

Dependent variable = Col2  
Independent variable = Col1

Total number of observations = 3  
Total number of records with missing values = 0  
Total number of parameters in model = 2  
Total number of specified parameters = 0  
**Degree of polynomial = 1**

Maximum number of iterations = 250  
 Relative Function Convergence has been set to: 1e-008  
 Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

Background = 0.0132945  
 Beta(1) = 0.0097738

Asymptotic Correlation Matrix of Parameter Estimates

	Background	Beta(1)
Background	1	-0.64
Beta(1)	-0.64	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval	
			Lower Conf. Limit	Upper Conf. Limit
Background	0.00409839	*	*	*
Beta(1)	0.0116288	*	*	*

\* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-28.6454	3			
Fitted model	-29.3468	2	1.40286	1	0.2362
Reduced model	-34.0451	1	10.7995	2	0.004518

AIC: 62.6936

Goodness of Fit

Dose	Est. Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0041	0.205	0.000	50	-0.454
1.3000	0.0190	0.952	2.000	50	1.084
14.2000	0.1557	7.784	7.000	50	-0.306

Chi<sup>2</sup> = 1.48    d.f. = 1    P-value = 0.2245

Benchmark Dose Computation

Specified effect =	0.04
Risk Type =	Extra risk
Confidence level =	0.95
BMD =	3.51044
BMDL =	1.99346
BMDU =	8.7003

Taken together, (1.99346, 8.7003) is a 90% two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0200657

# **EXHIBIT B**



United States  
Environmental Protection  
Agency

Office of Water  
Mail Code 4304T

EPA 822-R-16-004  
May 2016

---

# **Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS)**

**Drinking Water Health Advisory  
for Perfluorooctane Sulfonate (PFOS)**

Prepared by:

U.S. Environmental Protection Agency  
Office of Water (4304T)  
Health and Ecological Criteria Division  
Washington, DC 20460

EPA Document Number: 822-R-16-004

May 2016

## ACKNOWLEDGMENTS

This document was prepared by the Health and Ecological Criteria Division, Office of Science and Technology, Office of Water of the U.S. Environmental Protection Agency (EPA). The Agency gratefully acknowledges the valuable contributions of EPA scientists Barbara Glenn, Ph.D.; Erin Hines, Ph.D.; Michael Wright, Sc.D.; John Wambaugh, Ph.D.; Thomas Speth, Ph.D.; and Daniel Hautman.

This Health Advisory was provided for review by and comments were received from staff in the following EPA program Offices:

- Office of Chemical Safety and Pollution Prevention
- 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

## CONTENTS

ACKNOWLEDGMENTS .....	3
ABBREVIATIONS AND ACRONYMS .....	7
EXECUTIVE SUMMARY .....	10
1 INTRODUCTION AND BACKGROUND .....	12
1.1 Safe Drinking Water Act.....	12
1.2 Current Advisories and Guidelines .....	14
1.3 Uses of PFOS .....	15
2 NATURE OF THE STRESSOR.....	16
2.1 Physical and Chemical Properties .....	16
2.2 Occurrence and Sources of Exposure.....	17
2.2.1 Surface Water and Groundwater.....	17
2.2.2 Drinking Water .....	18
2.2.3 Food .....	19
2.2.4 Ambient Air .....	22
2.2.5 Indoor Dust .....	22
2.2.6 Soils.....	23
2.2.7 Biosolids .....	23
2.2.8 Consumer Products .....	24
2.3 Environmental Fate .....	25
2.3.1 Mobility.....	25
2.3.2 Persistence.....	25
2.3.3 Bioaccumulation .....	25
2.4 Toxicokinetics .....	26
2.5 Human Biomonitoring Data .....	27
3 PROBLEM FORMULATION .....	28
3.1 Conceptual Model .....	28
3.1.1 Conceptual Model Diagram for Exposure via Finished Drinking Water .....	28
3.1.2 Factors Considered in the Conceptual Model for PFOS.....	30
3.2 Analysis Plan.....	32
3.2.1 Health Advisory Guidelines.....	32
3.2.2 Establishing the Data Set .....	32
3.2.3 Approach for HA Calculation.....	33
3.2.4 Measures of Effect .....	34
3.2.5 Relative Source Contribution.....	35

4	EFFECTS ASSESSMENT .....	36
4.1	Noncancer Health Effects.....	36
4.1.1	Animal Toxicology .....	36
4.1.2	Human Epidemiology Studies .....	37
4.1.3	Noncancer Mode of Action (MOA).....	41
4.2	Cancer.....	42
4.2.1	Animal Cancer Bioassays .....	42
4.2.2	Human Epidemiology Studies .....	42
4.2.3	Cancer Mode of Action.....	43
4.2.4	Weight of Evidence Classification.....	43
5	DOSE-RESPONSE ASSESSMENT .....	43
5.1	Uncertainty Factors .....	46
5.2	RfD Determination .....	47
6	HEALTH ADVISORY VALUES .....	48
6.1	Relative Source Contribution .....	48
6.2	Lifetime Health Advisory .....	49
7	CANCER RISK .....	51
8	EFFECTS CHARACTERIZATION .....	51
8.1	Uncertainty and Variability .....	51
8.2	Use of Epidemiology Data .....	52
8.3	Consideration of Immunotoxicity .....	53
8.4	Alternative Exposure Scenarios .....	55
8.5	Relative Source Contribution Considerations .....	55
8.6	Sensitive Populations: Gender Differences.....	57
8.7	Sensitive Populations: Developmental Effects.....	57
9	ANALYTICAL METHODS .....	57
10	TREATMENT TECHNOLOGIES .....	58
11	REFERENCES .....	62

## TABLES

Table 1-1. State Guideline Values for PFOS .....	14
Table 1-2. International Guideline Values for PFOS.....	14
Table 2-1. Chemical and Physical Properties of PFOS .....	17
Table 5-1. Human Equivalent Doses Derived from the Modeled Animal Average Serum Values .....	45
Table 5-2. Candidate RfDs Derived from HEDs from the Pharmacokinetic Model Average Serum Values.....	47

## FIGURES

Figure 2-1. Chemical Structure of PFOS Anion.....	16
Figure 3-1. Conceptual Model for PFOS in Finished Drinking Water.....	29

## ABBREVIATIONS AND ACRONYMS

$\alpha$	alpha
AFFF	aqueous film forming foams
ALT	alanine transaminase
ASBT	apical sodium dependent bile acid transporter
AUC	area under the curve
$\beta$	beta
BAF	bioaccumulation factor
BCF	bioconcentration factor
BMF	biomagnification factor
BUN	blood urea nitrogen
bw	body weight
$^{\circ}\text{C}$	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 <sup>2</sup>	square meter
m <sup>3</sup>	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	polystyrenedivinybenzene
SDWA	Safe Drinking Water Act
SGA	small for gestational age
SPE	solid phase extraction
T3	triiodothyronine
T4	thyroxine
t <sub>1/2</sub>	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 <sub>A</sub>	interspecies uncertainty factor
UF <sub>D</sub>	database deficiency uncertainty factor
UF <sub>H</sub>	intraspecies uncertainty factor
UF <sub>L</sub>	LOAEL uncertainty factor
UF <sub>S</sub>	subchronic uncertainty factor
USGS	U.S. Geological Survey
UV	ultraviolet
V <sub>d</sub>	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 ( $\mu\text{g/L}$ ) 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.<sup>1</sup>

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).

---

<sup>1</sup> 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 [ $\mu\text{g/L}$ ]) by approximately 2% of PWSs nationwide. To-date, PFOS has been measured above 0.07  $\mu\text{g/L}$  by approximately 1% of PWSs. Approximately 1% of PWSs have reported data for which combined PFOA and PFOS results are above 0.07  $\mu\text{g/L}$ . 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, upholstery, 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, photomicro lithography, 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.

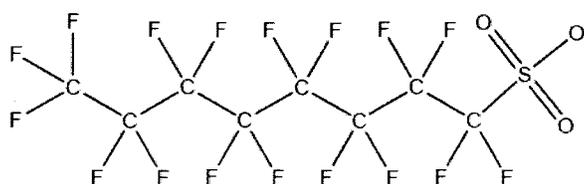
Given the limited ongoing uses of PFOS in the United States, releases to surface water and groundwater are expected to decline. Exposure to PFOS in the United States remains possible, however, because of its legacy uses, existing and legacy uses on imported goods, degradation of precursors, and the chemical’s 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 <sup>a</sup>	Source
Chemical Abstracts Service Registry No. (CASRN) <sup>b</sup>	1763-23-1	
Chemical Abstracts Index Name	1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptafluoro-1-octanesulfonic acid	
Synonyms	Perfluorooctane sulfonic acid; heptafluoro-1-octane sulfonic acid; PFOS acid	
Chemical Formula	C <sub>8</sub> HF <sub>17</sub> O <sub>3</sub> S	
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 <sup>-3</sup> mm Hg at 25 °C (estimate)	HSDB (2012)
Henry's Law Constant	Not measureable	ATSDR (2015)
K <sub>ow</sub>	Not measurable	ATSDR (2015); EFSA (2008)
K <sub>oc</sub>	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<sub>ow</sub> = octanol-water partition co-efficient; K<sub>oc</sub> = organic carbon-water partitioning coefficient

<sup>a</sup> PFOS is commonly produced as a potassium salt (CASRN 2795-39-3). Properties specific to the salt are not included.

<sup>b</sup> 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 Conasauga River (192–319 ng/L) and the Altamaha 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. 2010; Konwick 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)<sup>2</sup> *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  $\geq 200$  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).

Schechter 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

---

<sup>2</sup> 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 (Schechter 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 90<sup>th</sup> 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 99<sup>th</sup> 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<sup>2</sup> (4,282 mi<sup>2</sup>). 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 95<sup>th</sup> 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<sup>2</sup>).

#### **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<sup>3</sup>) and 2.3 pg/m<sup>3</sup>, 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<sup>3</sup> from eight samples collected in the summertime in Albany, New York; 0.6 (0.4–1.2) pg/m<sup>3</sup> 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<sup>3</sup>) and landfills (3.9 pg/m<sup>3</sup>) 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 95<sup>th</sup> 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  $403 \pm 127$   $\mu\text{g}/\text{kg}$  dry weight), followed by PFOA (mean  $34 \pm 22$   $\mu\text{g}/\text{kg}$  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  $22.5$   $\mu\text{g}/\text{kg}$  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  $20.4$   $\mu\text{g}/\text{kg}$ . 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<sup>3</sup>

---

<sup>3</sup> 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 [PPAR $\alpha$ ]), 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)  $\alpha/\beta$  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  $\mu\text{g/L}$  to 6.31  $\mu\text{g/L}$  and the 95<sup>th</sup> percentile concentration decreased from 75.7  $\mu\text{g/L}$  to 21.7  $\mu\text{g/L}$ . 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.

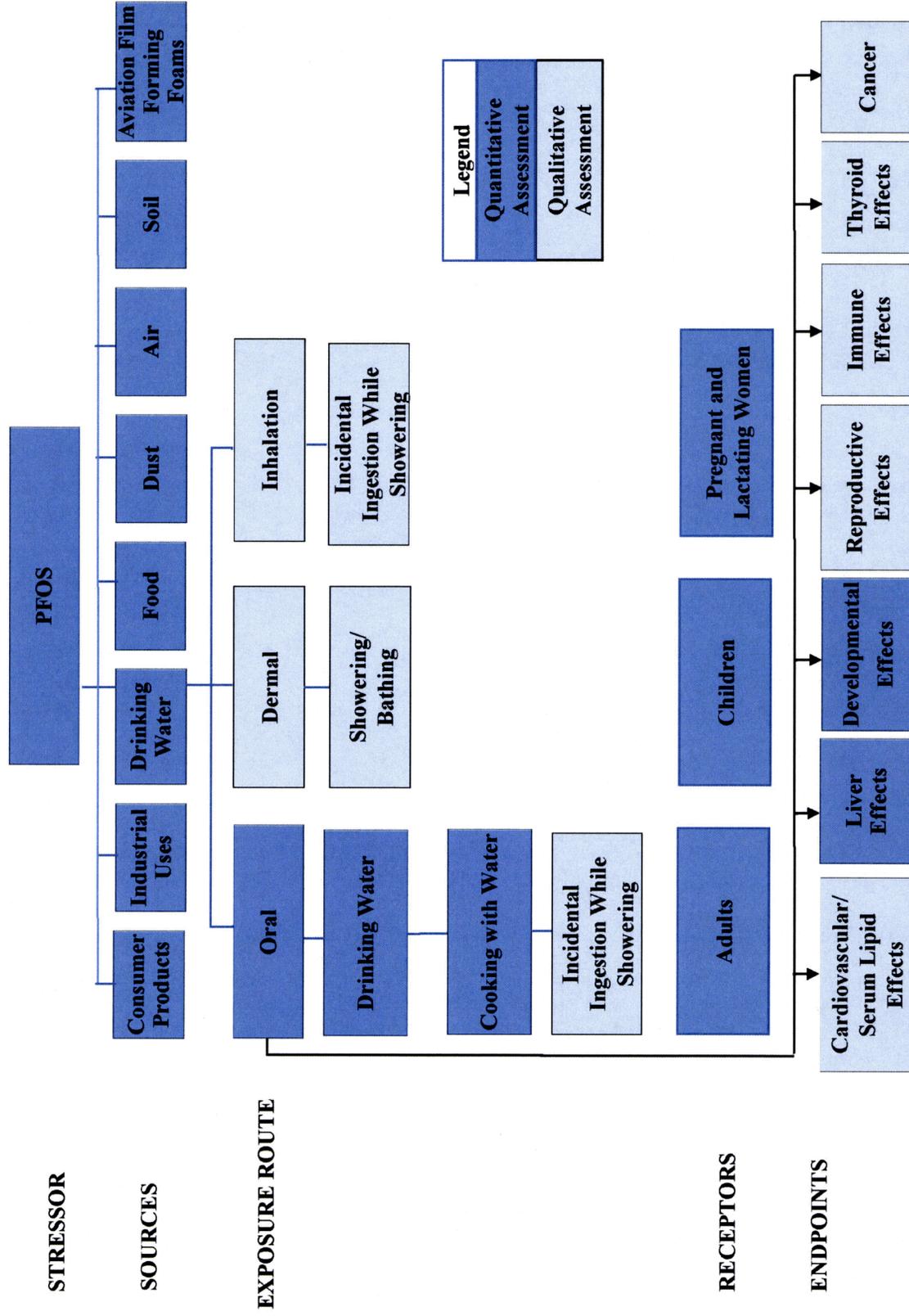


Figure 3-1. Conceptual Model for PFOS in Finished Drinking Water

### 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 ( $> 0.033 \mu\text{g/mL}$ ) 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  $\mu\text{g/mL}$  (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.<sup>4</sup>

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 PPAR $\alpha$  receptors, making it difficult to determine if this change is a reflection of PPAR $\alpha$  activation or an indication of PFOS toxicity. The PPAR $\alpha$  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).

---

<sup>4</sup> 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 to 12 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.

$$RfD = \frac{HED_{NOAEL} \text{ OR } HED_{LOAEL}}{UF}$$

Where:

HED<sub>NOAEL</sub> = The HED from the modeled average serum representing the highest of the given doses that lacked adverse effects (mg/kg/day).

HED<sub>LOAEL</sub> = 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.

$$DWEL = \frac{RfD \times bw}{DWI}$$

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.

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

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  $\mu\text{g}/\text{mL}$ . 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. PPAR $\alpha$  knockout (KO) and 129S1/SvImJ 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 PPAR $\alpha$  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).<sup>5</sup> 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  $\mu\text{g/mL}$  (Eriksen et al. 2009). Other studies that evaluated cancer risk for specific sites (e.g., prostate,

---

<sup>5</sup> 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 PPAR $\alpha$  agonism MOA could be responsible for observed liver tumors in animals. Several studies have demonstrated that PFOS can activate PPAR $\alpha$  (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  $8.1 \times 10^{-5}$  L/kg bw/day using the following equation:

$$CL = Vd \times (\ln 2 \div t_{1/2}) = 0.23 \text{ L/kg bw} \times (0.693 \div 1971 \text{ days}) = 0.000081 \text{ L/kg bw/day}$$

Where:

$$Vd = 0.23 \text{ L/kg}$$

$$\ln 2 = 0.693$$

$$t_{1/2} = 1971 \text{ days} (5.4 \text{ years} \times 365 \text{ days/year} = 1971 \text{ days})$$

Multiplying the derived average serum concentrations (in  $\mu\text{g/mL}$ ) for the NOAELs and LOAELs identified in the key animal studies by the clearance value predicts oral HEDs in  $\text{mg/kg/day}$  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 $\mu\text{g/mL}$	HED mg/kg/d	LOAEL mg/kg/d	LOAEL Av serum $\mu\text{g/mL}$	HED mg/kg/d
Seacat et al. (2003): male rat $\uparrow$ ALT, $\uparrow$ BUN	98	0.34	16.5	0.0013	1.33	64.6	0.0052
Luebker et al. (2005b): $\downarrow$ rat pup body weight	84	0.1	6.26	0.00051	0.4	25	0.002
Luebker et al. (2005a): $\downarrow$ rat pup body weight	63	None	None	None	0.4	19.9	0.0016
Luebker et al. (2005a): rat $\downarrow$ 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 ( $\uparrow$ motor activity; $\downarrow$ habituation)	41	0.3	10.4	0.00084	1.0	34.6	0.0028
Lau et al. (2003): $\downarrow$ rat pup survival; $\downarrow$ 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  $\mu\text{g/mL}$  (rat) to 19.9  $\mu\text{g/mL}$  (monkey). At the LOAEL, the average serum values range from 19.9  $\mu\text{g/mL}$  (rat) to 64.6  $\mu\text{g/mL}$  (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 in 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 <sub>H</sub>	UF <sub>A</sub>	UF <sub>L</sub>	UF <sub>S</sub>	UF <sub>D</sub>	UF <sub>total</sub>	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<sub>H</sub> = intra-individual uncertainty factor; UF<sub>A</sub> = interspecies uncertainty factor; UF<sub>S</sub> = subchronic to chronic uncertainty factor, UF<sub>L</sub> = LOAEL to NOAEL uncertainty factor; UF<sub>D</sub> = incomplete database uncertainty factor; UF<sub>total</sub> = 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<sub>H</sub> and 3 UF<sub>A</sub>) 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 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<sup>th</sup> 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.

$$DWEL = \frac{RfD \times bw}{DWI}$$

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

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; 90<sup>th</sup> 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:

$$\begin{aligned} \text{Lifetime HA} &= DWEL \times RSC \\ &= 0.00037 \text{ mg/L} \times 0.2 \\ &= 0.000074 \text{ mg/L (rounded to 0.00007 mg/L)} \\ &= 0.07 \text{ } \mu\text{g/L} \end{aligned}$$

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  $\mu\text{g/L}$  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 90<sup>th</sup> 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<sup>th</sup> percentile), intermediate (median values), and high (95<sup>th</sup> 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](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 adsorbability, a post-filter adsorber with a deeper bed is 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 (PPAR $\alpha$ ) 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](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.
- Beeson, 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. Bronson, 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 <sup>35</sup>S-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](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 offspring. *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 perfluorooctanesulfonic 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 Perfluorooctanoate sulfonate 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](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.
- Egghy, 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](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. Kärman, 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. Skakkebak, 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. Skakkebak, 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.
- Kärman, 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. Bureson, 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. Armstrong, B. Genser, K. Dhataria, 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-Escherichia 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](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 perfluorinated 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. *Determination 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 Fluorochemical 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. *Perfluorinated [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](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 PPAR $\alpha$ -null mice exposed to Perfluorooctane sulfonate reveals PPAR $\alpha$ -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.
- Schechter, 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.

