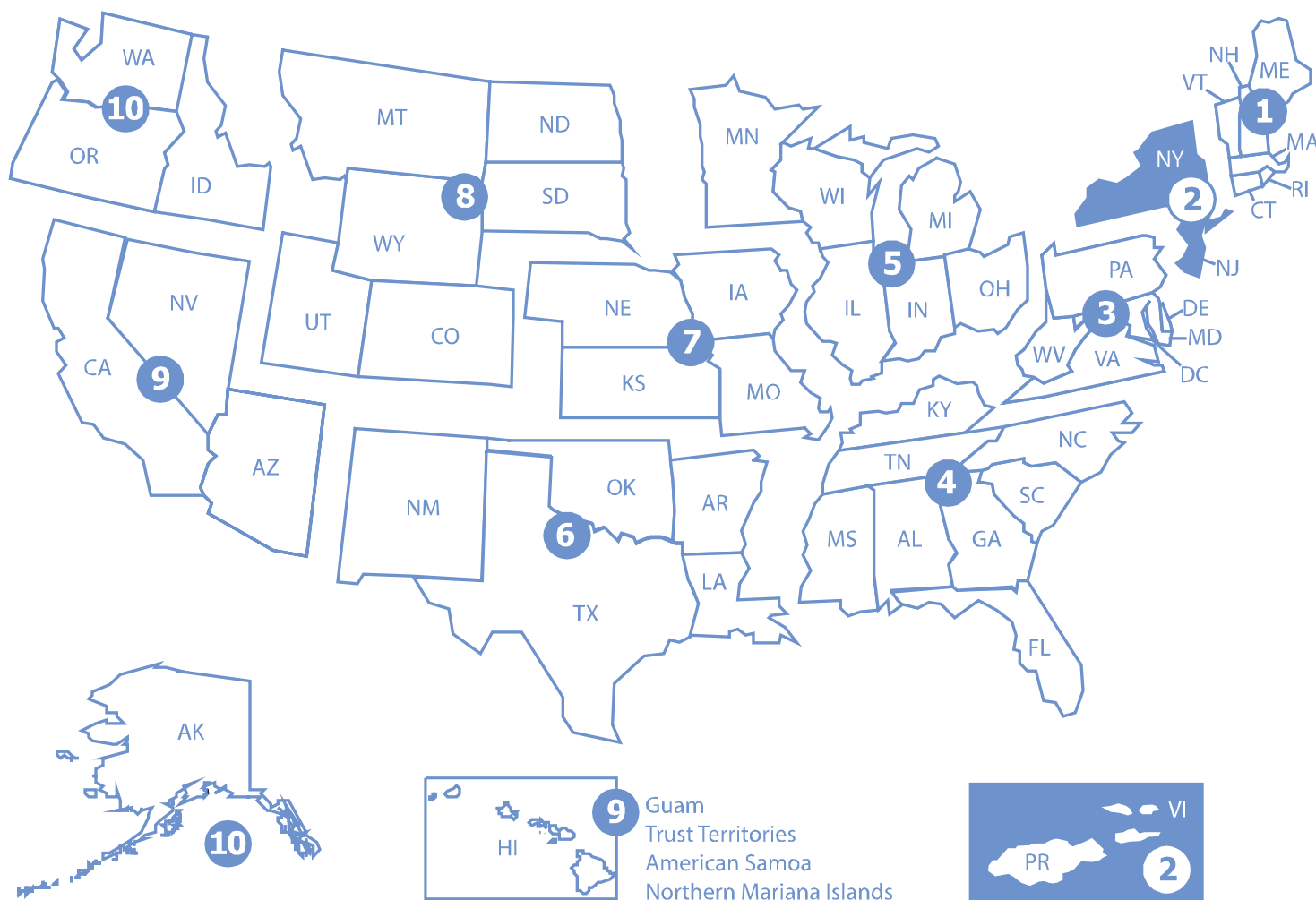




# Support Document for the Revised National Priorities List Final Rule – Saint-Gobain Performance Plastics



**Support Document for the  
Revised National Priorities List  
Final Rule  
Saint-Gobain Performance Plastics  
July 2017**

**Site Assessment and Remedy Decisions Branch  
Office of Superfund Remediation and Technology Innovation  
Office of Land and Emergency Management  
U.S. Environmental Protection Agency  
Washington, DC 20460**

## **Table of Contents**

<b>Executive Summary.....</b>	<b>iii</b>
<b>Introduction .....</b>	<b>iv</b>
Background of the NPL .....	iv
Development of the NPL .....	iv
Hazard Ranking System.....	v
Other Mechanisms for Listing .....	vi
Organization of this Document .....	vi
Glossary .....	vii
<b>1. List of Commenters and Correspondence.....</b>	<b>1</b>
<b>2. Site Description .....</b>	<b>2</b>
<b>3. Summary of Comments.....</b>	<b>5</b>
3.1 Support for Listing .....	6
3.2 Scope of the HRS Evaluation .....	8
3.3 Alternative to Listing/Defer to State.....	9
3.4 Need for Listing and Resulting Delay .....	10
3.5 Risk.....	12
3.6 Economic Impact-Stigma of Listing.....	13
3.7 Eligibility of PFOA for HRS Evaluation.....	14
3.8 Releases Below Regulatory Limits.....	15
3.9 Observed Releases.....	16
3.9.1 Observed Releases – Applicable Standards.....	16
3.9.2 Observed Releases – Attribution .....	22
3.10 Waste Characteristics .....	30
3.10.1 Ground Water Pathway Hazardous Waste Quantity Value .....	31
3.10.2 PFOA Toxicity .....	34
3.10.2.1 PFOA Reference Dose .....	37

3.10.2.1.1	Selection of Critical Effects .....	37
3.10.2.1.2	Use of Uncertainty Factors in Calculation of Reference Dose.....	49
3.10.2.2	PFOA Carcinogenicity .....	54
3.10.2.3	PFOA Human Epidemiology Studies.....	56
3.11	Targets .....	58
3.11.1	Level I Concentrations.....	58
3.11.2	Nearest Well .....	61
3.11.3	PSW 6 Population.....	63
3.12	HRS Score .....	67
4.	Conclusion .....	71

**Appendix A: May 2016, EPA Response to External Peer Review Comments on EPA Draft Documents:  
Health Effects Support Document for Perfluorooctanoic Acid (PFOA) and Health Effects  
Support Document for Perfluorooctane Sulfonate (PFOS). (99 pages)**

**Appendix B: January 3, 2017 Teleconference Note: Conversation with Jim Hurlburt, Hoosick Falls Water  
Department, Subject: Village Well 6. (1 page)**

## **Executive Summary**

Section 105(a)(8)(B) of CERCLA, as amended by SARA, requires that the EPA prepare a list of national priorities among the known releases or threatened releases of hazardous substances, pollutants, or contaminants throughout the United States. An original National Priorities List (NPL) was promulgated on September 8, 1983 (48 FR 40658). CERCLA requires that EPA update the list at least annually.

This document provides responses to public comments received on the Saint-Gobain Performance Plastics site, proposed on September 9, 2016 (81 FR 62428). This site is being added to the NPL based on an evaluation under EPA's Hazard Ranking System (HRS) in a final rule published in the *Federal Register* in July 2017.

## Introduction

This document explains the rationale for adding the Saint-Gobain Performance Plastics site in Village of Hoosick Falls, New York to the National Priorities List (NPL) of uncontrolled hazardous waste sites and provides responses to public comments received on this site listing proposal. The EPA proposed this site to the NPL on September 9, 2016 (81 FR 62428). This site is being added to the NPL based on an evaluation under the Hazard Ranking System (HRS) in a final rule published in the *Federal Register* in July 2017.