- Seecat, 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](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. Seecat, and D.J. Waxman. 2004. Trans-activation of PPAR $\alpha$  and induction of PPAR $\alpha$  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. *PHYSROP 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.
- Takaacs, M.L., and B.D. Abbott. 2007. Activation of mouse and human peroxisome proliferator-activated receptors ( $\alpha$ , $\beta$ / $\delta$ ,  $\gamma$ ) 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](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](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](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](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](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](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](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. Perfluorooctane 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 Obstetrica Et Gynecologica Scandinavica* 92:32–32.
- Vestergaard, S., F. Nielsen, A.M. Andersson, N.H. Hjöllund, 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  $\beta$ -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 (PPAR $\alpha$ ) 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  $\gamma$ . *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<sup>+</sup>/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.

# **EXHIBIT C**

## The Third Unregulated Contaminant Monitoring Rule (UCMR 3): Data Summary, April 2016

EPA uses the Unregulated Contaminant Monitoring Rule (UCMR) program to collect data for contaminants suspected to be present in drinking water, but that do not have health-based standards set under the Safe Drinking Water Act (SDWA). Every five years EPA develops a new list of UCMR contaminants, largely based on the Contaminant Candidate List (CCL). The SDWA Amendments of 1996 provide for:

- Monitoring no more than 30 contaminants per 5-year cycle
- Monitoring only a representative sample of public water systems serving less than or equal to 10,000 people
- Storing analytical results in a National Contaminant Occurrence Database (NCOD)

This dataset represents the tenth NCOD release of analytical results for UCMR 3. Updates will occur approximately quarterly and additional reference material is available to assist with the assessment of the UCMR 3 data.

- Visit EPA's UCMR 3 website for more information
- Find information regarding many of the UCMR 3 contaminants (including a description of their use) on the CCL website

### UCMR 3 Data Considerations

This dataset is not complete. UCMR 3 monitoring occurred through December 2015, and data are expected to be reported to EPA through the summer of 2016. Data are added and possibly removed or updated over the course of this reporting cycle. These results are subject to change following further review by the analytical laboratory, the public water system, the State and EPA. If you wish to perform additional data analyses, EPA suggests you import each field into your choice of software as text. Some of the IDs can be misinterpreted as long integer field types when they actually contain alpha characters.

Data are presented as tab delimited text files, with field names included in the first row of each file and no text qualifier:

- Method-specific text files (UCMR3\_*MethodNumber*.txt, example UCMR3\_200\_8 for EPA method 200.8)
- Text file containing Disinfectant residual type (UCMR3\_DRT.txt)
- Text file containing the U.S. Postal Service Zip Code(s) for all areas served by a PWS (UCMR3\_ZipCodes.txt)
- Text file containing all UCMR 3 data to date (UCMR3\_All.txt)

Samples collected at the maximum residence time in the distribution system (MR) are required to be analyzed for metals (including chromium-6) and chlorate. Water systems monitoring for Method 300.1 (chlorate) report disinfectant types. In addition to reporting occurrence data for UCMR 3 target analytes, EPA tasked its small-system contract-support laboratories with reporting results for sec-butylbenzene, n-propylbenzene, tellurium, germanium and manganese. These additional unregulated analytes are within the scope of the methods already being performed for the UCMR analytes. Population categories are based on retail population as indicated by the Safe Drinking Water Information System (Federal) (SDWIS/FED) as of December 31, 2010.

## UCMR 3 Data Field Names and Definitions

Field Name	Definition
PWSID	Public Water System Identification Code, 9-character identification code (Begins with the standard 2-character postal State abbreviation or Region code, and the remaining seven numbers are unique to each PWS in the state)
PWSName	Name of the Public Water System (PWS)
Size	Size category of the PWS for UCMR, based on retail population as of December 31, 2010: S ( $\leq 10,000$ ), L ( $> 10,000$ )
FacilityID	Public Water System Facility Identification Code, 5-digit identification code
FacilityName	Name of the facility at the PWS
FacilityWaterType	Source of water at the facility: SW (surface water), GW (ground water), GU (ground water under the direct influence of surface water), MX (Any combination of: SW, GW and GU)
SamplePointID	Identification code for each sample point location in the PWS
SamplePointName	Name of the sample point for every sample point ID at a PWS
SamplePointType	Sampling Point Type Code: EP (entry point to the distribution system), MR (distribution system at maximum residence time)
AssociatedFacilityID	The facility ID of the associated MR
AssociatedSamplePointID	The sample point ID of the associated MR
Disinfectant Type	CLGA (Gaseous Chlorine), CLOF (Offsite Generated Hypochlorite, stored as liquid), CLON (Onsite Generated Hypochlorite, no storage), CAGC (Chloramine, formed from gaseous chlorine), CAOF (Chloramine, formed from offsite hypochlorite), CAON (Chloramine, formed from onsite hypochlorite), CLDO (Chlorine Dioxide), OZON (Ozone), ULVL (Ultraviolet Light), OTHD (All other types of disinfectant), NODU (No Disinfectant Used)
CollectionDate	Date of sample collection (month, day, year)
SampleID	Identification code for each sample, as defined by the laboratory
Contaminant	Unregulated contaminant being analyzed in UCMR 3
MRL	Minimum Reporting Level defined by UCMR 3

Field Name	Definition
MethodID	Identification code of the analytical method
AnalyticalResultsSign	Less than (<) the minimum reporting level (MRL) or equal to (=) a numeric value at or above the MRL
AnalyticalResultValue	Numeric value of the analytical result, null values represent less than MRL
SampleEventCode	Identification code for each sample event. Includes sample event one (SE1), sample event two (SE2), sample event three (SE3), and sample event four (SE4).
MonitoringRequirement	AM (Assessment Monitoring, List 1), SS (Screening Survey, List 2), PST (Pre-Screen Testing, List 3)
Region	EPA Region (States): 1 (CT, ME, MA, NH, RI, VT), 2 (NJ, NY, PR (Puerto Rico), VI (Virgin Islands)), 3 (DE, DC, MD, PA, VA, WV), 4 (AL, FL, GA, KY, MS, NC, SC, TN), 5 (IL, IN, MI, MN, OH, WI), 6 (AR, LA, NM, OK, TX), 7 (IA, KS, MO, NE), 8 (CO, MT, ND, SD, UT, WY), 9 (AZ, CA, HI, NV, AS (American Samoa), GU (Guam), MP (Northern Marianas Islands), NN (Navajo Nation)), 10 (AK, ID, OR, WA)
State	State abbreviation
ZipCode	U.S. Postal Service zip code(s) for all areas being served water by a PWS

# UCMR 3 Chemical Contaminants and Methods

Contaminant	Contaminant Full Name	CAS <sup>1</sup> Number	Method ID	Method Name	Monitoring Requirement
1,2,3-trichloropropane	1,2,3-trichloropropane	96-18-4	524.3	Volatile Organic Compounds	AM
1,3-butadiene	1,3-butadiene	106-99-0	524.3	Volatile Organic Compounds	AM
Chloromethane	methyl chloride	74-87-3	524.3	Volatile Organic Compounds	AM
1,1-dichloroethane	1,1-dichloroethane	75-34-3	524.3	Volatile Organic Compounds	AM
Bromomethane	methyl bromide	74-83-9	524.3	Volatile Organic Compounds	AM
HCFC-22	Chlorodifluoromethane	75-45-6	524.3	Volatile Organic Compounds	AM
Halon 1011	Bromochloromethane	74-97-5	524.3	Volatile Organic Compounds	AM
1,4-dioxane	1,4-dioxane	123-91-1	522	Synthetic Organic Compound	AM
Vanadium	Vanadium	7440-62-2	200.8	Metals	AM
Molybdenum	Molybdenum	7439-98-7	200.8	Metals	AM
Cobalt	Cobalt	7440-48-4	200.8	Metals	AM
Strontium	Strontium	7440-24-6	200.8	Metals	AM
Chromium	total chromium	N/A	200.8	Metals	AM
Chromium-6	chromium-6	18540-29-9	218.7	Chromium-6	AM
Chlorate	Chlorate	14866-68-3	300.1	Oxyhalide Anion	AM
PFOS	perfluorooctanesulfonic acid	1763-23-1	537	Perfluorinated Compounds	AM
PFOA	perfluorooctanoic acid	335-67-1	537	Perfluorinated Compounds	AM
PFNA	perfluorononanoic acid	375-95-1	537	Perfluorinated Compounds	AM
PFHxS	perfluorohexanesulfonic acid	355-46-4	537	Perfluorinated Compounds	AM
PFHpA	perfluoroheptanoic acid	375-85-9	537	Perfluorinated Compounds	AM
PFBS	perfluorobutanesulfonic acid	375-73-5	537	Perfluorinated Compounds	AM
17β-estradiol	estradiol	50-28-2	539	Hormones	SS
17α-ethynylestradiol	ethinyl estradiol	57-63-6	539	Hormones	SS
Estriol	16-α-hydroxyestradiol	50-27-1	539	Hormones	SS
Equilin	Equilin	474-86-2	539	Hormones	SS
Estrone	Estrone	53-16-7	539	Hormones	SS
Testosterone	testosterone	58-22-0	539	Hormones	SS
4-androstene-3,17-dione	4-androstene-3,17-dione	63-05-8	539	Hormones	SS

<sup>1</sup>Chemical Abstract Service

### UCMR 3 Microbiological Contaminants and Methods

Contaminant	Method ID	Method Name	Monitoring Requirement
Enteroviruses	EPA 1615A	Enterovirus cell culture	PST
Enteroviruses	EPA 1615B	Enterovirus RT-qPCR	PST
Noroviruses	EPA 1615C	Norovirus genogroup I with RT-qPCR primer set A	PST
Noroviruses	EPA 1615D	Norovirus genogroup I with RT-qPCR primer set B	PST
Noroviruses	EPA 1615E	Noroviruses genogroup II	PST
Total coliforms	SM 9223B	Colilert®	PST
E.coli	SM 9223B	Colilert®	PST
Enterococci	ASTM D6503-99	Enterolert®	PST
Aerobic spores	SM 9218	Aerobic endospores	PST
Somatic phage	EPA 1602	Bacteriophage	PST
Male specific phage	EPA 1602	Bacteriophage	PST

## UCMR 3 Reference Concentrations for Chemical Contaminants

Under the current cycle of the Unregulated Contaminant Monitoring Rule (UCMR 3) chemicals are being studied at levels that are often significantly below those in prior UCMR cycles. Importantly, UCMR 3 minimum reporting levels (MRLs) were established based on the capability of the analytical method, not based on a level established as “significant” or “harmful.” In fact, the UCMR 3 MRLs are often below current “health reference levels” (to the extent that HRLs have been established).

Results of UCMR 3 measurements should be interpreted accordingly. The detection of a UCMR 3 contaminant above the MRL does not represent cause for concern, in and of itself. Rather, the implications of the detection should be judged considering health effects information (which is often still under development or being refined for unregulated contaminants).

The intent of the following table is to identify draft UCMR reference concentrations, where possible, to provide context around the detection of a particular UCMR contaminant above the MRL. The draft reference concentration does not represent an “action level” (EPA requires no particular action<sup>1,2</sup> based simply on the fact that UCMR monitoring results exceed draft reference concentrations), nor should the draft reference concentration be interpreted as any indication of an Agency intent to establish a future drinking water regulation for the contaminant at this or any other level. Decisions as to whether or not to regulate the contaminant in drinking water will continue to be made following the Agency’s Regulatory Determination process. [Visit EPA’s Regulatory Determination website for more information.](#)

The following key principles guided the development of the table:

- (1) The reference concentrations are based on publically-available health information found in the following EPA resources: 2012 Drinking Water Standards and Health Advisories, the CCL 3 Contaminant Information Sheets, the Human Health Benchmark for Pesticides (HHBPs), the Integrated Information Risk System (IRIS), or the 2014 Preliminary Regulatory Determinations for Contaminants on CCL 3. The primary/secondary sources of health information vary with respect to scientific rigor from health assessment to single studies and are cited in the table.
- (2) If health information was available from more than one of the EPA resources listed above, the most recent health information was used for the draft reference concentrations.
- (3) Where both cancer and non-cancer draft reference concentrations existed, the lower (more conservative) of the two concentrations was used. For chemicals with reference concentrations based on a cancer endpoint, the table presents a range of values associated with  $10^{-6}$  to  $10^{-4}$  cancer risk. For chemicals with reference concentrations based on a non-cancer endpoint, the duration of exposure (short-term, intermediate/long-term, chronic) of the toxicity factor (e.g. Reference Dose) used as the basis for the reference concentration is shown.

Recognizing that additional health effects information will become available over time, EPA will periodically update the following table. Those attempting to assess UCMR occurrence data are encouraged to visit EPA’s website for the most recent information.

---

<sup>1</sup> Consumer Confidence Report (CCR) and Public Notification (PN) reporting requirements (see 40 CFR 141.153(d) and 141.207, respectively) apply to public water systems; CCR requires particular reporting based on measurements relative to the UCMR method reporting limits (MRLs) defined in 40 CFR 141.40.

<sup>2</sup>States may establish requirements for drinking water contaminants not yet regulated by EPA, and those requirements may be based on State-established levels that differ from EPA’s reference concentrations. Public Water Systems are responsible for being aware of and complying with their State’s requirements, if any.

Contaminant	MRL (µg/L)	Reference Concentration (µg/L)	Reference Concentration based on a Cancer Endpoint (Y/N)	EPA Reference(s)
Cobalt <sup>1</sup>	1	70	N (intermediate exposure)	<u>CCL 3 Contaminant Information Sheets</u>
Molybdenum <sup>2</sup>	1	40	N (chronic exposure)	<u>2012 Edition of the Health Advisories Table</u>
Strontium <sup>3</sup>	0.3	1,500	N (chronic exposure)	<u>Federal Register Notice for the Preliminary Regulatory Determinations for Contaminants on CCL 3</u>
Vanadium <sup>1,4</sup>	0.2	21	N (intermediate exposure)	<u>CCL 3 Contaminant Information Sheets</u>
Chromium (Total)	0.2	100	N (chronic exposure)	The MCL for the National Primary Drinking Water Regulation
Chromium-6 <sup>1</sup>	0.03	NA	-	-
Chlorate	20	210	N (chronic exposure)	<u>CCL 3 Contaminant Information Sheets</u>
1,4-dioxane <sup>5</sup>	0.07	0.35 to 35	Y	<u>2012 Edition of the Health Advisories Table</u>
1,1-dichloroethane <sup>5</sup>	0.03	6.14 to 614	Y	<u>CCL 3 Contaminant Information Sheets</u>
1,2,3-trichloropropane <sup>5,6,7</sup>	0.03	0.0004 to 0.04	Y	<u>2009 IRIS Assessment</u>

<sup>1</sup> The contaminant is on the IRIS 2012 Agenda for either a new assessment or an updated assessment (Federal Register Notice May 7, 2012).

<sup>2</sup> The 2012 Edition of the Health Advisories Table and the CCL 3 Contaminant Information Sheets (35 µg/L) have slightly different numbers due to rounding.

<sup>3</sup> The reference concentration has been updated based on the HRL cited in the preliminary regulatory determination for strontium [Docket No. EPA-HQ-OW-2012-0155].

<sup>4</sup> The ATSDR, 1992 used for the CCL 3 Contaminant Information Sheets is no longer publicly available and has been replaced by a new assessment (ATSDR, 2013).

The minimum risk level (RfD equivalent) was 0.003 mg/kg/day for minor renal effects in an animal study (ATSDR, 1992) compared to 0.01 mg/kg/day for lack of minor effects in blood pressure, body weight, and hematological parameters in a human study with a 12 week exposure (ATSDR, 2013).

<sup>5</sup> Reference Concentration range based on cancer risk of 10<sup>-6</sup> to 10<sup>-4</sup>.

<sup>6</sup> 10<sup>-6</sup> cancer risk < MRL < 10<sup>-4</sup> cancer risk.

<sup>7</sup> To derive the reference concentration, age dependent adjustment factors were applied to the IRIS oral slope factor of 30 per mg/kg-day (calculated using adult exposure data) to address presumed early-life susceptibility for this chemical (per EPA's Guidelines for Carcinogen Risk Assessment).

<b>Contaminant</b>	<b>MRL (µg/L)</b>	<b>Reference Concentration (µg/L)</b>	<b>Reference Concentration based on a Cancer Endpoint (Y/N)</b>	<b>EPA Reference(s)</b>
1,3-butadiene <sup>5,6</sup>	0.1	0.0103 to 1.03	Y	<u>CCL 3 Contaminant Information Sheets</u>
HCFC-22 (chlorodifluoromethane) <sup>8</sup>	0.08	NA	-	-
Chloromethane (methyl chloride) <sup>5</sup>	0.2	2.69 to 269	Y	<u>CCL 3 Contaminant Information Sheets</u>
Halon 1011 (bromochloromethane) <sup>9</sup>	0.06	90	N (chronic exposure)	<u>2012 Edition of the Health Advisories Table</u>
Bromomethane (methyl bromide)	0.2	140	N (chronic exposure)	<u>Human Health Benchmark for Pesticides (HHBPs)</u>
PFBS	0.09	NA	-	-
PFHpA	0.01	NA	-	-
PFHxS	0.03	NA	-	-
PFNA	0.02	NA	-	-
PFOS	0.04	0.07	N (chronic exposure)	<u>Health Advisory and Supporting Documentation for PFOS</u>
PFOA	0.02	0.07	N (chronic exposure)	<u>Health Advisory and Supporting Documentation for PFOA</u>
17α-ethynylestradiol (ethinyl estradiol) <sup>10</sup>	0.0009	0.035	N (chronic exposure)	<u>CCL 3 Contaminant Information Sheets</u>
17β-estradiol (estradiol) <sup>5</sup>	0.0004	0.0009 to 0.09	Y	<u>CCL 3 Contaminant Information Sheets</u>

<sup>8</sup> The CCL 3 Contaminant Information Sheets provide a reference level of 31.5 µg/L; the number is based on a single LOAEL from a 1983 study.

<sup>9</sup> The 2012 Edition of the Health Advisories Table and the CCL 3 Contaminant Information Sheets (70 µg/L) have slightly different numbers due to rounding.

<sup>10</sup> This corrects the CCL 3 Contaminant Information Sheet (originally listed as 0.28 µg/L).

<b>Contaminant</b>	<b>MRL (µg/L)</b>	<b>Reference Concentration (µg/L)</b>	<b>Reference Concentration based on a Cancer Endpoint (Y/N)</b>	<b>EPA Reference(s)</b>
Equilin	0.004	0.35	N (chronic exposure)	<u>CCL 3 Contaminant Information Sheets</u>
Estriol (16-α-hydroxyestradiol)	0.0008	0.35	N (chronic exposure)	<u>CCL 3 Contaminant Information Sheets</u>
Estrone	0.002	0.35	N (chronic exposure)	<u>CCL 3 Contaminant Information Sheets</u>
4-androstene-3,17-dione	0.0003	NA	-	-
Testosterone	0.0001	NA	-	-

## Terms

- a) UCMR Draft Reference Concentration = The reference concentrations are based on publically-available health information found in the following EPA resources: 2012 Drinking Water Standards and Health Advisories, the CCL 3 Contaminant Information Sheets, the Human Health Benchmark for Pesticides (HHBPs), or the 2014 Preliminary Regulatory Determinations for Contaminants on CCL 3. The primary/secondary sources of health information vary with respect to scientific rigor from health assessment to single studies. Many of the contaminants are currently under regulatory review or development and are subject to change as new health assessments are completed.
- b) MRL = UCMR Minimum Reporting Level. *[Note that the Agency for Toxic Substances & Disease Registry (ATSDR) uses the term "MRL" for a different purpose (i.e., to describe "Minimal Risk Levels"). The UCMR term and the ATSDR term have no relationship to each other.]*
- c) HRLs = Health Reference Levels. HRLs are not final determinations about the level of a contaminant in drinking water that is necessary to protect any particular population and are derived prior to development of a complete exposure assessment. HRLs are risk derived concentrations against which to evaluate the occurrence data to determine if contaminants occur at levels of potential public health concern.
- d) MCL = Maximum Contaminant Level. The highest level of a contaminant allowed in drinking water. MCLs are enforceable standards.
- e) Cancer Risk of  $10^{-6}$  to  $10^{-4}$  = the concentration of a contaminant in drinking water corresponding to an excess estimated lifetime cancer risk of one-in-a-million ( $1 \times 10^{-6}$ ) to one-in-ten-thousand ( $1 \times 10^{-4}$ ). The 2012 Drinking Water Standards and Health Advisories provide the cancer risk at  $1 \times 10^{-4}$ . The CCL 3 Contaminant Information Sheets provide the cancer risk at  $1 \times 10^{-6}$ .
- f) LOAEL = Lowest Observed Adverse Effect Level
- g) NA = Not Available
- h) Short-term = Typically refers to animal toxicological studies with an exposure duration of days to weeks.
- i) Intermediate/Longer-term = Typically refers to animal toxicological studies with an exposure duration of weeks to months.
- j) Chronic = Typically refers to animal toxicological studies with an exposure duration of months to years; representing a lifetime exposure in humans.

## References

- 2012 Drinking Water Standards and Health Advisories (<http://www.epa.gov/sites/production/files/2015-09/documents/dwstandards2012.pdf>)
- CCL 3 Contaminant Information Sheets (<http://www.epa.gov/sites/production/files/2014-05/documents/final-ccl-3-contaminant-information-sheets.pdf>)
- Human Health Benchmark for Pesticides (HHBPs) (<http://iaspub.epa.gov/apex/pesticides/f?p=HHBP:home>)
- Announcement of Preliminary Regulatory Determinations for Contaminants on the Third Drinking Water Contaminant Candidate List (<https://www.federalregister.gov/articles/2014/10/20/2014-24582/announcement-of-preliminary-regulatory-determinations-for-contaminants-on-the-third-drinking-water>)
- Integrated Risk Information System (IRIS) (<http://cfpub.epa.gov/ncea/iris2/atoz.cfm>)

# April 2016 UCMR 3 Data Summary for Chemical Contaminants

Contaminant	MRL (µg/L)	Reference Concentration (µg/L)	Total number of results	Number of results ≥MRL	Number of results >Reference Concentration	% of total results >Reference Concentration	Total number of PWSs with results	Number of PWSs with results ≥MRL	Number of PWSs with results >Reference Concentration	% of PWSs with results >Reference Concentration
1,2,3-trichloropropane	0.03	0.0004 / 0.04 <sup>1</sup>	35,931	249	249 / 191 <sup>1</sup>	0.7% / 0.5% <sup>1</sup>	4,850	64	64 / 53 <sup>1</sup>	1.3% / 1.1% <sup>1</sup>
1,3-butadiene	0.1	0.0103 / 1.03 <sup>1</sup>	35,931	1	1 / 0 <sup>1</sup>	0.003% / 0% <sup>1</sup>	4,850	1	1 / 0 <sup>1</sup>	0.02% / 0% <sup>1</sup>
Chloromethane	0.2	2.69 / 269 <sup>1</sup>	35,929	273	18 / 0 <sup>1</sup>	0.05% / 0% <sup>1</sup>	4,850	134	7 / 0 <sup>1</sup>	0.1% / 0% <sup>1</sup>
1,1-dichloroethane	0.03	6.14 / 614 <sup>1</sup>	35,929	821	1 / 0 <sup>1</sup>	0.003% / 0% <sup>1</sup>	4,850	239	1 / 0 <sup>1</sup>	0.02% / 0% <sup>1</sup>
Bromomethane	0.2	140	35,930	114	0	0%	4,850	49	0	0%
HCFC-22	0.08	NA	35,931	813	--	--	4,850	279	--	--
Halon 1011	0.06	90	35,930	632	0	0%	4,850	302	0	0%
1,4-dioxane	0.07	0.35 / 35 <sup>1</sup>	35,856	4,145	1,069 / 0 <sup>1</sup>	3% / 0% <sup>1</sup>	4,849	1,062	336 / 0 <sup>1</sup>	7% / 0% <sup>1</sup>
Vanadium	0.2	21	61,483	36,974	1,664	2.7%	4,862	3,579	161	3.3%
Molybdenum	1	40	61,490	24,950	145	0.2%	4,862	2,510	38	0.8%
Cobalt	1	70	61,484	822	3	0.005%	4,862	241	3	0.06%
Strontium	0.3	1,500	61,419	61,271	1,698	2.8%	4,862	4,862	278	5.7%
Chromium	0.2	100	61,414	31,159	1	0.002%	4,862	3,602	1	0.02%
Chromium-6	0.03	NA	61,392	46,411	--	--	4,862	4,343	--	--
Chlorate	20	210	61,298	33,733	9,547	15.6%	4,852	3,344	1,850	38.1%
PFOS	0.04	0.07	36,149	285	119	0.3%	4,864	94	46	0.9%
PFOA	0.02	0.07	36,148	354	31	0.09%	4,864	108	13	0.3%
PFNA	0.02	NA	36,150	19	--	--	4,864	14	--	--
PFHxS	0.03	NA	36,149	204	--	--	4,864	55	--	--
PFHpA	0.01	NA	36,150	231	--	--	4,864	84	--	--
PFBS	0.09	NA	36,150	18	--	--	4,864	8	--	--
17β-estradiol	0.0004	0.0009 / 0.09 <sup>1</sup>	11,322	3	1 / 0 <sup>1</sup>	0.009% / 0% <sup>1</sup>	1,186	1	1 / 0 <sup>1</sup>	0.08% / 0% <sup>1</sup>
17α-ethynylestradiol	0.0009	0.035	11,323	4	0	0%	1,186	4	0	0%
Estrilol	0.0008	0.35	11,323	2	0	0%	1,186	2	0	0%
Equilin	0.004	0.35	11,323	0	0	0%	1,186	0	0	0%
Estrone	0.002	0.35	11,323	0	0	0%	1,186	0	0	0%
Testosterone	0.0001	NA	11,322	65	--	--	1,186	58	--	--
4-androstene-3,17-dione	0.0003	NA	11,323	95	--	--	1,186	73	--	--

<sup>1</sup>Where two reference concentrations are listed, the first number is associated with a 10<sup>-6</sup> cancer risk; the second number is associated with a 10<sup>-4</sup> cancer risk. Where two results are presented the first number is associated with the first reference concentration; the second number is associated with the second reference concentration.

# April 2016 UCMR 3 Data Summary for Microbiological Contaminants

Contaminant	MRL	Unit	Total number of results	Number of results $\geq$ MRL	Total number of PWSs with results	Number of PWSs with results $\geq$ MRL
Aerobic spores	1	SFO <sup>1</sup> /100 mL <sup>2</sup>	1,004	304	793	251
E. coli	1	MPN <sup>3</sup> /100 mL	1,002	3	791	3
Enterococci	1	MPN/100 mL	1,001	41	792	41
Enteroviruses (cell culture)	0.002	MPN/L <sup>4</sup>	1,001	2	789	2
Enteroviruses (RT-qPCR <sup>5</sup> )	0.398	GC <sup>6</sup> /L	1,001	6	789	6
Male specific phage	1	PFU <sup>7</sup> /100 mL	986	14	781	14
Noroviruses GIA <sup>8</sup>	0.398	GC/L	1,001	4	789	4
Noroviruses GIB <sup>9</sup>	0.398	GC/L	1,001	2	789	2
Noroviruses GII <sup>10</sup>	0.398	GC/L	1,001	4	789	4
Somatic phage	1	PFU/100 mL	986	5	781	5
Total coliforms	1	MPN/100 mL	1,002	55	791	51

<sup>1</sup>SFO = Spore Forming Units

<sup>2</sup>mL = milliliters

<sup>3</sup>MPN = Most Probable Number

<sup>4</sup>L = liters

<sup>5</sup>RT-qPCR = Reverse Transcription-Polymerase Chain Reaction

<sup>6</sup>GC = Genomic Copies

<sup>7</sup>PFU = Plaque Forming Units

<sup>8</sup>Noroviruses GIA = qPCR analysis of Norovirus genogroup I with RT-qPCR primer set A

<sup>9</sup>Noroviruses GIB = qPCR analysis of Norovirus genogroup I with RT-qPCR primer set B

<sup>10</sup>Noroviruses GII = qPCR analysis of Norovirus genogroup II

## UCMR 3 Minimum Reporting Levels for Microbiological Contaminants

Under UCMR 3 microbe analytical results are reported as “below”, “at” or “above” MRL. UCMR 3 MRLs were established based on the capability of the analytical method.

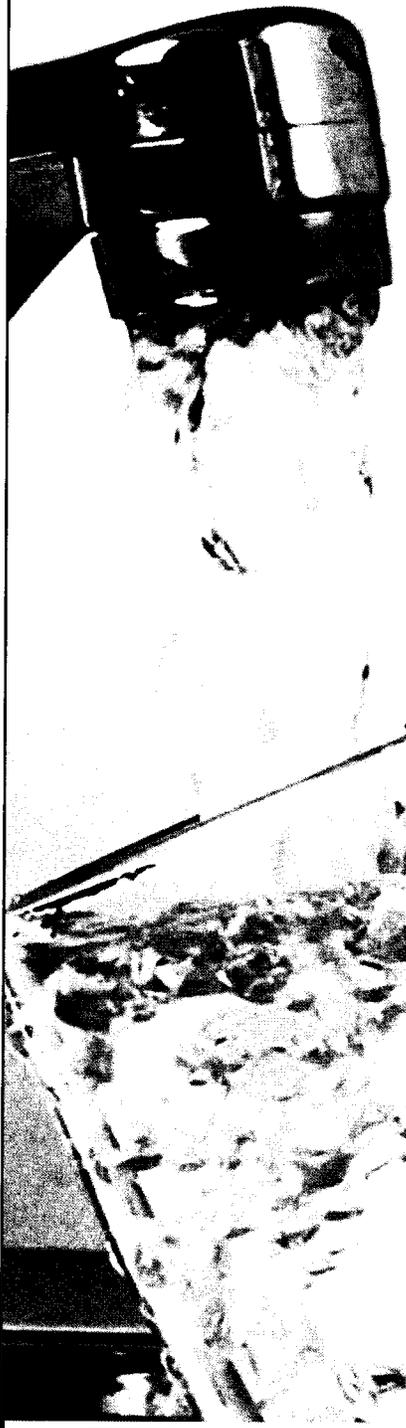
It is important to note that microbial contamination can be transient in nature and microbial detections under UCMR 3 should be interpreted in the context of the time samples were collected. However, the presence of any UCMR 3 microbe indicates a potential vulnerability of the PWS to contamination.

# **EXHIBIT D**



## FACT SHEET

# PFOA & PFOS Drinking Water Health Advisories



### Overview

EPA has established health advisories for PFOA and PFOS based on the agency's assessment of the latest peer-reviewed science to provide drinking water system operators, and state, tribal and local officials who have the primary responsibility for overseeing these systems, with information on the health risks of these chemicals, so they can take the appropriate actions to protect their residents. EPA is committed to supporting states and public water systems as they determine the appropriate steps to reduce exposure to PFOA and PFOS in drinking water. As science on health effects of these chemicals evolves, EPA will continue to evaluate new evidence.

### Background on PFOA and PFOS

PFOA and PFOS are fluorinated organic chemicals that are part of a larger group of chemicals referred to as perfluoroalkyl substances (PFASs). PFOA and PFOS have been the most extensively produced and studied of these chemicals. They have been used to make carpets, clothing, fabrics for furniture, paper packaging for food and other materials (e.g., cookware) that are resistant to water, grease or stains. They are also used for firefighting at airfields and in a number of industrial processes.

Because these chemicals have been used in an array of consumer products, most people have been exposed to them. Between 2000 and 2002, PFOS was voluntarily phased out of production in the U.S. by its primary manufacturer. In 2006, eight major companies voluntarily agreed to phase out their global production of PFOA and PFOA-related chemicals, although there are a limited number of ongoing uses. Scientists have found PFOA and PFOS in the blood of nearly all the people they tested, but these studies show that the levels of PFOA and PFOS in blood have been decreasing. While consumer products and food are a large source of exposure to these chemicals for most people, drinking water can be an additional source in the small percentage of communities where these chemicals have contaminated water supplies. Such contamination is typically localized and associated with a specific facility, for example, an industrial facility where these chemicals were produced or used to manufacture other products or an airfield at which they were used for firefighting.

### EPA's 2016 Lifetime Health Advisories

EPA develops health advisories to provide information on contaminants that can cause human health effects and are known or anticipated to occur in drinking water. EPA's health advisories are non-enforceable and non-regulatory and provide technical information to states agencies and other public health officials on health effects, analytical methodologies, and treatment technologies associated with drinking water contamination. In 2009, EPA published provisional health advisories for PFOA and PFOS based on the evidence available at that time. The science has evolved since then and EPA is now replacing the 2009 provisional advisories with new, lifetime health advisories.

# FACT SHEET

## PFOA & PFOS Drinking Water Health Advisories

### EPA's 2016 Lifetime Health Advisories, continued

To provide Americans, including the most sensitive populations, with a margin of protection from a lifetime of exposure to PFOA and PFOS from drinking water, EPA established the health advisory levels at 70 parts per trillion. When both PFOA and PFOS are found in drinking water, the combined concentrations of PFOA and PFOS should be compared with the 70 parts per trillion health advisory level. This health advisory level offers a margin of protection for all Americans throughout their life from adverse health effects resulting from exposure to PFOA and PFOS in drinking water.

#### *How the Health Advisories were developed*

EPA's health advisories are based on the best available peer-reviewed studies of the effects of PFOA and PFOS on laboratory animals (rats and mice) and were also informed by epidemiological studies of human populations that have been exposed to PFASs. These studies indicate that exposure to PFOA and PFOS over certain levels may result in adverse health effects, including developmental effects to fetuses during pregnancy or to breastfed infants (e.g., low birth weight, accelerated puberty, skeletal variations), cancer (e.g., testicular, kidney), liver effects (e.g., tissue damage), immune effects (e.g., antibody production and immunity), thyroid effects and other effects (e.g., cholesterol changes).

EPA's health advisory levels were calculated to offer a margin of protection against adverse health effects to the most sensitive populations: fetuses during pregnancy and breastfed infants. The health advisory levels are calculated based on the drinking water intake of lactating women, who drink more water than other people and can pass these chemicals along to nursing infants through breastmilk.

### Recommended Actions for Drinking Water Systems

#### *Steps to Assess Contamination*

If water sampling results confirm that drinking water contains PFOA and PFOS at individual or combined concentrations greater than 70 parts per trillion, water systems should quickly undertake additional sampling to assess the level, scope and localized source of contamination to inform next steps

#### *Steps to Inform*

If water sampling results confirm that drinking water contains PFOA and PFOS at individual or combined concentrations greater than 70 parts per trillion, water systems should promptly notify their State drinking water safety agency (or with EPA in jurisdictions for which EPA is the primary drinking water safety agency) and consult with the relevant agency on the best approach to conduct additional sampling.

Drinking water systems and public health officials should also promptly provide consumers with information about the levels of PFOA and PFOS in their drinking water. This notice should include specific information on the risks to fetuses during pregnancy and breastfed and formula-fed infants from exposure to drinking water with an individual or combined concentration of PFOA and PFOS above EPA's health advisory level of 70 parts per trillion. In addition, the notification should include actions they are taking and identify options that consumers may consider to reduce risk such as seeking an alternative drinking water source, or in the case of parents of formula-fed infants, using formula that does not require adding water.

# FACT SHEET

## PFOA & PFOS Drinking Water Health Advisories

### Recommended Actions for Drinking Water Systems, continued

#### *Steps to Limit Exposure*

A number of options are available to drinking water systems to lower concentrations of PFOA and PFOS in their drinking water supply. In some cases, drinking water systems can reduce concentrations of perfluoralkyl substances, including PFOA and PFOS, by closing contaminated wells or changing rates of blending of water sources. Alternatively, public water systems can treat source water with activated carbon or high pressure membrane systems (e.g., reverse osmosis) to remove PFOA and PFOS from drinking water. These treatment systems are used by some public water systems today, but should be carefully designed and maintained to ensure that they are effective for treating PFOA and PFOS. In some communities, entities have provided bottled water to consumers while steps to reduce or remove PFOA or PFOS from drinking water or to establish a new water supply are completed.