## Background of the NPL

In 1980, Congress enacted the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), 42 U.S.C. Sections 9601 *et seq.* in response to the dangers of uncontrolled hazardous waste sites. CERCLA was amended on October 17, 1986, by the Superfund Amendments and Reauthorization Act (SARA), Public Law No. 99-499, stat., 1613 *et seq.* To implement CERCLA, EPA promulgated the revised National Oil and Hazardous Substances Pollution Contingency Plan (NCP), 40 CFR Part 300, on July 16, 1982 (47 FR 31180), pursuant to CERCLA Section 105 and Executive Order 12316 (46 FR 42237, August 20, 1981). The NCP, further revised by EPA on September 16, 1985 (50 FR 37624) and November 20, 1985 (50 FR 47912), sets forth guidelines and procedures needed to respond under CERCLA to releases and threatened releases of hazardous substances, pollutants, or contaminants. On March 8, 1990 (55 FR 8666), EPA further revised the NCP in response to SARA.

Section 105(a)(8)(A) of CERCLA, as amended by SARA, requires that the NCP include

criteria for determining priorities among releases or threatened releases throughout the United States for the purpose of taking remedial action and, to the extent practicable, take into account the potential urgency of such action, for the purpose of taking removal action.

Removal action involves cleanup or other actions that are taken in response to emergency conditions or on a short-term or temporary basis (CERCLA Section 101). Remedial action is generally long-term in nature and involves response actions that are consistent with a permanent remedy for a release (CERCLA Section 101). Criteria for placing sites on the NPL, which makes them eligible for remedial actions financed by the Trust Fund established under CERCLA, were included in the HRS. EPA promulgated the HRS as Appendix A of the NCP (47 FR 31219, July 16, 1982). On December 14, 1990 (56 FR 51532), EPA promulgated revisions to the HRS in response to SARA, and established the effective date for the HRS revisions as March 15, 1991.

Section 105(a)(8)(B) of CERCLA, as amended, requires that the statutory criteria provided by the HRS be used to prepare a list of national priorities among the known releases or threatened releases of hazardous substances, pollutants, or contaminants throughout the United States. The list, which is Appendix B of the NCP, is the NPL.

An original NPL of 406 sites was promulgated on September 8, 1983 (48 FR 40658). At that time, an HRS score of 28.5 was established as the cutoff for listing because it yielded an initial NPL of at least 400 sites, as suggested by CERCLA. The NPL has been expanded several times since then, most recently on September 9, 2016 (81 FR 62397). The Agency also has published a number of proposed rulemakings to add sites to the NPL. The most recent proposal was on September 9, 2016 (81 FR 62428).

## Development of the NPL

The primary purpose of the NPL is stated in the legislative history of CERCLA (Report of the Committee on Environment and Public Works, Senate Report No. 96-848, 96th Cong., 2d Sess. 60 [1980]).

The priority list serves primarily informational purposes, identifying for the States and the public those facilities and sites or other releases which appear to warrant remedial actions. Inclusion of a facility or site on the list does not in itself reflect a judgment of the activities of its owner or operator, it does not require those persons to undertake any action, nor does it assign liability to any person. Subsequent government actions will be necessary in order to do so, and these actions will be attended by all appropriate procedural safeguards.

The NPL, therefore, is primarily an informational and management tool. The identification of a site for the NPL is intended primarily to guide EPA in determining which sites warrant further investigation to assess the nature and extent of the human health and environmental risks associated with the site and to determine what CERCLA-financed remedial action(s), if any, may be appropriate. The NPL also serves to notify the public of sites EPA believes warrant further investigation. Finally, listing a site may, to the extent potentially responsible parties are identifiable at the time of listing, serve as notice to such parties that the Agency may initiate CERCLA-financed remedial action.