Home drinking water treatment units are typically certified by independent third party organizations against American National Standards Institute (ANSI) standards to verify their contaminant removal claims. Some home filters remove impurities using activated carbon and reverse osmosis, which are the same technologies utilized by public water supply systems to remove PFOA and PFOS. However, there currently are no ANSI protocols for testing home treatment systems to verify that these devices effectively remove PFOA and PFOS or how frequently the filters should be changed in order to maintain removal efficiency. NSF International is currently developing such protocols.

### Other Actions Relating to PFOA and PFOS

Between 2000 and 2002, PFOS was voluntarily phased out of production in the U.S. by its primary manufacturer, 3M. EPA also issued regulations to limit future manufacturing, including importation, of PFOS and its precursors, without first having EPA review the new use. A limited set of existing uses for PFOS (fire resistant aviation hydraulic fluids, photography and film products, photomicroolithography process to produce semiconductors, metal finishing and plating baths, component of an etchant) was excluded from these regulations because these uses were ongoing and alternatives were not available.

In 2006, EPA asked eight major companies to commit to working toward the elimination of their production and use of PFOA, and chemicals that degrade to PFOA, from emissions and products by the end of 2015. All eight companies have indicated that they have phased out PFOA, and chemicals that degrade to PFOA, from emissions and products by the end of 2015. Additionally, PFOA is included in EPA's proposed Toxic Substance Control Act's Significant New Use Rule (SNUR) issued in January 2015 which will ensure that EPA has an opportunity to review any efforts to reintroduce the chemical into the marketplace and take action, as necessary, to address potential concerns.

EPA has not established national primary drinking water regulations for PFOA and PFOS. EPA is evaluating PFOA and PFOS as drinking water contaminants in accordance with the process required by the Safe Drinking Water Act (SDWA). To regulate a contaminant under SDWA, EPA must find that it: (1) may have adverse health effects; (2) occurs frequently (or there is a substantial likelihood that it occurs frequently) at levels of public health concern; and (3) there is a meaningful opportunity for health risk reduction for people served by public water systems.

# FACT SHEET

## PFOA & PFOS Drinking Water Health Advisories

### Other Actions Relating to PFOA and PFOS, continued

EPA included PFOA and PFOS among the list of contaminants that water systems are required to monitor under the third Unregulated Contaminant Monitoring Rule (UCMR 3) in 2012. Results of this monitoring effort are updated regularly and can be found on the publicly-available National Contaminant Occurrence Database (NCOD) (<https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule#3>). In accordance with SDWA, EPA will consider the occurrence data from UCMR 3, along with the peer reviewed health effects assessments supporting the PFOA and PFOS Health Advisories, to make a regulatory determination on whether to initiate the process to develop a national primary drinking water regulation.

In addition, EPA plans to begin a separate effort to determine the range of PFAS for which an Integrated Risk Information System (IRIS) assessment is needed. The IRIS Program identifies and characterizes the health hazards of chemicals found in the environment. IRIS assessments inform the first two steps of the risk assessment process: hazard identification, and dose-response. As indicated in the 2015 IRIS Multi-Year Agenda, the IRIS Program will be working with other EPA offices to determine the range of PFAS compounds and the scope of assessment required to best meet Agency needs. More about this effort can be found at <https://www.epa.gov/iris/iris-agenda>.

### Where Can I Learn More?

- EPA's Drinking Water Health Advisories for PFOA and PFOS can be found at: <https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos>
- PFOA and PFOS data collected under EPA's Unregulated Contaminant Monitoring Rule are available: <https://www.epa.gov/dwucmr/occurrence-data-unregulated-contaminant-monitoring-rule>
- EPA's stewardship program for PFAS related to TSCA: <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/and-polyfluoroalkyl-substances-pfass-under-tsca>
- EPA's research activities on PFASs can be found at: <http://www.epa.gov/chemical-research/perfluorinated-chemical-pfc-research>
- The Centers for Disease Control and Prevention's Public Health Statement for PFASs can be found at: <http://www.atsdr.cdc.gov/phs/phs.asp?id=1115&tid=237>



# **EXHIBIT E**

## Todd Wiley

---

**From:** Daniel Czecholinski <Czecholinski.Daniel@azdeq.gov>  
**Sent:** Friday, May 20, 2016 2:45 PM  
**To:** Matthew Garlick  
**Cc:** Rick Rhoads; Todd Wiley  
**Subject:** RE: Meeting Verification

Mr. Garlick,

ADEQ agrees that the reasonable and prudent measures to resolve the PFOA and PFOS issue in the affected wells would be to remove the wells above 70 part per trillion (ppt) from service, blend the well to a level below 70 ppt and/or install treatment on the wells to reduce the PFOA and/or PFOS to less than 70 ppt. ADEQ agrees that taking action to reduce the PFOA and PFOS to less than the 70 ppt in the EPA health advisory and to inform the utilities customer's about the potential health effects are proactive measures to reassure the utilities' customers.

The health advisory that EPA issued on PFOA and PFOS is non-enforceable and non-regulatory and is based on the best available peer-reviewed studies.

If I can be of further assistance please do not hesitate to contact me.

Thanks,

Daniel Czecholinski, CHMM  
Manager  
Drinking Water Section  
Water Quality Division  
(602) 771-4617

**From:** Matthew Garlick [mailto:Matthew.Garlick@libertyutilities.com]  
**Sent:** Friday, May 20, 2016 8:03 AM  
**To:** Daniel Czecholinski <Czecholinski.Daniel@azdeq.gov>  
**Cc:** Rick Rhoads <Rick.Rhoads@libertyutilities.com>; Todd Wiley <Todd.Wiley@libertyutilities.com>  
**Subject:** Meeting Verification

Dear Mr. Czecholinski,

As you know, I am the President of Liberty Utilities (Litchfield Park Water & Sewer) Corp. Yesterday (May 19<sup>th</sup>), I attended the conference call conducted by EPA Region 9 to inform local municipalities and counties (Avondale, Glendale, Goodyear, Litchfield Park and Maricopa County) regarding a health advisory issued by relating to PFOA and PFOS. Specifically, EPA released drinking water health advisories regarding the health risks of PFOA and PFO, and advisories regarding appropriate steps to be taken by water providers to address PFOA and PFOS as necessary. EPA's assessment indicates that drinking water with individual or combined concentrations of PFOA and PFOS below 70 parts per trillion (PPT) is not expected to result in adverse health effects over a lifetime of exposure. You attended that conference call along with representatives of the various governmental entities and EPA.

During the call, I requested clarification from ADEQ on what wells need to be treated based on the newly released EPA Health Advisory for PFOA and PFOS. During that conversation, both you and EPA directed Liberty Utilities that all wells above 70 PPT will need to be (1) removed from service, (2) blended to a level below 70 PPT or (3) provided with a treatment technology to reduce concentrations of PFOA and PFOS below 70 PPT. Both you and EPA further stated the best and preferred method of treatment is granular activated carbon (GAC).

By this email, I am confirming that ADEQ and EPA have directed Liberty Utilities (Litchfield Park Water & Sewer) Corp. to remove wells above 70 PPT from service, blend wells to a level below 70 PPT as possible, and/or install GAC on wells above 70 PPT as reasonable, necessary and prudent measures to resolve the PFOA and PFOS issues on our wells.

Liberty Utilities (Litchfield Park Water & Sewer) Corp. intends to comply with that directive, and I simply ask that you acknowledge that directive by reply email.

Thanks for all your help.

Sincerely,

**Matthew Garlick | Liberty Utilities | President - Arizona**

P: 623-298-3763 | C: 602-757-2821 | F: 623-935-1020

E: [Matthew.Garlick@libertyutilities.com](mailto:Matthew.Garlick@libertyutilities.com)

12725 W Indian School Rd, Ste D101, Avondale, AZ 85392



## **CONFIDENTIALITY NOTICE**

The information contained in this e-mail and all attachments may contain privileged or confidential information. If you are not the intended recipient or received this communication by error, please notify the sender and delete the message and all attachments from your system without copying or disclosing it.

## **CONFIDENTIALITY NOTICE**

The information contained in this e-mail and all attachments may contain privileged or confidential information. If you are not the intended recipient or received this communication by error, please notify the sender and delete the message and all attachments from your system without copying or disclosing it.

---

NOTICE: This e-mail (and any attachments) may contain PRIVILEGED OR CONFIDENTIAL information and is intended only for the use of the specific individual(s) to whom it is addressed. It may contain information that is privileged and confidential under state and federal law. This information may be used or disclosed only in accordance with law, and you may be subject to penalties under law for improper use or further disclosure of the information in this e-mail and its attachments. If you have received this e-mail in error, please immediately notify the person named above by reply e-mail, and then delete the original e-mail. Thank you.

# **EXHIBIT F**

respondents into groups that align with the source categories identified in the rule.

Reporting facilities include, but are not limited to, those operating one or more units that exceed the CO<sub>2e</sub> threshold for the industry sectors listed in Table A-4 of 40 CFR 98.2(a)(2) or those in the categories in which all must report, such as petroleum refining facilities and all other large emitters listed in Table A-3 of 40 CFR 98.2(a)(1). Additionally, the GHGRP requires reporting of GHGs from certain suppliers as listed in Table A-5 of 40 CFR 98.2(a)(4) and of certain emissions information associated with mobile sources (e.g., for permit applications or emissions control certification testing procedures).

*Respondent's Obligation To Respond:* Mandatory (Sections 114 and 208 of the Clean Air Act provide EPA authority to require the information mandated by the Greenhouse Gas Reporting Program because such data will inform and are relevant to future policy decisions).

*Estimated Number of Respondents:* 11,080 (total).

*Frequency of Response:* Annual.

*Total Estimated Burden:* 739,187 hours (per year). Burden is defined at 5 CFR 1320.03(b).

*Total Estimated Cost:* \$99,831,931 per year, which includes \$30,621,791 for capital investment and operation and maintenance costs for respondents, labor cost of \$57,210,010 for respondents, and \$12,000,130 for the EPA.

*Changes in the Estimates:* This change in burden reflects an update in the number of respondents, an adjustment of labor rates to 2014 Bureau of Labor and Statistics (BLS) labor rates, an adjustment of capital costs to reflect 2013 dollars, a re-evaluation of the costs to monitor and report combustion emissions across the entire program, a re-evaluation of the activities and costs associated with Petroleum and Natural Gas Systems (Subpart W) and Geologic Sequestration of Carbon Dioxide (Subpart RR), and the addition of new segments and new reporters under Subpart W.

**Courtney Kerwin,**

*Acting Director, Collection Strategies Division.*

[FR Doc. 2016-12310 Filed 5-24-16; 8:45 am]

BILLING CODE 6560-50-P

## ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-OW-2014-0138; FRL-9946-91-OW]

### Lifetime Health Advisories and Health Effects Support Documents for Perfluorooctanoic Acid and Perfluorooctane Sulfonate

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Notice of availability.

**SUMMARY:** The Environmental Protection Agency (EPA) announces the release of lifetime health advisories (HAs) and health effects support documents for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS). EPA developed the HAs 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. EPA's HAs, which identify the concentration of PFOA and PFOS in drinking water at or below which adverse health effects are not anticipated to occur over a lifetime of exposure, are: 0.07 parts per billion (70 parts per trillion) for PFOA and PFOS. HAs are non-regulatory and reflect EPA's assessment of the best available peer-reviewed science. These HAs supersede EPA's 2009 provisional HAs for PFOA and PFOS.

**FOR FURTHER INFORMATION CONTACT:** Jamie Strong, Health and Ecological Criteria Division, Office of Water (Mail Code 4304T), Environmental Protection Agency, 1200 Pennsylvania Avenue NW., Washington, DC 20460; telephone number: (202) 566-0056; email address: [strong.jamie@epa.gov](mailto:strong.jamie@epa.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. General Information

*A. How can I get copies of this document and other related information?*

1. *Docket.* EPA has established a docket for this action under Docket ID No. EPA-HQ-OW-2014-0138. Publicly available docket materials are available either electronically through [www.regulations.gov](http://www.regulations.gov) or in hard copy at the Water Docket in the EPA Docket Center, (EPA/DC) EPA West, Room 3334, 1301 Constitution Ave. NW., Washington, DC. The EPA Docket Center Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday, excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the Water Docket is (202) 566-2426.

2. *Electronic Access.* You may access this Federal Register document electronically from the Government Printing Office under the "Federal Register" listings FDSys (<http://www.gpo.gov/fdsys/browse/collection.action?collectionCode=FR>).

## II. What are perfluorooctanoic acid and perfluorooctane sulfonate and why is EPA concerned about them?

PFOA and PFOS are fluorinated organic chemicals that are part of a larger group of chemicals referred to as perfluoroalkyl substances. They were used to make carpets, clothing, fabrics for furniture, paper packaging for food and other materials (e.g., cookware) that are resistant to water, grease or stains. They are also used for firefighting at airfields and in a number of industrial processes. Both PFOA and PFOS are persistent in the environment and in the human body. Over time both chemicals have become widely distributed in the environment and have accumulated in the blood of humans, wildlife, and fish. Studies indicate that exposure to PFOA and PFOS over certain levels may result in adverse health effects, including developmental effects to fetuses during pregnancy or to breast-fed infants (e.g., low birth weight, accelerated puberty, skeletal variations), cancer (e.g., testicular, kidney), liver effects (e.g., tissue damage), immune effects (e.g., antibody production and immunity), and other effects (e.g., cholesterol changes).

## III. What are health advisories?

Under the Safe Drinking Water Act, EPA may publish HAs for contaminants that are not subject to any national primary drinking water regulation. SDWA section 1412(b)(1)(F). EPA develops HAs to provide information on the chemical and physical properties, occurrence and exposure, health effects, quantification of toxicological effects, other regulatory standards, analytical methods, and treatment technology for drinking water contaminants. HAs describe concentrations of drinking water contaminants at which adverse health effects are not anticipated to occur over specific exposure durations (e.g., one-day, ten-days, and a lifetime). HAs serve as informal technical guidance to assist federal, state and local officials, as well as managers of public or community water systems in protecting public health. They are not regulations and should not be construed as legally enforceable federal standards. HAs may change as new information becomes available.

#### IV. Information on the Drinking Water Health Advisories for PFOA and PFOS

EPA's HA levels, which identify the concentration of PFOA and PFOS in drinking water at or below which adverse health effects are not anticipated to occur over a lifetime of exposure, are: 0.07 parts per billion (70 parts per trillion) for PFOA and PFOS. Because these two chemicals cause similar types of adverse health effects, EPA recommends that when both PFOA and PFOS are found in drinking water the combined concentrations of PFOA and PFOS be compared with the 0.07 part per billion HA level.

EPA's lifetime HAs are based on peer-reviewed toxicological studies of exposure of animals to PFOA and PFOS, applying scientifically appropriate uncertainty factors. The development of the HAs was also informed by epidemiological studies of human populations that have been exposed to PFOA and PFOS. The HAs are set at levels that EPA concluded will not result in adverse developmental effects to fetuses during pregnancy or to breast-fed infants, who are the groups most sensitive to the potential harmful effects of PFOA and PFOS. EPA's analysis indicates that exposure to these same levels will not result in adverse health effects (including cancer and non-cancer) to the general population over a lifetime (or any shorter period) of exposure to these chemicals.

EPA's HAs for PFOA and PFOS are supported by peer-reviewed health effects support documents that summarize and analyze available peer-reviewed studies on toxicokinetics, human epidemiology, animal toxicity, and provide a cancer classification and a dose response assessment for noncancer effects. On February 28, 2014, EPA released draft versions of these health effects support documents for a 60-day public comment period and initiated a contractor-led, independent public panel peer review process (79 FR 11429). The peer review panel meeting occurred on August 21–22, 2014, and included seven experts in the following areas: Epidemiology, toxicology (liver, immune, neurological and reproductive and developmental effects), membrane transport, risk assessment, pharmacokinetic models, and mode-of-action for cancer and noncancer effects (79 FR 39386). Comments submitted to EPA's public docket during the 60-day public comment period were provided to the peer reviewers ahead of the meeting for their consideration. A peer review summary report and other supporting documents may be found at:

<http://www.regulations.gov> under the docket EPA–HQ–OW–2014–0138.

Dated: May 19, 2016.

**Joel Beauvais,**

*Deputy Assistant Administrator, Office of Water.*

[FR Doc. 2016–12361 Filed 5–24–16; 8:45 am]

BILLING CODE 6560–50–P

#### ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPP–2015–0021; FRL–9946–40]

#### Pesticide Product Registration; Receipt of Applications for New Active Ingredients

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Notice.

**SUMMARY:** EPA has received applications to register pesticide products containing active ingredients not included in any currently registered pesticide products. Pursuant to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA is hereby providing notice of receipt and opportunity to comment on these applications.

**DATES:** Comments must be received on or before June 24, 2016.

**ADDRESSES:** Submit your comments, identified by docket identification (ID) number and the File Symbol of interest as shown in the body of this document, by one of the following methods:

- *Federal eRulemaking Portal:* <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute.

- *Mail:* OPP Docket, Environmental Protection Agency Docket Center (EPA/DC), (28221T), 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001.

- *Hand Delivery:* To make special arrangements for hand delivery or delivery of boxed information, please follow the instructions at <http://www.epa.gov/dockets/contacts.html>.

Additional instructions on commenting or visiting the docket, along with more information about dockets generally, is available at <http://www.epa.gov/dockets>.

#### FOR FURTHER INFORMATION CONTACT:

Robert McNally, Biopesticides and Pollution Prevention Division (7511P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave. NW., Washington, DC 20460–0001; main telephone

number: (703) 305–7090; email address: [BPPDFRNotices@epa.gov](mailto:BPPDFRNotices@epa.gov).

#### SUPPLEMENTARY INFORMATION:

##### I. General Information

##### A. Does this action apply to me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

##### B. What should I consider as I prepare my comments for EPA?

1. *Submitting CBI.* Do not submit this information to EPA through [www.regulations.gov](http://www.regulations.gov) or email. Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD-ROM that you mail to EPA, mark the outside of the disk or CD-ROM as CBI and then identify electronically within the disk or CD-ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. Information so marked will not be disclosed except in accordance with procedures set forth in 40 CFR part 2.