CERCLA Section 105(a)(8)(B) directs EPA to list priority sites among the known releases or threatened release of hazardous substances, pollutants, or contaminants, and Section 105(a)(8)(A) directs EPA to consider certain enumerated and other appropriate factors in doing so. Thus, as a matter of policy, EPA has the discretion not to use CERCLA to respond to certain types of releases. Where other authorities exist, placing sites on the NPL for possible remedial action under CERCLA may not be appropriate. Therefore, EPA has chosen not to place certain types of sites on the NPL even though CERCLA does not exclude such action. If, however, the Agency later determines that sites not listed as a matter of policy are not being properly responded to, the Agency may consider placing them on the NPL.

## Hazard Ranking System

The HRS is the principle mechanism EPA uses to place uncontrolled waste sites on the NPL. It is a numerically based screening system that uses information from initial, limited investigations -- the preliminary assessment and site inspection -- to assess the relative potential of sites to pose a threat to human health or the environment. HRS scores, however, do not determine the sequence in which EPA funds remedial response actions, because the information collected to develop HRS scores is not sufficient in itself to determine either the extent of contamination or the appropriate response for a particular site. Moreover, the sites with the highest scores do not necessarily come to the Agency's attention first, so that addressing sites strictly on the basis of ranking would in some cases require stopping work at sites where it was already underway. Thus, EPA relies on further, more detailed studies in the remedial investigation/feasibility study that typically follows listing.

The HRS uses a structured value analysis approach to scoring sites. This approach assigns numerical values to factors that relate to or indicate risk, based on conditions at the site. The factors are grouped into three categories. Each category has a maximum value. The categories are:

- likelihood that a site has released or has the potential to release hazardous substances into the environment;
- characteristics of the waste (e.g., toxicity and waste quantity); and
- targets (e.g., people or sensitive environments) affected by the release.

Under the HRS, four pathways can be scored for one or more components and threats as identified below:

- Ground Water Migration ( $S_{gw}$ )

- Surface Water Migration ( $S_{sw}$ )  
The following threats are evaluated for two separate migration components, overland/flood migration and ground water to surface water.
  - drinking water
  - human food chain
  - sensitive environments
- Soil Exposure ( $S_s$ )
  - resident population
  - nearby population
- Air Migration ( $S_a$ )
  - population

After scores are calculated for one or more pathways according to prescribed guidelines, they are combined using the following root-mean-square equation to determine the overall site score ( $S$ ), which ranges from 0 to 100:

$$S = \sqrt{\frac{S_{gw}^2 + S_{sw}^2 + S_s^2 + S_a^2}{4}}$$

If all pathway scores are low, the HRS score is low. However, the HRS score can be relatively high even if only one pathway score is high. This is an important requirement for HRS scoring because some extremely dangerous sites pose threats through only one pathway. For example, buried leaking drums of hazardous substances can contaminate drinking water wells, but -- if the drums are buried deep enough and the substances not very volatile -- not surface water or air.

## Other Mechanisms for Listing

There are two mechanisms other than the HRS by which sites can be placed on the NPL. The first of these mechanisms, authorized by the NCP at 40 CFR 300.425(c)(2), allows each State and Territory to designate one site as its highest priority regardless of score. The last mechanism, authorized by the NCP at 40 CFR 300.425(c)(3), allows listing a site if it meets the following three requirements:

- Agency for Toxic Substances and Disease Registry (ATSDR) of the U.S. Public Health Service has issued a health advisory that recommends dissociation of individuals from the release;
- EPA determines the site poses a significant threat to public health; and
- EPA anticipates it will be more cost-effective to use its remedial authority than to use its emergency removal authority to respond to the site.

## Organization of this Document

The following section contains EPA responses to site-specific public comments received on the proposal of the Saint-Gobain Performance Plastics site on September 9, 2016 (81 FR 62428). The site discussion begins with a list of commenters, followed by a site description, a summary of comments, and Agency responses to each comment. A concluding statement indicates the effect of the comments on the HRS score for the site.



## Glossary

The following acronyms and abbreviations are used throughout the text:

<b>Agency</b>	U.S. Environmental Protection Agency
<b>ATSDR</b>	Agency for Toxic Substances and Disease Registry
<b>BMC</b>	Benchmark concentration
<b>BMD</b>	Benchmark dose
<b>BMDL</b>	Benchmark dose limit
<b>BMR</b>	Benchmark response
<b>CAR</b>	Constitutive androstane receptor
<b>CERCLA</b>	Comprehensive Environmental Response, Compensation, and Liability Act of 1980, 42 U.S.C. Sections 9601 <i>et seq.</i> , also known as Superfund
<b>CFR</b>	Code of Federal Regulations
<b>cis-1,2-DCE</b>	cis-1, 2-dichloroethene
<b>CLP</b>	EPA Contract Laboratory Program
<b>CRQL</b>	Contract-required quantitation limit
<b>DL</b>	Detection limit
<b>EPA</b>	U.S. Environmental Protection Agency
<b>ESA</b>	Environmental site assessment
<b>FR</b>	Federal Register
<b>FXR</b>	Farnesoid receptor
<b>GD</b>	Gestational day
<b>GAC</b>	Granular activated carbon
<b>HED</b>	Human equivalent dose
<b>HRS</b>	Hazard Ranking System, Appendix A of the NCP
<b>HRS score</b>	Overall site score calculated using the Hazard Ranking System; ranges from 0 to 100
<b>HWQ</b>	Hazardous waste quantity
<b>LOAEL</b>	Lowest observed adverse effect level
<b>MCL</b>	Maximum contaminant level
<b>MDL</b>	Method detection limit
<b>µg/kg</b>	Microgram per kilogram
<b>µg/L</b>	Microgram per liter
<b>mg/kg/day</b>	Milligram per kilogram per day
<b>MW</b>	Monitoring well
<b>MWS</b>	Municipal water supply

<b>NCP</b>	National Oil and Hazardous Substances Pollution Contingency Plan, 40 C.F.R. Part 300
<b>ng/L</b>	Nanograms per liter
<b>NOAEL</b>	No observed adverse effect level
<b>NPL</b>	National Priorities List, Appendix B of the NCP
<b>NYDEC</b>	New York State Department of Environmental Conservation
<b>PCB</b>	Polychlorinated biphenyl
<b>PFAA</b>	Perfluoroalkyl acid
<b>PFOA</b>	Perfluorooctanoic acid
<b>PFOS</b>	Perfluorooctane sulfonate
<b>PK</b>	Pharmacokinetic
<b>POD</b>	Point of departure
<b>PPAR<math>\alpha</math></b>	Peroxisome proliferator-activated receptor
<b>PPB</b>	Parts per billion
<b>PPM</b>	Parts per million
<b>PPT</b>	Parts per trillion
<b>PRP</b>	Potentially responsible party
<b>PSW</b>	Public supply well
<b>PXR</b>	Pregnane X receptor
<b>RDL</b>	Reporting detection limit
<b>RfD</b>	Reference dose
<b>RI</b>	Remedial investigation
<b>RI/FS</b>	Remedial Investigation/feasibility study
<b>SARA</b>	Superfund Amendments and Reauthorization Act
<b>SCDM</b>	Superfund Chemical Data Matrix
<b>SGPP</b>	Saint-Gobain Performance Plastics
<b>SOW</b>	Statement of work
<b>SQL</b>	Sample quantitation limit
<b>TAL</b>	Target analyte list
<b>TCE</b>	Trichloroethylene
<b>TSCA</b>	Toxic Substances Control Act
<b>UF</b>	Uncertainty factor
<b>VC</b>	Vinyl chloride
<b>Vd</b>	Volume of distribution
<b>VOC</b>	Volatile organic compounds