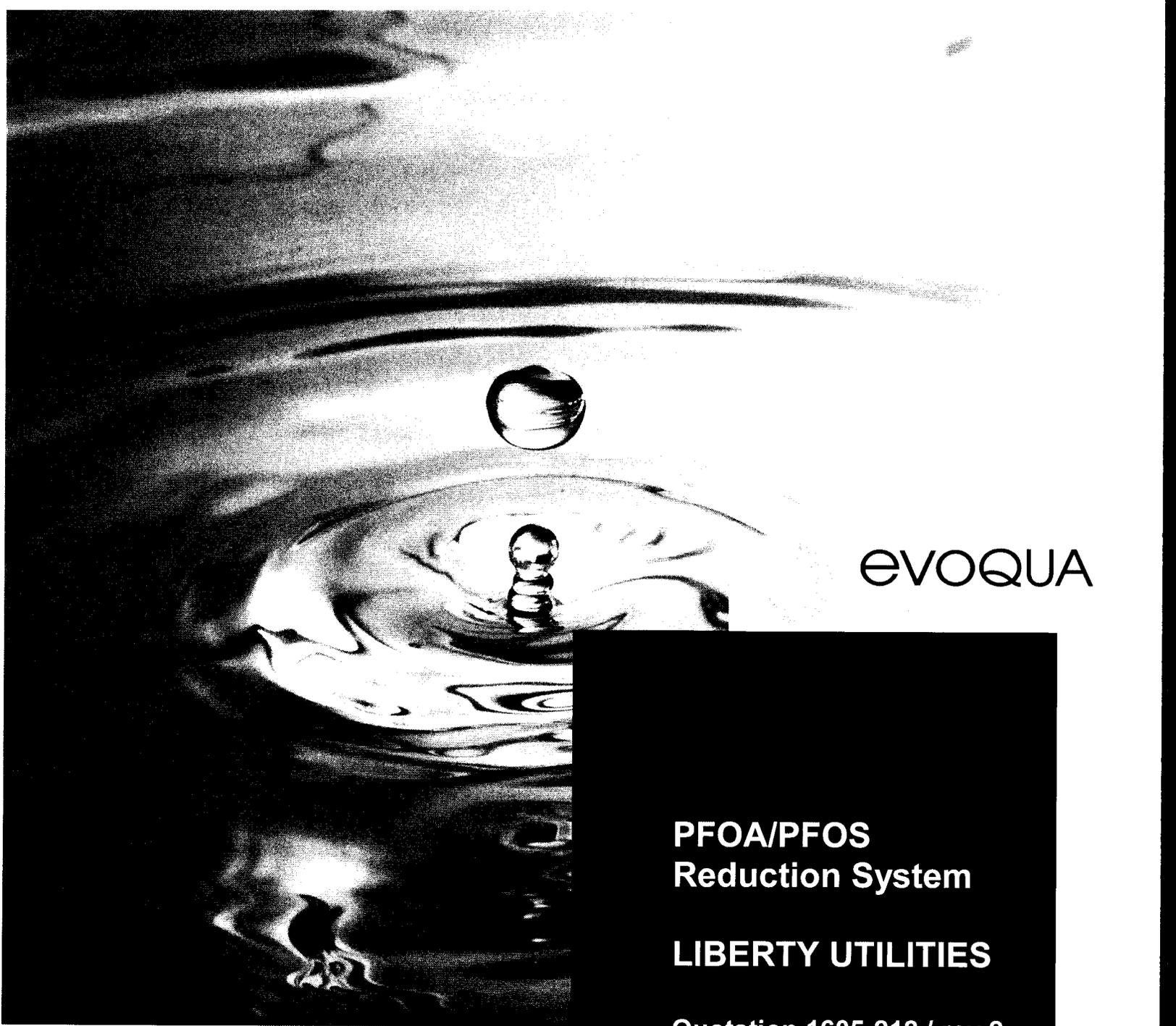
2. *Tips for preparing your comments.* When preparing and submitting your comments, see the commenting tips at <http://www.epa.gov/dockets/comments.html>.

##### II. Registration Applications

EPA has received applications to register pesticide products containing active ingredients not included in any currently registered pesticide products. Pursuant to the provisions of FIFRA section 3(c)(4) (7 U.S.C. 136a(c)(4)), EPA is hereby providing notice of receipt and opportunity to comment on these applications. Notice of receipt of these applications does not imply a decision by the Agency on these applications.

1. File Symbol: 91197–E. Docket ID number: EPA–HQ–OPP–2016–0251. Applicant: AFS009 Plant Protection,

# **EXHIBIT G**



eVOQUA

**PFOA/PFOS  
Reduction System**

**LIBERTY UTILITIES**

**Quotation 1605-212 / rev 2  
5/25/16**

### **Confidentiality Statement**

*This document and all information contained herein are the property of Evoqua Water Technologies LLC. The design concepts and information contained herein are proprietary to Evoqua Water Technologies LLC and are submitted in confidence. They are not transferable and must be used only for the purpose for which the document is expressly loaned. They must not be disclosed, reproduced, loaned or used in any other manner without the express written consent of Evoqua Water Technologies LLC. In no event shall they be used in any manner detrimental to the interest of Evoqua Water Technologies LLC. All patent rights are reserved. Upon the demand of Evoqua Water Technologies LLC, this document, along with all copies or extracts, and all related notes and analyses, must be returned to Evoqua Water Technologies LLC or destroyed, as instructed by Evoqua Water Technologies LLC. Acceptance of the delivery of this document constitutes agreement to these terms and conditions.*

### **Terms and Conditions**

*In the event Evoqua Water Technologies LLC is the selected vendor for the products and services contemplated in the subject bid, Evoqua Water Technologies LLC desires to negotiate a mutually agreeable set of terms and conditions to govern such transaction (including issues such as warranty, indemnity, appropriate limitations of liability and other substantive terms and conditions). Evoqua Water Technologies LLC will not be obligated to supply products or services pursuant to such bid unless and until the parties have entered into an agreement with terms and conditions mutually agreed in writing by the parties.*

5/20/16

Re: Potable Well Systems

Evoqua Water Technologies (Evoqua) is pleased to submit proposal in referenced to subject project.

### **DESIGN CRITERIA**

Reduce PFOA/PFOS reduction in two (2) municipal well locations in Goodyear, AZ. Well 2AL flows at 1,100 gpm and well 4AL flows at 1,000 gpm.

### **MAJOR LEASED COMPONENTS**

#### **LEASED HP1020 SYSTEM MOBILIZATION FOR SITE 4AL**

Pricing includes:

- HP1020 System includes two durable, carbon steel adsorbers with vinyl ester liners and an interconnecting piping manifold delivered to customer site. System to be operated in parallel (500/gpm per adsorber. 1,000 gpm total flow)
  - Rated for maximum of 750 gpm series/1,500 gpm parallel and 125 psig.
  - Inlet and outlet connections 8in 150lb flange. .
  - Each adsorber holds 20,000 lb of AC1230AWC carbon
  - Offload and installation of equipment on client provided pad
  - Disinfection of installed system
  - 40,000 lbs of AC1230AWC delivered and loaded into adsorbers onsite via slurry trailer.
  - Carbon soaking, backwashing, start-up and training by Evoqua
- *Customer is responsible for connection of Evoqua provided system to distribution*
- *Customer is responsible for providing clean water for carbon slurry (Evoqua to provide air).*
- *Customer is responsible for providing clean water for initial backwash and collection of backwash water.*

#### **LEASED HP1220 SYSTEM MOBILIZATION FOR SITE 2AL**

Pricing includes:

- HP1220 System includes two durable, carbon steel adsorbers with vinyl ester liners and an interconnecting piping manifold delivered to customer site. System to be operated in parallel (550/gpm per adsorber. 1,100 gpm total flow)
  - Rated for maximum of 1,100 gpm series/2,200 gpm parallel and 125 psig.
  - Inlet and outlet connections 8in 150lb flange. .
  - Each adsorber holds 20,000 lb of AC1230AWC carbon
  - Offload and installation of equipment on client provided pad
  - Disinfection of installed system
  - 40,000 lbs of AC1230AWC delivered and loaded into adsorbers onsite via slurry trailer.
  - Carbon soaking, backwashing, start-up and training by Evoqua
- *Customer is responsible for connection of Evoqua provided system to distribution*
- *Customer is responsible for providing clean water for carbon slurry (Evoqua to provide air).*

- *Customer is responsible for providing clean water for initial backwash and collection of backwash water.*
- **NOTE:** The carbon system proposed must be placed on a firm and level surface capable of supporting the weight of the system, including carbon and water (approx. 170,000 lb). Typically a concrete area, blacktop area covered with steel plates, compacted road gravel area covered with steel plates or crane mats is sufficient. See attached data on system leg configuration and operating weight. Failure to adequately support the system could result in system instability and failure.

**DEMOB TURNKEY**

Pricing includes:

- Freight to deliver slurry trailers to customer site.
- Removal of spent carbon via transfer into slurry trailer.
- Freight to deliver spent carbon to Evoqua reactivation facility.
- Reactivation of spent carbon.
- Disassembly and loading of equipment to pad
- Freight to return system to Evoqua.
- *Customer is responsible for providing water, and a dewatering area near the system (Evoqua to provide air).*

**SYSTEM PRICING**

<b><u>Mobilization Fee</u></b>	
<i>Supply and Delivery of rental equipment, carbon and services as described in proposal.</i>	<b>\$309,935</b>
<hr/>	
<b><u>Demobilization Fee</u></b>	
<i>Removal of carbon, rental equipment and services as described in proposal. Pricing assumes non-hazardous declaration of spent GAC</i>	<b>\$152,195</b>
<hr/>	
<b><u>Monthly Rental Fee</u></b>	
<i>Monthly rental fee. Please note that a minimum of three (3) month rental is required.</i>	<b>\$17,500 / month</b>

**Delivery**

- Shipment can occur within 2-10 days of receipt of approved purchase order
- Please note that all rental assets are subject availability at the time of order

**Prices Do Not Include The Following:**

- Permits
- Site preparation including developing a concrete pad, grouting, weather protection, etc.
- Foundation Design
- Anchor Bolts
- Please note: Evoqua excludes all other items not specifically identified in the proposal

**Also Please Note:**

- Proposal pricing valid for 30 days from date of proposal.

- Please note that rental equipment information is attached. Actual rental equipment may vary as these are leased assets vs. purchase. The functionality will remain the same. Rental equipment availability is dependent upon inventory at time of rental.
- All activities outside of scope will be provided on a time and material basis.
- Delivered pricing includes standard freight. Pricing is based on standard weekday service hours of 8 am - 5 pm. Weekend and after-hours callouts have a 4-hour minimum charge and time and a half rates.
- Demurrage hours due to customer operations, requests, or carbon condition will be bill ad an additional fee
- Pricing is contingent upon free flowing spent carbon that can be removed with Evoqua's slurry and reactivation equipment. If additional equipment is needed, additional fees will be applied.
- Onsite service pricing is contingent upon (1) service truck access within 25' of adsorber; (2) work being performed in level "C" or "D" PPE; (3) minimum manway opening of 4"; and (4) minimum overhead clearance of 4'.
- Evoqua Water Technologies LLC terms and conditions are attached hereto and are incorporated into this proposal by reference
- Evoqua has not considered any client specifications in the preparation of this proposal. Equipment quoted will be provided in complete accordance with Evoqua internal standards only.
- Terms of payment are net 30 days, 100% upon completion. Quoted terms are subject to credit approval.
- FOB factory, freight allowed to jobsite.
- Please note that no throughput or performance warranty is provided with this proposal.
- GAC exchanges are not included in this pricing and pricing can be made available as requested.
- Evoqua Water Technologies LLC's price does not include, and Evoqua Water Technologies LLC shall not be responsible for, any taxes, permits, tariffs, duties or fees (or any incremental increases to such taxes, permits, tariffs, duties or fees enacted by governmental agencies) unless specifically agreed herein or otherwise by Evoqua Water Technologies LLC in writing.
- All spent carbon returning for reactivation require a valid, approved spent carbon profile prior to scheduling the shipment. Prior to the initial spent carbon pickup, the spent carbon must be analyzed and an application submitted for approval. Once the profile is approved, the spent carbon can be scheduled for pickup. A new profile takes approximately 3 weeks to complete and has a one-time profile fee of:

RCRA Non-Hazardous or Sludge Exempt Spent Carbon	\$450
RCRA Hazardous Spent Carbon	\$750

If you have questions, please do not hesitate to contact me. We look forward to working with you now, and on future applications.

Sincerely,

Ben Buchsieb  
Territory Manager  
Evoqua Water Technologies LLC  
Environmental Services

## EVOQUA WATER TECHNOLOGIES LLC

### Standard Terms of Sale

1. **Applicable Terms.** These terms govern the purchase and sale of equipment, products, related services, leased products, and media goods if any (collectively herein "Work"), referred to in Seller's proposal ("Seller's Documentation"). Whether these terms are included in an offer or an acceptance by Seller, such offer or acceptance is expressly conditioned on Buyer's assent to these terms.
2. **Payment.** Buyer shall pay Seller the full purchase price as set forth in Seller's Documentation. Unless Seller's Documentation specifically provides otherwise, freight, storage, insurance and all taxes, levies, duties, tariffs, permits or license fees or other governmental charges relating to the Work or any incremental increases thereto shall be paid by Buyer. If Seller is required to pay any such charges, Buyer shall immediately reimburse Seller. If Buyer claims a tax or other exemption or direct payment permit, it shall provide Seller with a valid exemption certificate or permit and indemnify, defend and hold Seller harmless from any taxes, costs and penalties arising out of same. All payments are due within 30 days after receipt of invoice. Buyer shall be charged the lower of 1 ½% interest per month or the maximum legal rate on all amounts not received by the due date and shall pay all of Seller's reasonable costs (including attorneys' fees) of collecting amounts due but unpaid. All orders are subject to credit approval by Seller. Back charges without Seller's prior written approval shall not be accepted.
3. **Delivery.** Delivery of the Work shall be in material compliance with the schedule in Seller's Documentation. Unless Seller's Documentation provides otherwise, delivery terms are ExWorks Seller's factory (Incoterms 2010). Title to all Work shall pass upon receipt of payment for the Work under the respective invoice. Unless otherwise agreed to in writing by Seller, shipping dates are approximate only and Seller shall not be liable for any loss or expense (consequential or otherwise) incurred by Buyer or Buyer's customer if Seller fails to meet the specified delivery schedule.
4. **Ownership of Materials and Licenses.** All devices, designs (including drawings, plans and specifications), estimates, prices, notes, electronic data, software and other documents or information prepared or disclosed by Seller, and all related intellectual property rights, shall remain Seller's property. Seller grants Buyer a non-exclusive, non-transferable license to use any such material solely for Buyer's use of the Work. Buyer shall not disclose any such material to third parties without Seller's prior written consent.
5. **Changes.** Neither party shall implement any changes in the scope of Work described in Seller's Documentation without a mutually agreed upon change order. Any change to the scope of the Work, delivery schedule for the Work, any Force Majeure Event, any law, rule, regulation, order, code, standard or requirement which requires any change hereunder shall entitle Seller to an equitable adjustment in the price and time of performance.
6. **Force Majeure Event.** Neither Buyer nor Seller shall have any liability for any breach or delay (except for breach of payment obligations) caused by a Force Majeure Event. If a Force Majeure Event exceeds six (6) months in duration, the Seller shall have the right to terminate the Agreement without liability, upon fifteen (15) days written notice to Buyer, and shall be entitled to payment for work performed prior to the date of termination. "Force Majeure Event" shall mean events or circumstances that are beyond the affected party's control and could not reasonably have been easily avoided or overcome by the affected party and are not substantially attributable to the other party. Force Majeure Event may include, but is not limited to, the following circumstances or events: war, act of foreign enemies, terrorism, riot, strike, or lockout by persons other than by Seller or its sub-suppliers, natural catastrophes or (with respect to on-site work), unusual weather conditions.
7. **Warranty.** Subject to the following sentence, Seller warrants to Buyer that the (i) Work shall materially conform to the description in Seller's Documentation and shall be free from defects in material and workmanship and (ii) the Services shall be performed in a timely and workmanlike manner. Determination of suitability of treated water for any use by Buyer shall be the sole and exclusive responsibility of Buyer. The foregoing warranty shall not apply to any Work that is specified or otherwise demanded by Buyer and is not manufactured or selected by Seller, as to which (i) Seller hereby assigns to Buyer, to the extent assignable, any warranties made to Seller and (ii) Seller shall have no other liability to Buyer under warranty, tort or any other legal theory. The Seller warrants the Work, or any components thereof, through the earlier of (i) eighteen (18) months from delivery of the Work or (ii) twelve (12) months from initial operation of the Work or ninety (90) days from the performance of services (the "Warranty Period"). If Buyer gives Seller prompt written notice of breach of this warranty within the Warranty Period, Seller shall, at its sole option and as Buyer's sole and exclusive remedy, repair or replace the subject parts, re-perform the Service or refund the purchase price. Unless otherwise agreed to in writing by Seller, (i) Buyer shall be responsible for any labor required to gain access to the Work so that Seller can assess the available remedies and (ii) Buyer shall be responsible for all costs of installation of repaired or replaced Work. If Seller determines that any claimed breach is not, in fact, covered by this warranty, Buyer shall pay Seller its then customary charges for any repair or replacement made by Seller. Seller's warranty is conditioned on Buyer's (a) operating and maintaining the Work in accordance with Seller's instructions, (b) not making any unauthorized repairs or alterations, and (c) not being in default of any payment obligation to Seller. Seller's warranty does not cover (i) damage caused by chemical action or abrasive material, misuse or improper installation (unless installed by Seller) and (ii) media goods (such as, but not limited to, resin, membranes, or granular activated carbon media) once media goods are installed. THE WARRANTIES SET FORTH IN THIS SECTION 7 ARE THE SELLER'S SOLE AND EXCLUSIVE WARRANTIES AND ARE SUBJECT TO THE LIMITATION OF LIABILITY PROVISION BELOW. SELLER MAKES NO OTHER WARRANTIES OF ANY KIND, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION, ANY WARRANTY OF MERCHANTABILITY OR FITNESS FOR PURPOSE.
8. **Indemnity.** Seller shall indemnify, defend and hold Buyer harmless from any claim, cause of action or liability incurred by Buyer as a result of third party claims for personal injury, death or damage to tangible property, to the extent caused by Seller's negligence. Seller shall have the sole authority to direct the defense of and settle any indemnified claim. Seller's indemnification is conditioned on Buyer (a) promptly, within the Warranty Period, notifying Seller of any claim, and (b) providing reasonable cooperation in the defense of any claim.
9. **Assignment.** Neither party may assign this Agreement, in whole or in part, nor any rights or obligations hereunder without the prior written consent of the other party; provided, however, the Seller may assign its rights and obligations under these terms to its affiliates or in connection with

the sale or transfer of the Seller's business and Seller may grant a security interest in the Agreement and/or assign proceeds of the agreement without Buyer's consent.