## **1. List of Commenters and Correspondence**

EPA-HQ-OLEM-2016-0434-0004	Correspondence, undated, from Basil Seggos, Acting Commissioner, Office of the Commissioner, New York State Department of Environmental Conservation.
EPA-HQ-OLEM-2016-0434-0005	Comment, dated September 20, 2016, submitted by Kathy Marchione, State Senator, 43rd District, State of New York.
EPA-HQ-OLEM-2016-0434-0006	Comment, submitted by Anonymous Commenter.
EPA-HQ-OLEM-2016-0434-0007	Correspondence, dated January 14, 2016, from Basil Seggos, Acting Commissioner, Office of the Commissioner, New York State Department of Environmental Conservation.
EPA-HQ-OLEM-2016-0434-0008	Comment, dated November 4, 2016, submitted by Stan Brownell, Chairman, and Lester Goodermote, Legislator, Office of the Majority, Rensselaer County Legislature, New York.
EPA-HQ-OLEM-2016-0434-0009	Comment, dated November 6, 2016, submitted by David B. Borge, Mayor, Village of Hoosick Falls, New York.
EPA-HQ-OLEM-2016-0434-0010	Comment, submitted by James Donovan, Hoosick Falls, New York.
EPA-HQ-OLEM-2016-0434-0011	Comment, submitted by Anonymous Commenter, Hoosick Falls, New York.
EPA-HQ-OLEM-2016-0434-0012	Comment, submitted by Anonymous Commenter, Hoosick Falls, New York.
EPA-HQ-OLEM-2016-0434-0013	Comment, dated September 25, 2016, submitted by John Bozeman, Lackland, Texas.
EPA-HQ-OLEM-2016-0434-0014	Correspondence, undated, from Terry Jeng, Office of Superfund Remediation and Technology Innovation, USEPA.
EPA-HQ-OLEM-2016-0434-0015	Comment, dated November 8, 2016, submitted by Christoper R. Gibson, Archer Attorneys at Law, on behalf of Saint-Gobain Performance Plastics Corporation.

## **2. Site Description**

The Saint-Gobain Performance Plastics (SGPP) site for HRS scoring purposes consists of soil and ground water contaminated with trichloroethylene (TCE), cis-1, 2-dichloroethene (cis-1, 2-DCE), vinyl chloride, polychlorinated biphenyls (PCBs), and perfluorooctanoic acid (PFOA) as a result of the historical release from activities at the SGPP facility located at 14 McCaffrey Street in the Village of Hoosick Falls, NY. The EPA sampling conducted in April–May 2016 document the presence of TCE, cis-1,2-DCE, PCBs and PFOA in facility soils, and TCE, vinyl chloride and PFOA in ground water (See Figure 1, Site Location Map and Figure 2, Sample Results Map, of this support document). Sampling and analysis by the EPA of the Village of Hoosick Falls municipal water supply in May 2016 document contamination of vinyl chloride above the cancer risk screening concentration in the Village of Hoosick Falls drinking water well number 6. The Village of Hoosick Falls drinking water wells were also found to be contaminated with PFOA (in Village wells 3 and 7). In addition, information provided by SGPP to the EPA in December 2014 documents an observed release by direct observation of PFOA to the aquifer of concern.

Chlorinated solvents such as TCE are associated with historical manufacturing activities performed at the SGPP facility. Cis-1, 2-DCE and vinyl chloride are degradation products of TCE. Manufacturing processes at the facility included the use of certain non-stick coatings, the manufacture of a variety of polymer-based products including high-performance polymeric films and membranes as well as foams for bonding and sealing. Fluoropolymers used to manufacture non-stick coatings are known to include PFOA.