10. **Termination.** Either party may terminate this agreement, upon issuance of a written notice of breach and a thirty (30) day cure period, for a material breach (including but not limited to, filing of bankruptcy, or failure to fulfill the material obligations of this agreement). If Buyer suspends an order without a change order for ninety (90) or more days, Seller may thereafter terminate this Agreement without liability, upon fifteen (15) days written notice to Buyer, and shall be entitled to payment for work performed, whether delivered or undelivered, prior to the date of termination.

11. **Dispute Resolution.** Seller and Buyer shall negotiate in good faith to resolve any dispute relating hereto. If, despite good faith efforts, the parties are unable to resolve a dispute or claim arising out of or relating to this Agreement or its breach, termination, enforcement, interpretation or validity, the parties will first seek to agree on a forum for mediation to be held in a mutually agreeable site. If the parties are unable to resolve the dispute through mediation, then any dispute, claim or controversy arising out of or relating to this Agreement or the breach, termination, enforcement, interpretation or validity thereof, including the determination of the scope or applicability of this agreement to arbitrate, shall be determined by arbitration in Pittsburgh, Pennsylvania before three arbitrators who are lawyers experienced in the discipline that is the subject of the dispute and shall be jointly selected by Seller and Buyer. The arbitration shall be administered by JAMS pursuant to its Comprehensive Arbitration Rules and Procedures. The Arbitrators shall issue a reasoned decision of a majority of the arbitrators, which shall be the decision of the panel. Judgment may be entered upon the arbitrators' decision in any court of competent jurisdiction. The substantially prevailing party as determined by the arbitrators shall be reimbursed by the other party for all costs, expenses and charges, including without limitation reasonable attorneys' fees, incurred by the prevailing party in connection with the arbitration. For any order shipped outside of the United States, any dispute shall be referred to and finally determined by the International Center for Dispute Resolution in accordance with the provisions of its International Arbitration Rules, enforceable under the New York Convention (Convention on the Recognition and Enforcement of Foreign Arbitral Awards) and the governing language shall be English.

12. **Export Compliance.** Buyer acknowledges that Seller is required to comply with applicable export laws and regulations relating to the sale, exportation, transfer, assignment, disposal and usage of the Work provided under this Agreement, including any export license requirements. Buyer agrees that such Work shall not at any time directly or indirectly be used, exported, sold, transferred, assigned or otherwise disposed of in a manner which will result in non-compliance with such applicable export laws and regulations. It shall be a condition of the continuing performance by Seller of its obligations hereunder that compliance with such export laws and regulations be maintained at all times. BUYER AGREES TO INDEMNIFY AND HOLD SELLER HARMLESS FROM ANY AND ALL COSTS, LIABILITIES, PENALTIES, SANCTIONS AND FINES RELATED TO NON-COMPLIANCE WITH APPLICABLE EXPORT LAWS AND REGULATIONS.

13. **LIMITATION OF LIABILITY.** NOTWITHSTANDING ANYTHING ELSE TO THE CONTRARY, SELLER SHALL NOT BE LIABLE FOR ANY CONSEQUENTIAL, INCIDENTAL, SPECIAL, PUNITIVE OR OTHER INDIRECT DAMAGES, AND SELLER'S TOTAL LIABILITY ARISING AT ANY TIME FROM THE SALE OR USE OF THE WORK, INCLUDING WITHOUT LIMITATION ANY LIABILITY FOR ALL WARRANTY CLAIMS OR FOR ANY BREACH OR FAILURE TO PERFORM ANY OBLIGATION UNDER THE CONTRACT, SHALL NOT EXCEED THE PURCHASE PRICE PAID FOR THE WORK. THESE LIMITATIONS APPLY WHETHER THE LIABILITY IS BASED ON CONTRACT, TORT, STRICT LIABILITY OR ANY OTHER THEORY.

14. **Rental Equipment / Services.** Any leased or rented equipment ("Leased Equipment") provided by Seller shall at all times be the property of Seller with the exception of certain miscellaneous installation materials purchased by the Buyer, and no right or property interest is transferred to the Buyer, except the right to use any such Leased Equipment as provided herein. Buyer agrees that it shall not pledge, lend, or create a security interest in, part with possession of, or relocate the Leased Equipment. Buyer shall be responsible to maintain the Leased Equipment in good and efficient working order. At the end of the initial three (3) month term specified in the order, the terms shall automatically renew on a month-to-month period basis unless canceled in writing by Buyer or Seller not sooner than one (1) month from termination of the initial order or any renewal terms. Upon any renewal, Seller shall have the right to issue notice of increased pricing which shall be effective for any renewed terms unless Buyer objects in writing within fifteen (15) days of issuance of said notice. If Buyer timely cancels service in writing prior to the end of the initial or any renewal term this shall not relieve Buyer of its obligations under the order for the monthly rental service charge which shall continue to be due and owing. Upon the expiration or termination of this Agreement, Buyer shall promptly make any Leased Equipment available to Seller for removal. Buyer hereby agrees that it shall grant Seller access to the Leased Equipment location and shall permit Seller to take possession of and remove the Leased Equipment without resort to legal process and hereby releases Seller from any claim or right of action for trespass or damages caused by reason of such entry and removal.

15. **Miscellaneous.** These terms, together with any Contract Documents issued or signed by the Seller, comprise the complete and exclusive statement of the agreement between the parties (the "Agreement") and supersede any terms contained in Buyer's documents, unless separately signed by Seller. No part of the Agreement may be changed or cancelled except by a written document signed by Seller and Buyer. No course of dealing or performance, usage of trade or failure to enforce any term shall be used to modify the Agreement. To the extent the Agreement is considered a subcontract under Buyer's prime contract with an agency of the United States government, in case of Federal Acquisition Regulations (FARs) flow down terms, Seller will be in compliance with Section 44.403 of the FAR relating to commercial items and those additional clauses as specifically listed in 52.244-6, Subcontracts for Commercial Items (OCT 2014). If any of these terms is unenforceable, such term shall be limited only to the extent necessary to make it enforceable, and all other terms shall remain in full force and effect. The Agreement shall be governed by the laws of the Commonwealth of Pennsylvania without regard to its conflict of laws provisions. Both Buyer and Seller reject the applicability of the United Nations Convention on Contracts for the international sales of goods to the relationship between the parties and to all transactions arising from said relationship.

\*\*\*SIGNATURE PAGE FOLLOWS\*\*\*

IN WITNESS WHEREOF, the terms and conditions of this proposal are hereby accepted by both Buyer and Seller, who have caused this Agreement to be executed by the signatures of their duly authorized representatives below:

**EVOQUA WATER TECHNOLOGIES LLC (SELLER)**

NAME: \_\_\_\_\_

SIGNATURE: \_\_\_\_\_

TITLE: \_\_\_\_\_

DATE: \_\_\_\_\_

**LIBERTY UTILITIES (LITCHFIELD PARK WATER & SEWER) CORP.**

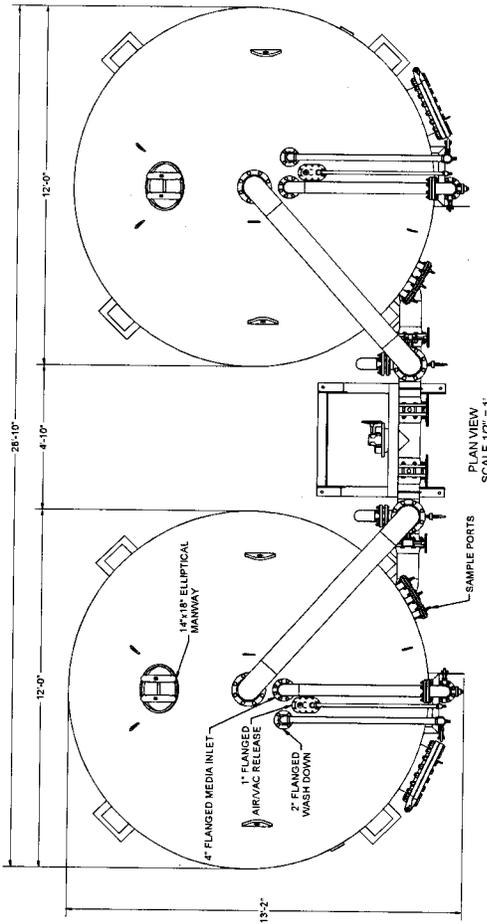
NAME: \_\_\_\_\_

SIGNATURE: \_\_\_\_\_

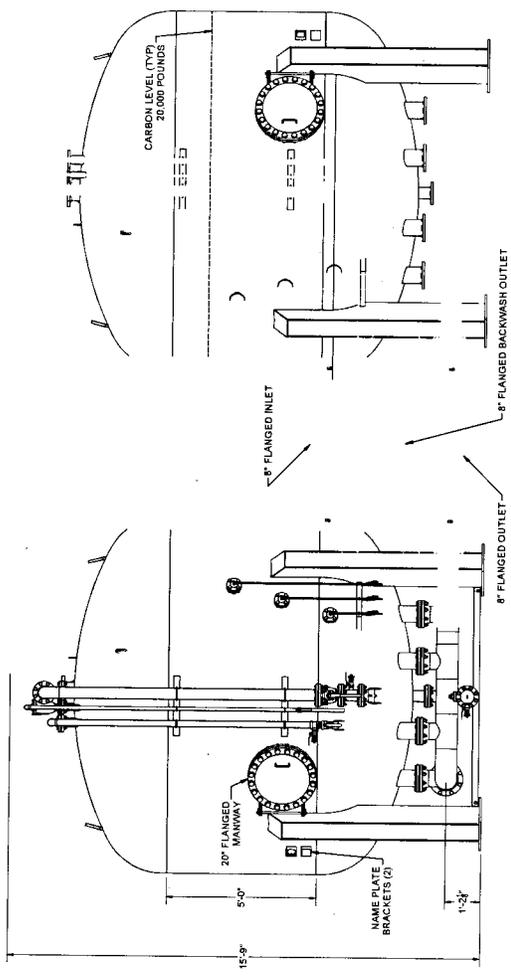
TITLE: \_\_\_\_\_

DATE: \_\_\_\_\_

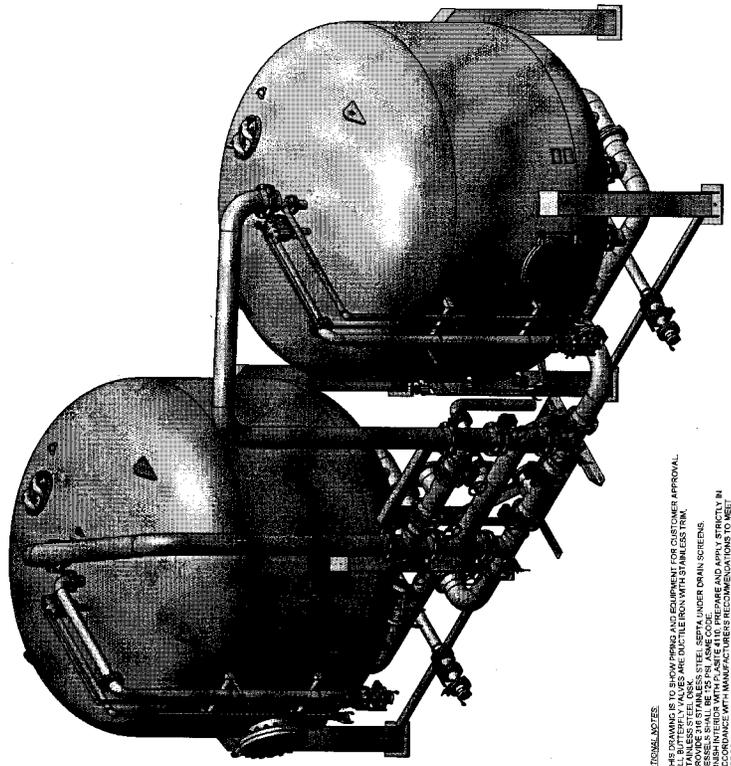




PLAN VIEW  
SCALE 1/2" = 1'

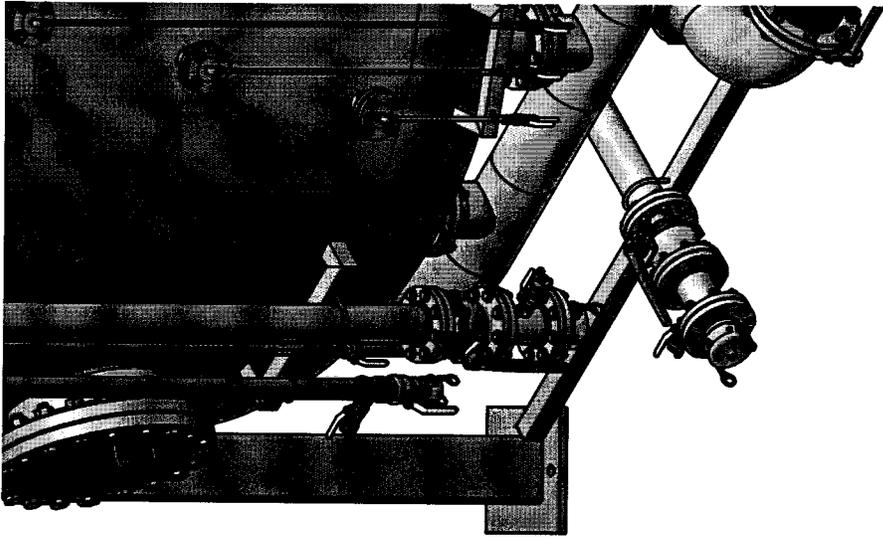


ELEVATION VIEW  
SCALE 1/2" = 1'

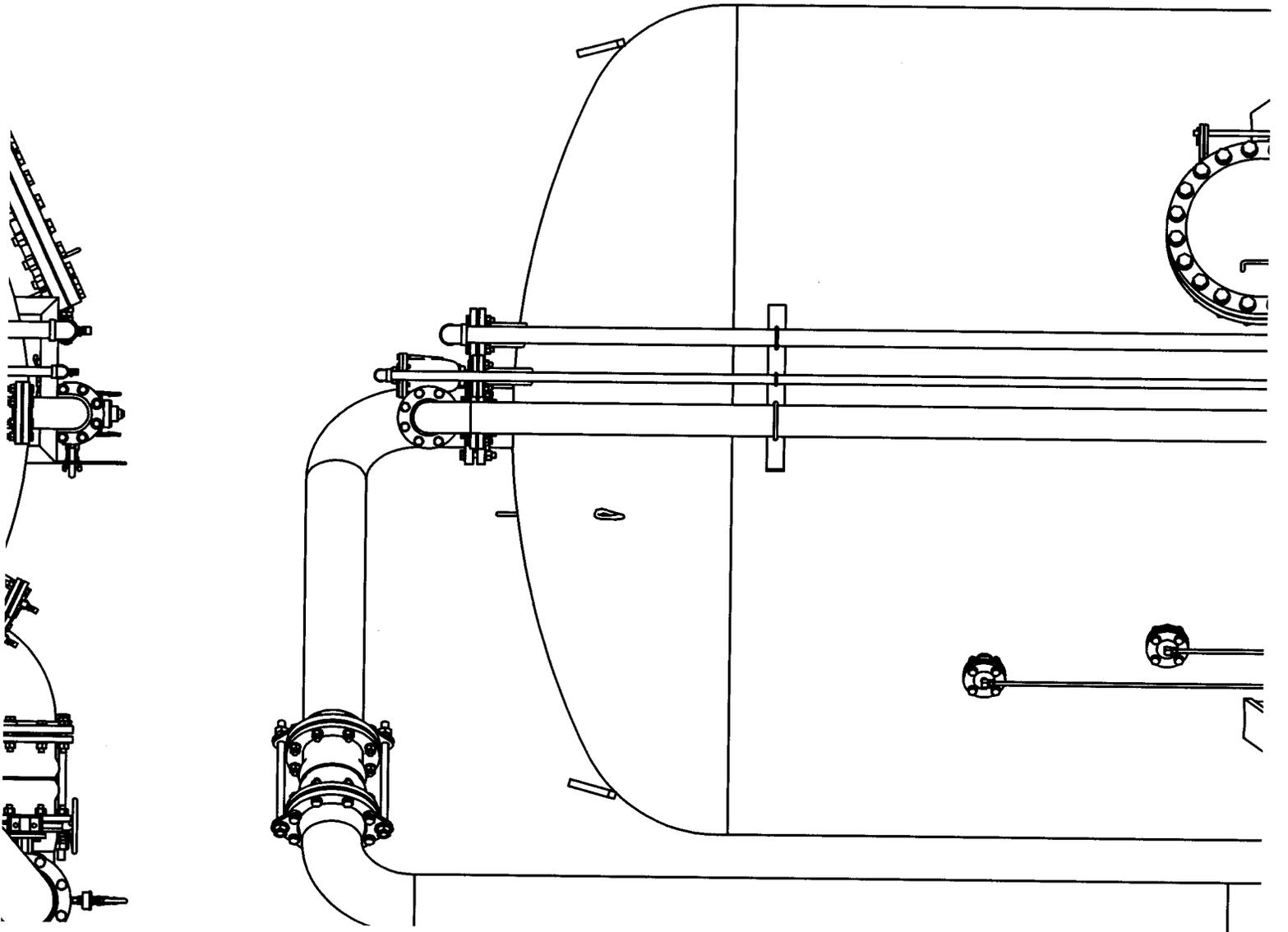


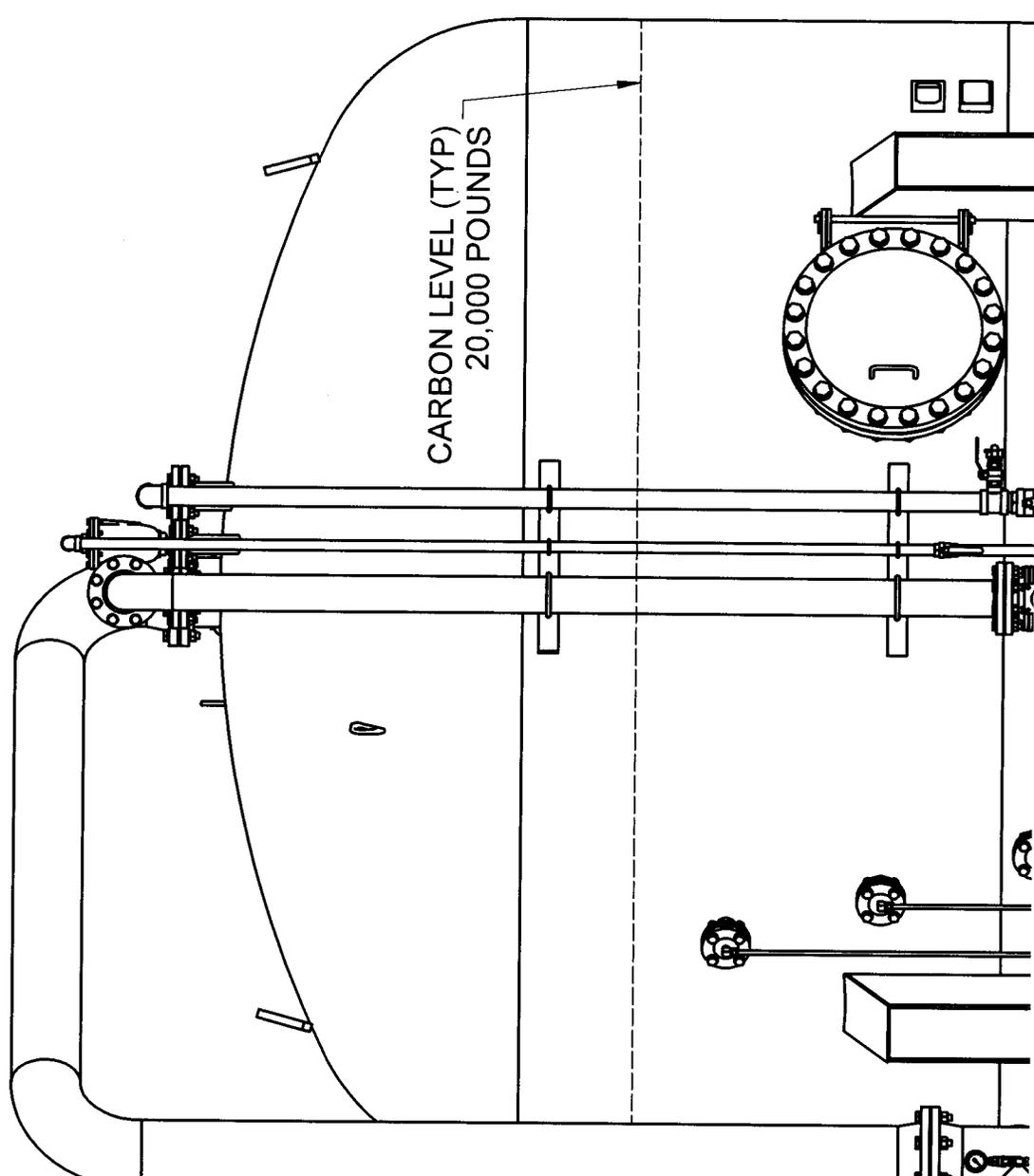
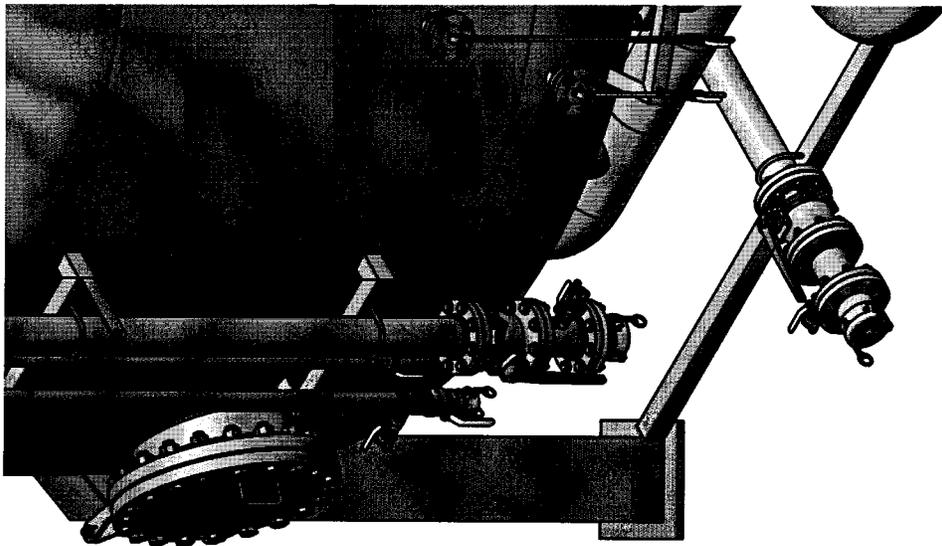
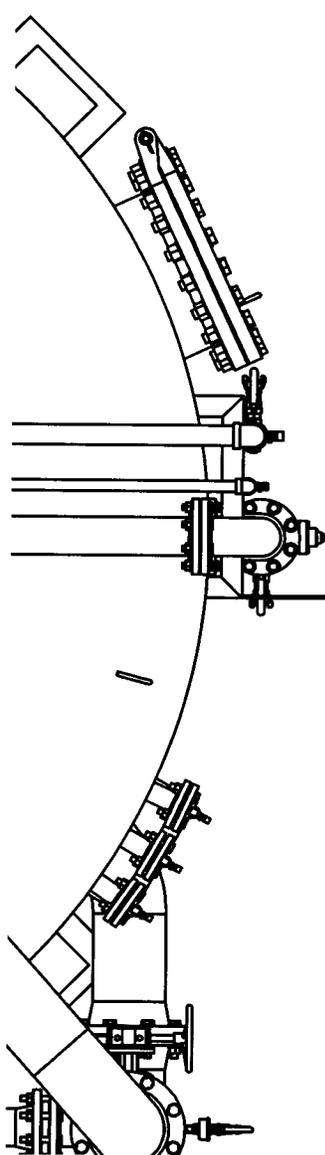
- ADDITIONAL NOTES:**
- 1) THIS DRAWING IS TO SHOW Piping AND EQUIPMENT FOR CUSTOMER APPROVAL.
  - 2) ALL VESSEL AND PIPING SHALL BE CONSTRUCTED OF 304 STAINLESS STEEL UNLESS OTHERWISE SPECIFIED.
  - 3) STAINLESS STEEL WELDS ARE TO BE MADE WITH STAINLESS STEEL WIRE.
  - 4) WELDS SHALL BE MADE UNDER DRY AIR OR ARGON GAS.
  - 5) FINISH INTERIOR WITH 316 SS POLISH AND APPLY PROTECTIVE COATING TO MEET USER'S REQUIREMENTS.
  - 6) FINISH EXTERIOR WITH 316 SS POLISH AND APPLY PROTECTIVE COATING TO MEET USER'S REQUIREMENTS.
  - 7) ALL FITTINGS SHALL BE 316 SS WITH 1/2" NPT CONNECTIONS.
  - 8) ALL FITTINGS SHALL BE 316 SS WITH 1/2" NPT CONNECTIONS.
  - 9) ALL FITTINGS SHALL BE 316 SS WITH 1/2" NPT CONNECTIONS.
  - 10) ALL FITTINGS SHALL BE 316 SS WITH 1/2" NPT CONNECTIONS.
  - 11) ALL FITTINGS SHALL BE 316 SS WITH 1/2" NPT CONNECTIONS.
  - 12) CENTER LINE CONNECTIONS IF 100# RF FLANGES BOLT STRADDLE.
  - 13) GROSS CAPACITY: 20,000 LBS PER VESSEL.
  - 14) NET WEIGHT: 10,000 LBS PER VESSEL.
  - 15) TYPICAL BACKWASH RATE (BASED ON 50% CARBON 50% AIR): 1000 GPM.
  - 16) TYPICAL BACKWASH RATE (BASED ON 50% CARBON 50% AIR): 1000 GPM.
  - 17) 1/2" TOLERANCE ON CONNECTION DIMENSIONS.

DESIGNER		DATE	TITLE	REV
AW	04/20/05		VESSEL 12FT 20K LB HP 12PSI SYS CS	0
CHECKER	DATE	CUSTOMER		
PKR/ELK				
DRAWN	DATE	PROJECT		
W/ST				
SCALE	1/2" = 1'	SALES		
NO. OF SHEETS	1	OF	1	
COMPANY CONTACT INFO				
1000 W. 10TH AVENUE SUITE 100 DENVER, CO 80202 TEL: 303.733.1111 FAX: 303.733.1112 WWW.EVOQUA.COM		<b>evoqua</b> WATER TECHNOLOGIES INDUSTRY, INC. 530-527-2664 530-527-2664 HP12PSI-SYS-CS		
STD. BORDER: 101.32X340	INT. REF.	BAR # 1 AT PLOT SCALE	DESCRIPTION	REV



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100





ADDITIONAL NOTES:



# eVOQUA

WATER TECHNOLOGIES

## **WESTATES® COCONUT SHELL BASED GRANULAR ACTIVATED CARBON — AQUACARB® 1230AWC AND 1240AWC CARBONS**

FOR USE IN POTABLE WATER, AND PROCESS WATER APPLICATIONS

### Description

AquaCarb® 1230AWC and 1240AWC carbons are high activity coconut shell based granular activated carbons. These hard, attrition resistant high surface area carbons are designed to remove difficult to adsorb organics from potable and process water. They are especially effective for adsorbing chlorine, disinfection by-products, TCE, PCE, MTBE and other trace level organics. These carbons are acid washed yielding a very low ash content, pH neutral carbon that is ideally suited for use in potable water and high purity water systems for the microelectronics and other industries.

### Applications

Cost effective AquaCarb activated carbons developed by Evoqua have been demonstrated to provide superior performance in an extensive array of liquid phase treatment applications. AquaCarb activated carbons are available for:

- Removal of trace organic contaminants
- Pesticide removal
- MTBE removal
- Disinfection by-product (DBP) removal
- Drinking water treatment
- Industrial process water treatment
- High purity water applications
- Home water filtration systems
- Bottling applications (soft drinks, bottled water)

### Quality Control

AquaCarb activated carbons are extensively quality checked at our State of California certified environmental and carbon testing laboratory located in Los Angeles, CA. Evoqua's laboratory is fully equipped to provide complete quality control analyses using ASTM standard test methods in order to assure the consistent quality of all Westates® carbons.

Our technical staff offers hands-on guidance in selecting the most appropriate system, operating conditions and carbon to meet your needs. For more information, contact your nearest Evoqua representative.

### Features and Benefits

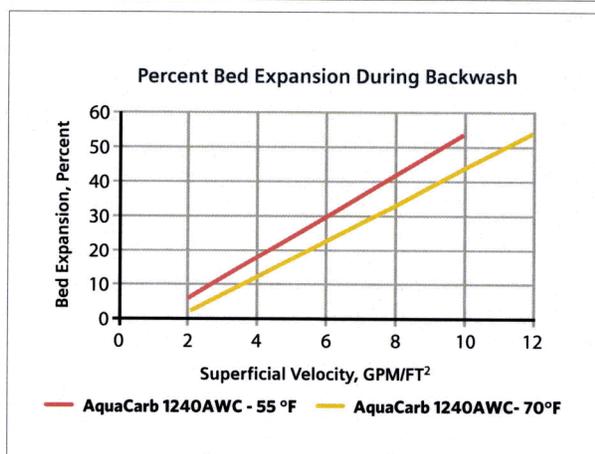
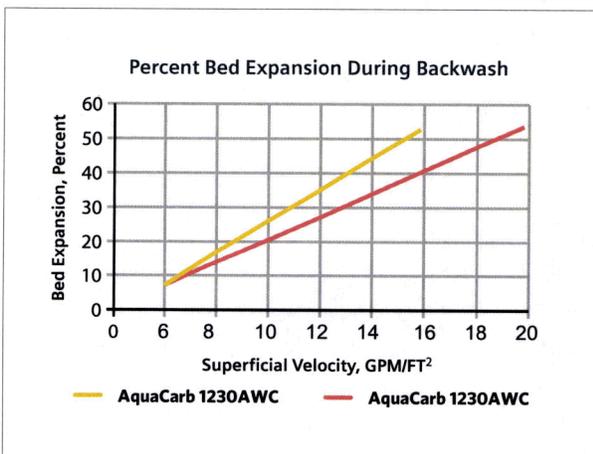
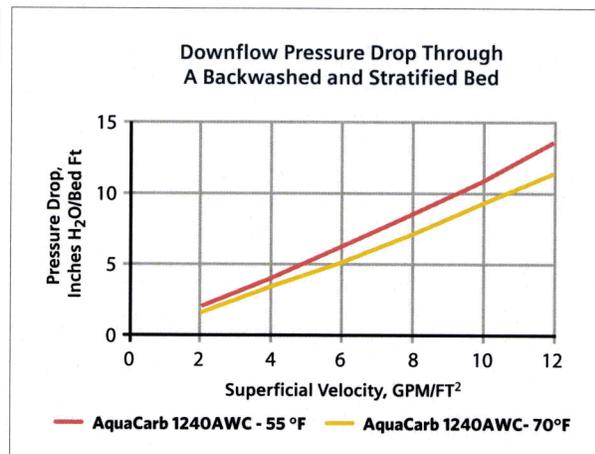
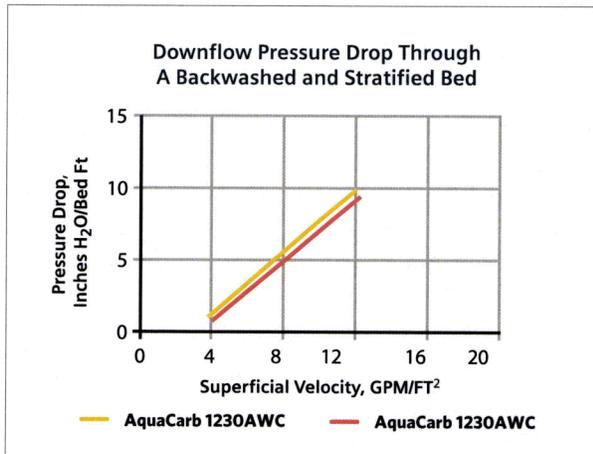
- ANSI/NSF Standard 61 classified for use in potable water applications
- Fully conforms to physical, performance and leachability requirements established by the current ANSI/AWWA B604 (which includes the Food Chemical Codex requirements)
- A detailed quality assurance program guarantees consistent quality from lot to lot and shipment to shipment

## TYPICAL PROPERTIES

PARAMETER	AQUACARB® 1230AWC	AQUACARB® 1240AWC
Carbon Type	Coconut Shell	Coconut Shell
Mesh Size, U.S. Sieve	12 x 30	12 x 40
Effective Size, mm	0.6-0.85	0.55-0.75
Uniformity Coefficient	2.0	1.9
Iodine No., mg I <sub>2</sub> /g	1100	1100
Hardness No., Wt. %	95	95
Abrasion No., Wt. %	85	85
Apparent Density, g/cc	0.45-0.52	0.45-0.52
Water Soluble Ash, Wt. %	0.2	0.2
Contact pH	6.5-8	6.5-8

**Safety Note:** Under certain conditions, some compounds may oxidize, decompose or polymerize in the presence of activated carbon causing a carbon bed temperature rise that is sufficient to cause ignition. Particular care must be exercised when compounds that have a peroxide-forming tendency are being adsorbed. In addition the adsorption of VOCs will lead to the generation of heat within a carbon bed. These heats of reaction and adsorption need to be properly dissipated in order to fully assure the safe operation of the bed.

Wet activated carbon readily adsorbs atmospheric oxygen. Dangerously low oxygen levels may exist in closed vessels or poorly ventilated storage areas. Workers should follow all applicable state and federal safety guidelines for entering oxygen depleted areas.



181 Thorn Hill Road, Warrendale, PA 15086

+1 (866) 926-8420 (toll-free)

+1 (978) 614-7233 (toll)

[www.evoqua.com](http://www.evoqua.com)

AquaCarb and Westates are trademarks of Evoqua, its subsidiaries or affiliates, in some countries.

All information presented herein is believed reliable and in accordance with accepted engineering practices. Evoqua makes no warranties as to the completeness of this information. Users are responsible for evaluating individual product suitability for specific applications. Evoqua assumes no liability whatsoever for any special, indirect or consequential damages arising from the sale, resale or misuse of its products.

© 2015 Evoqua Water Technologies LLC

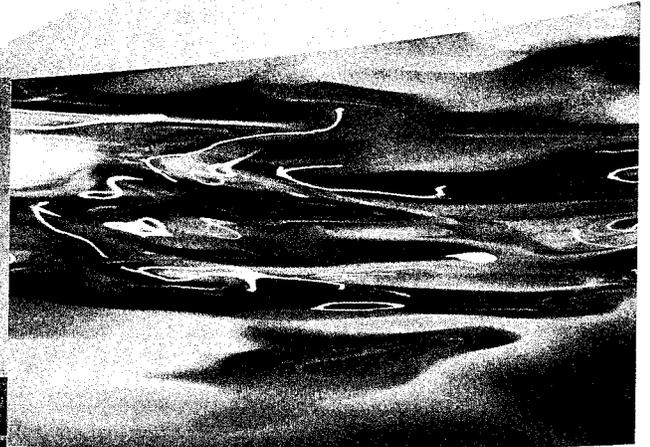
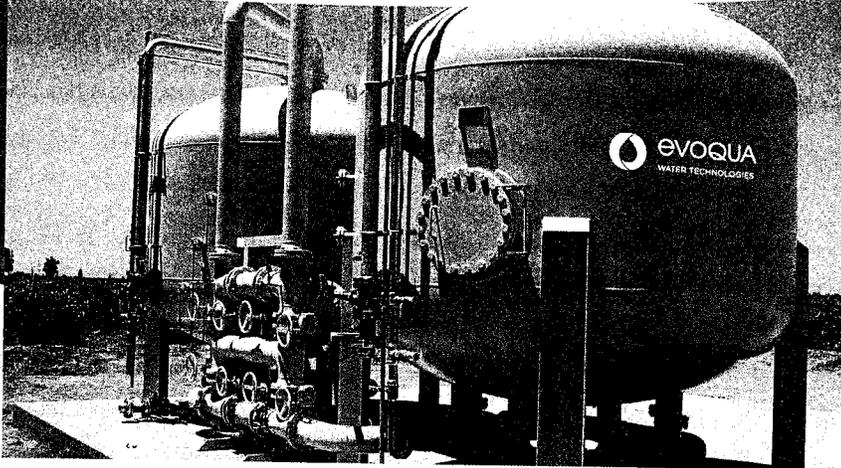
Subject to change without notice

WS-AQ1240-DS-0815



# evoqua

WATER TECHNOLOGIES



## HP® SERIES LIQUID PHASE ADSORPTION SYSTEMS (ASME CODE)

### Applications

The HP® Series Adsorption Systems are designed to remove dissolved organic contaminants from water. These systems are cost effectively used in applications including:

- Groundwater remediation
- Wastewater filtration
- Tank rinse water treatment
- Pilot testing
- Underground storage tank clean up
- Leachate treatment
- Dechlorination
- Spill cleanup
- Food grade
- Drinking water

### Installation, Startup and Operation

The HP 810, HP 1020 and HP 1220 systems are shipped as separate components—two adsorbers and a piping skid module. The piping module allows the adsorbers to operate in series or parallel configurations. The systems requires minimal field assembly and site connections.