The Village of Hoosick Falls obtains its drinking water from three public supply wells, each of which is evaluated in the HRS package for the SGPP site (PSW 3, 6, and 7). The wells draw water from the lower portion of the sand and gravel aquifer underlying the Village of Hoosick Falls and the Hoosic River. The areal extent of the sand and gravel aquifer is generally limited to the Hoosic River valley. This lower portion of the aquifer is overlain by approximately 8 feet of poorly permeable clay and silt under much of the Village and at the facility, but the thickness of this layer varies considerably. This clay and silt layer can be a local barrier to downward water flow and separates the lower portion of the sand and gravel aquifer from the shallow portion of the sand and gravel aquifer, which overlays the clay and silt layer in areas where the clay layer is present. However, because the lower aquifer exhibits “leaky artesian conditions” and there is evidence of site-attributable hazardous substance migration across the silt and clay layer, the upper and lower portions of the aquifer are evaluated together as a single hydrologic unit (discussed further in section 3.9.2, Observed Releases – Attribution, of this support document). Although the pre-well development ground water flow direction in the vicinity of the SGPP facility and the Village of Hoosick Falls wells was likely northward in the direction of flow of the Hoosic River, the pumping of the village wells has created a radius of influence (i.e., causes flow gradients to be toward the wells) that extends out as far as 0.67 mile and encompasses the SGPP facility. Shallow ground water flow beneath the SGPP facility is northwest to southeast toward the Village of Hoosick Falls wells.

The Village of Hoosick Falls public well system presently serves a population of approximately 4,000 people based on information obtained from the Hoosick Falls Water Department.