Evoqua can provide a total service package that includes utilizing OSHA trained personnel providing on-site carbon changeouts, packaging and transportation of spent carbon for recycling at our RCRA permitted reactivation facilities, where the contaminants are thermally destroyed.

We can provide instructions on sampling the spent carbon and completion of our spent carbon profile form. Spent carbon acceptance testing can be performed at our certified laboratory. When requested, a certificate of reactivation will be issued.

### FEATURES AND BENEFITS

- ASME code section VIII (stamped), carbon steel vessel
- SSPC-SP5 surface preparation, NSF approved Plaste vinyl ester lining; rust preventative epoxy/urethane exterior
- Uniform, continuous internal lining flange to flange (HP 1020/1220 Systems)
- Proprietary vertical 316 stainless steel externally removable septa nozzles (HP 1020/1220 Systems) allows maintenance of underdrain without vessel entry
- Modular design for easy handling and installation
- Internal spray nozzle ensures complete removal of all spent carbon
- Schedule 40 carbon steel pipe, supplied with cast iron gear/wheel operated butterfly valves with EPDM seats
- Carbon slurry piping made from schedule 40 carbon steel
- In-bed water sample collection ports —25 - 50 - 75% bed depths
- Top and side manway allows for easy internal inspection

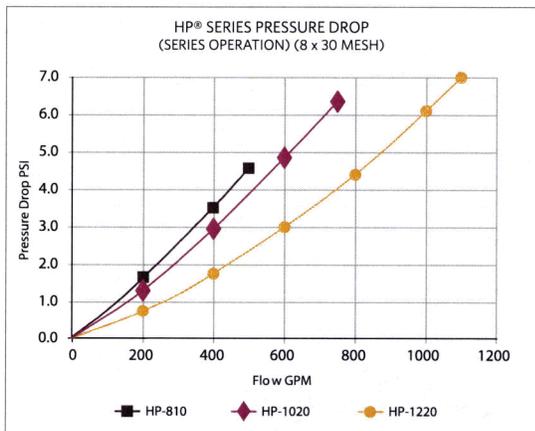
## SPECIFICATIONS/TYPICAL PROPERTIES

	HP® 810SYS	HP® 1020SYS	HP® 1220SYS
Dimensions (each adsorber - dia. x sidewall height)	96" x 84"	120" x 96"	144" x 60"
Overall Height	15' 2"	18' 2"	16' 4"
System Length	22' 8"	26' 10"	28' 10"
System Width	10'	11' 3"	13' 2"
Process Piping	6"	8"	8"
Flanged Inlet/Outlet (150# ANSI)	6"	8"	8"
Carbon Fill/Discharge	4"	4"	4"
Flanged Backwash/Vent	6"	8"	8"
Manway (dia., side shell location)	20"	20"	20"
Manway (top)	14" x 18"	14" x 18"	14" x 18"
Utility Water/Air (hose connection) <sup>①</sup>	2"	2"	2"
Interior Coating	Vinyl Ester	Vinyl Ester	Vinyl Ester
Exterior Coating	Urethane	Urethane	Urethane
Empty System Weight (lbs.)	15,500	34,000	35,000
Carbon Weight/Vessel (lbs.) <sup>②</sup>	10,000	20,000	20,000
Operating Weight (lbs.)	85,000	138,000	155,000
Design Pressure (PSIG) @ 140°F	125	125	125
Max. Flow (GPM) Series/Parallel	500/1,000	750/1,500	1,100/2,200
Backwash Rate (GPM) (8 x 30 mesh @ 55°F)	450	710	1,000

① Kamlock type

For detailed specifications or dimensional information or drawings, contact your local Evoqua sales representative.

② Weight of carbon based on density of 29.5 lb./ft<sup>3</sup>. Loaded weight can vary depending on actual density of GAC.



**Safety Note:** Wet activated carbon readily adsorbs atmospheric oxygen. Dangerously low oxygen levels may exist in closed vessels or poorly ventilated storage areas. Workers should follow all applicable state and federal safety guidelines for entering oxygen depleted areas.



4800 North Point Parkway, Suite 250, Alpharetta, GA 30022

+1 (866) 926-8420 (toll-free)

+1 (978) 614-7233 (toll)

[www.evoqua.com](http://www.evoqua.com)

HP is a trademark of Evoqua, its subsidiaries or affiliates, in some countries.

All information presented herein is believed reliable and in accordance with accepted engineering practices. Evoqua makes no warranties as to the completeness of this information. Users are responsible for evaluating individual product suitability for specific applications. Evoqua assumes no liability whatsoever for any special, indirect or consequential damages arising from the sale, resale or misuse of its products.

© 2014 Evoqua Water Technologies LLC

Subject to change without notice

WS-HP-DS-0614



CARBON REACTIVATION FACILITY

## CARBON REACTIVATION SERVICES

### A COST-EFFECTIVE, ENVIRONMENTALLY SAFE OPTION FOR ACTIVATED CARBON

In recent years, a variety of market dynamics have driven the cost of virgin activated carbon upward. These cost increases, coupled with a greater desire for "green" processes that minimize waste and recycle raw materials, have driven many activated carbon users to reconsider a tried and true process: carbon reactivation.

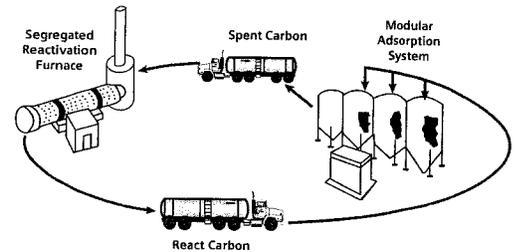
Carbon reactivation is the process of utilizing elevated temperatures followed by steam in a rotating kiln or multiple hearth furnace to remove organic compounds adsorbed onto the carbon during normal service use. Furthermore, reactivation destroys 99.99% of the removed organic contaminants through a combination of chemical reactions and oxidation in the reactivation plant's afterburner. The reactivation process thus ends the liability associated with disposing and handling of the adsorbed contaminants, while restoring the surface area and pore volume of the spent carbon to near virgin-grade levels.

The reactivation process recycles spent carbons into new activated carbon materials that continue to provide excellent performance in many treatment applications.

Reactivation can be applied to carbons used in both liquid phase and vapor phase applications. Spent carbons can be segregated from other spent carbons and returned to the same customer for reuse, or pooled with other spent carbons and sold into other applications as a cost-effective alternative to virgin carbon. Evoqua has extensive experience with all of these types of reactivation services.

### REACTIVATION FACILITIES

Evoqua operates three U.S.-based carbon reactivation facilities and is the only activated carbon services supplier with RCRA- permitted reactivation capacity serving both the East and West Coasts. All three facilities are ISO 14001 certified for environmental management. We have safely reactivated more than 600 million pounds of spent carbon over the past 25 years. Whether it be custom reactivation, pool reactivation, liquid phase applications, or vapor phase applications, Evoqua can cost-effectively handle your reactivation needs.



### Markets that Use Reactivated Carbon

- Municipalities (Drinking Water and Wastewater)
- Refineries
- Groundwater Remediation
- Environmental Cleanup
- Chemical Processing
- Power Plants

## SPENT CARBON REACTIVATION PROGRAMS

Evoqua reactivated carbon programs utilize our network of service technicians that are trained in performing carbon exchanges from both larger hard piped adsorber vessels by vacuum and slurry exchange and smaller adsorber vessels by direct vessel exchange.

**React and Return** is a highly controlled program where the customer's spent activated carbon is removed, reactivated, and returned for reuse to the same customer. The carbon is segregated from other carbons during reactivation and storage. Virgin carbon is used to offset normal losses that occur during handling and reactivation to ensure that 100% of the original carbon volume is returned to the customer. For react and return services provided for drinking water applications at our Darlington, PA and Red Bluff, CA facilities, the reactivated carbon is certified to ANSI / NSF Standard 61 for potable water treatment.

**Pool reactivation** is where spent carbons are removed and the resulting reactivated carbons are then pooled according to application type (vapor phase/liquid phase) and mesh size. These pooled carbons can then be sold into many applications as a substitute for virgin carbons to lower operating costs. Our pool reactivated carbons provided under this program are as follows:  
 AquaCarb® S Series - for non-potable, liquid phase applications  
 VOCarb® S Series - for vapor phase applications

## Additional Features and Benefits of Evoqua' Reactivation Programs

- Spent carbon sampling/profiling can be performed at our own certified environmental carbon testing laboratory
- Removal and packaging/labeling of spent carbon in D.O.T approved containers
- Transportation coordination of spent carbon to a Evoqua reactivation facility
- Inspection and maintenance of carbon adsorber vessels
- Rebedding - either virgin grade, custom reactivated carbon, or pool reactivated carbon
- A "Certificate of Reactivation" for each shipment confirming that the spent carbon has been recycled in a manner that meets or exceeds all applicable RCRA and Benzene NESHAP regulations.
- Reactivation facilities are ISO 14001 certified. ISO 14001 is part of a series of voluntary standards for environmental management tools and systems. As part of ISO 14001, our facilities all have Environmental Management Systems which ensure that our impact on the environment is minimized, that we continuously measure against best practice standards for environmental management, and that we are positioned to manage increasingly stringent environmental regulations.

## REACTIVATION FACILITIES OVERVIEW

Facility	Darlington, PA	Red Bluff, CA	Parker, AZ
In Operation Since	1989	1999	1992
Type of Furnace	Rotary Kiln	Rotary Kiln	Multiple Hearth
Number of Furnaces	5	1	1
Operation	24/7	24/7	24/7
Freight Access	Bulk Truck, Bulk Bag	Rail, Bulk Truck, Bulk Bag	Bulk Truck, Bulk Bag
Permitting	RCRA Permitted	Non-RCRA	RCRA Permitted
Custom Reactivation	Yes	Yes	No
Food Grade / Potable Reactivation	Yes*	Yes**	No
Environmental Controls	High Temperature Afterburner and Wet Scrubbing System		

\* Kiln operated in accordance with AWWA Standard B605-07 for reactivation of granular activated carbon and certified to ANSI / NSF Standard 61

\*\* Certified to ANSI / NSF Standard 61



181 Thorn Hill Road, Warrendale, PA 15086

+1 (866) 926-8420 (toll-free)

+1 (978) 614-7233 (toll)

[www.evoqua.com](http://www.evoqua.com)

AquaCarb and VOCarb are registered trademarks of Evoqua Water Technologies, its subsidiaries or affiliates, in some countries.

All information presented herein is believed reliable and in accordance with accepted engineering practices. Evoqua makes no warranties as to the completeness of this information. Users are responsible for evaluating individual product suitability for specific applications. Evoqua assumes no liability whatsoever for any special, indirect or consequential damages arising from the sale, resale or misuse of its products.



# eVOQUA

WATER TECHNOLOGIES

## ENVIRONMENTAL SERVICES

Evoqua Water Technologies offers a range of Environmental Services to remove organic and inorganic contaminants from groundwater, surface and process water, wastewater and air/vapor streams. Combining the strengths of trusted, industry-leading businesses and proven technologies, Environmental Services is uniquely positioned to meet the needs of municipal, industrial and government customers.

At Evoqua, providing our customers with high quality, reliable service is our priority. Our Environmental Services include a technical support staff of 12 applications engineers/process specialists, 14 applications engineers and greater than 50 dedicated Evoqua field service technicians. In broader terms, our branch service network is unmatched in North America, with over 85 local branches and 550 field technicians. This provides us with the ability to service greater than 85% of the North American population within 2 hours or less.

### Activated Carbon and Media

#### Medias for organic and inorganic removal

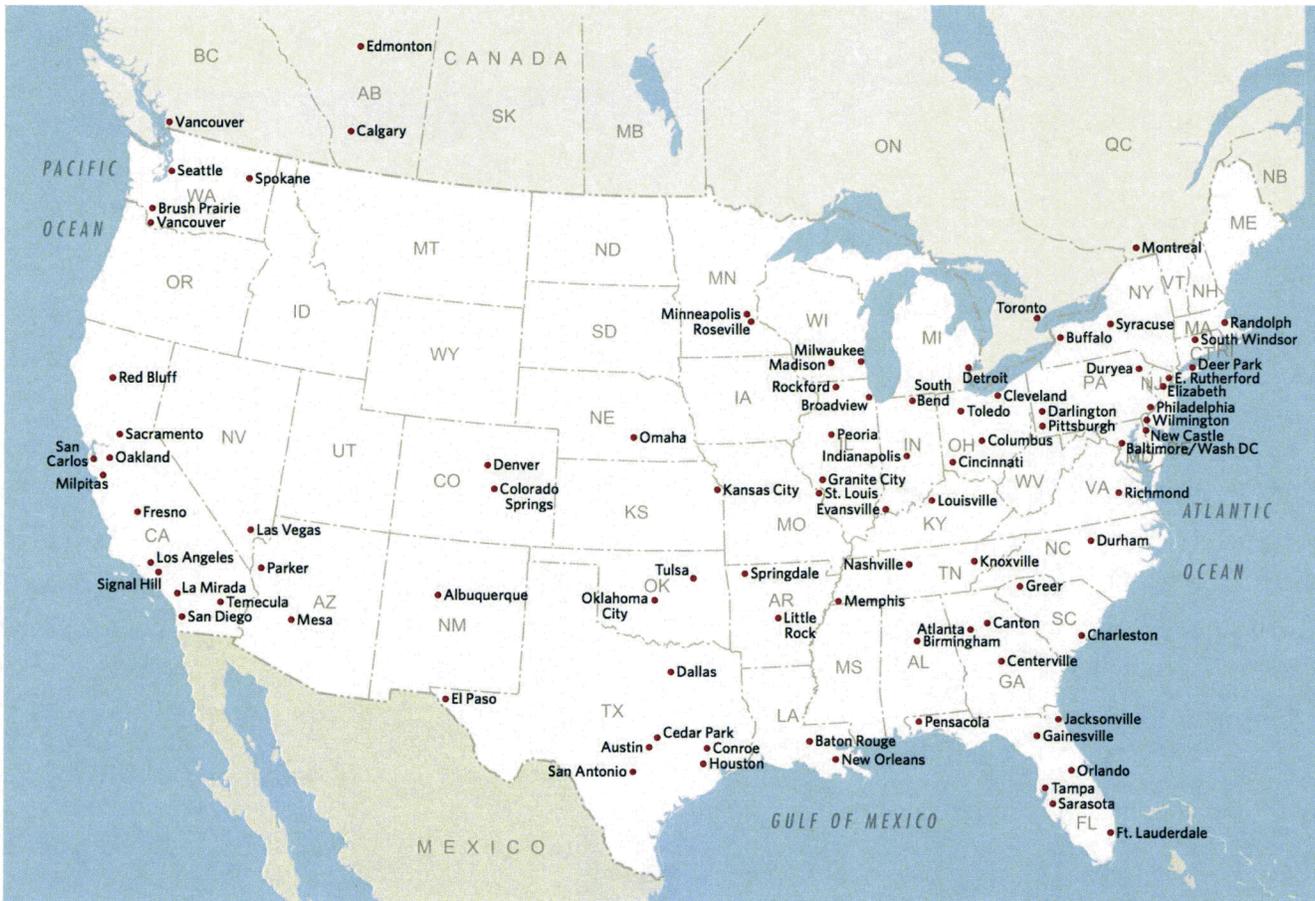
- AquaCarb® liquid phase carbons
- VOCarb® vapor phase carbons
- GFH® Granular Ferric Hydroxide
- Midas® OCM odor control carbon
- Ion exchange resins from all the leading manufacturers and our USF™ resin

### Carbon Filtration and Ion Exchange Systems

- Liquid phase adsorption systems  
Aqua-Scrub® Series, PV® Series, HP® Series, PG Series, LP Series
- Vapor Phase Adsorption System  
Vent-Scrub® Series, RB Series
- Wastewater ion exchange (WWIX) systems
- Aquasaver™ chemical feed and pump skids
- Mobile water treatment systems -Demineralization, Reverse Osmosis, Clarification, Filtration

### Services

- Laboratory and pilot testing
- OSHA trained, Evoqua Certified Field Service Technicians
- Media analysis and performance testing
- Media removal and replacement
- TCLP Analysis / RSSCT Test / Isotherm Testing
- Service and preventative maintenance contracts
- Benzene NESHAP Compliance
- Carbon reactivation and Regeneration Services (hazardous/non-hazardous)
- Engineering Design and Support
- Project Management Services
- Complete System Fabrication
- Installation Services (Class A Contractor in some states)
- Our services qualify for EPA Recycling Credits
- System decommissioning
- Short-term equipment rental and long-term equipment leasing
- Financial Services
- Build Own Operate



EVOQUA WATER TECHNOLOGIES NORTH AMERICA SERVICE NETWORK

Evoqua Water Technologies, has over 80 years of experience in the water treatment industry with over 200,000 customer installations supported by over 170 branches, plants, and factories worldwide. The company holds over 1,600 patents and offers over 900 products and technologies.

**SPECIAL PERMITS AND PROCESSING FACILITIES**

- (6) Analytical testing laboratories for pilot plant design, media capacity, water analysis
- (3) Manufacturing operations and engineering/construction of integrated systems
- (4) Engineering and mechanical design offices for applications, project management, custom engineering and design
- (3) RCRA-approved waste treatment facilities for CERCLA waste
- (3) Carbon reactivation plants, Authorized by the USEPA to process/treat CERCLA (Superfund) waste
- (12) Resin regeneration plants
- (1) Custom resin processing/blending facility



4800 North Point Parkway, Suite 250, Alpharetta, GA 30022  
 +1 (866) 926-8420 (toll-free) +1 (978) 614-7233 (toll) [www.evoqua.com](http://www.evoqua.com)

Aquasaver, Aqua-Scrub, Vent-Scrub, Midas, GFH, PV, HP, USF, AquaCarb and VOCarb are trademarks of Evoqua, its subsidiaries or affiliates, in some countries.

All information presented herein is believed reliable and in accordance with accepted engineering practices. Evoqua makes no warranties as to the completeness of this information. Users are responsible for evaluating individual product suitability for specific applications. Evoqua assumes no liability whatsoever for any special, indirect or consequential damages arising from the sale, resale or misuse of its products.