Figure 1: Site Location Map

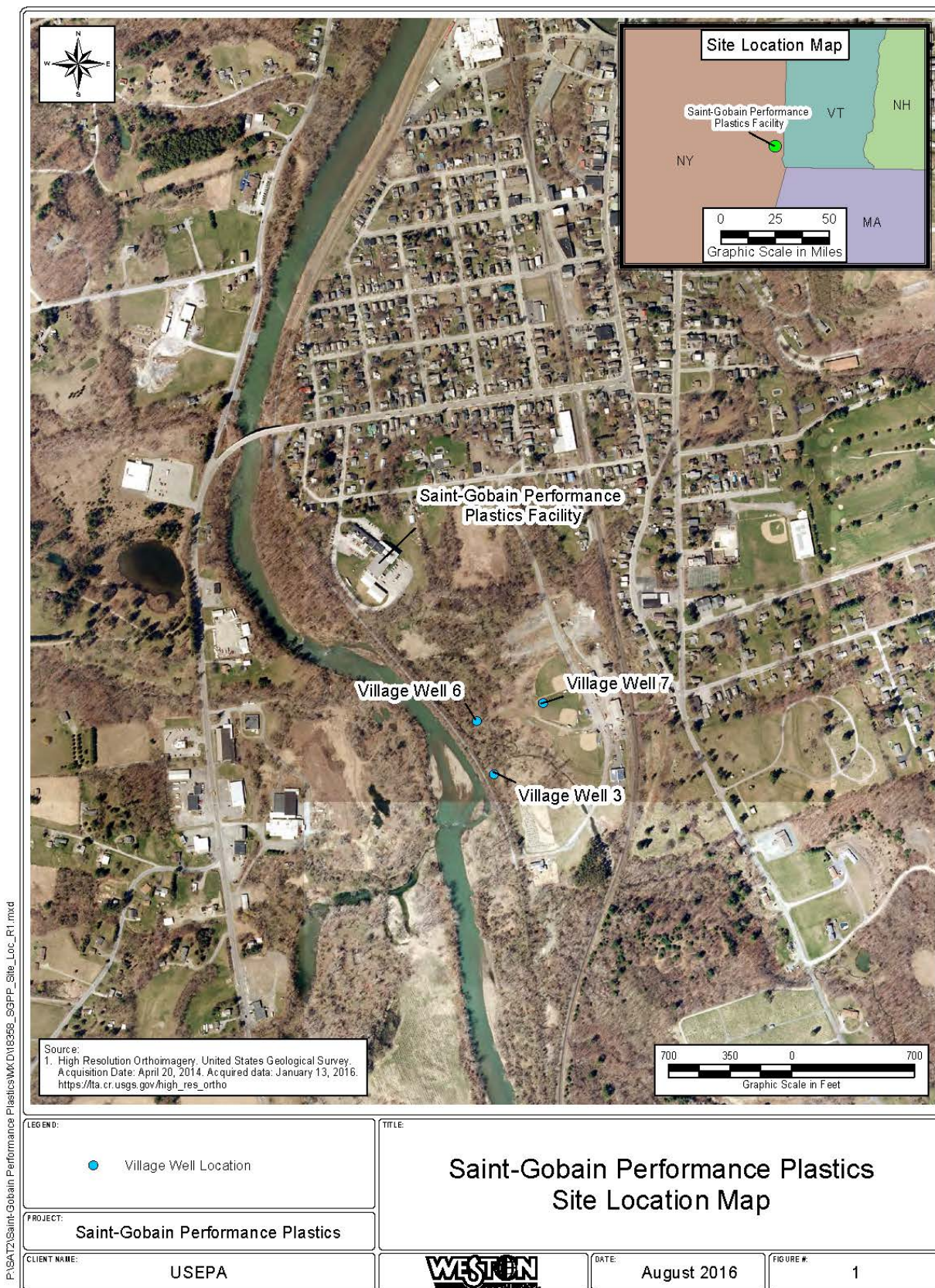




Figure 2: Sample Results Map



### **3. Summary of Comments**

Commenters both supported and questioned the proposed addition of the Saint-Gobain Performance Plastics site to the NPL. The supporting commenters included the State of New York, a State Government representative, the Mayor of the Village of Hoosick Falls, two Rensselaer County Legislators, residents of the Village of Hoosick Falls and other individuals.

Acting Commissioner, Basil Seggos of the Office of the Commissioner, New York State Department of Environmental Conservation, requested that the Saint-Gobain Performance Plastics site be included on the NPL after the EPA conducts an investigation. He indicated that he looks forward to continuing collaboration at all levels of the government to address the PFOA contamination and ensuring no additional hardship on Village residents.

Nine commenters, which included State Senator Kathy Marchione, 43<sup>rd</sup> District, New York; Stan Brownell and Lester Goodermote of the Rensselaer County Legislature, New York; Mayor David B. Borge, Village of Hoosick Falls, New York; three anonymous commenters; two Hoosick Falls residents; and 1 additional public commenter, John Bozeman of Lackland, Texas, supported listing the Site on the NPL. They expressed concerns for public health, remediation, impact on property values, other pollution in Hoosick Falls, collaboration with the New York State Department of Environmental Conservation, and Superfund resources to address the Site.

Commenters, while not opposing the placement of the Site on the NPL, included individuals concerned with the impact of the listing on the community. Mr. Brownell and Mr. Goodermote of the Rensselaer County Legislature, New York, stated that the discovery of PFOAs has affected the image of the Village and has possibly impacted property values, but an effective remediation effort can do a great deal to restore the standing of the Village and address the reasonable concerns regarding health and safety. An anonymous commenter indicated that his/her home is not worth anything.

Saint-Gobain Performance Plastics Corporation opposed listing the Site on the NPL and questioned the need for the listing as they asserted that the contamination from their facility is already being addressed in an agreement with the State. SGPP also commented that the EPA made multiple errors in its HRS evaluation of the Site, including identifying vinyl chloride contamination in a Village of Hoosick Falls wells as attributable to a release from their facility, considering PFOAs in the site scoring, including in the scoring a release below regulatory limits, in determining the population utilizing the contaminated wells as a water supply and the degree the wells were contaminated. Specifically:

- SGPP commented that the overall HRS site score is based on several errors and unsound assumptions that resulted in an inflated site score that is not reflective of site conditions.
- SGPP commented that the EPA should have included information on the soil exposure pathway to complete the record. SGPP added that the soil sampling is relevant in determining whether the Site should be placed on the NPL, considering that the EPA concluded no offsite cleanup work is required.
- SGPP commented that it and the prior owner of the facility, Honeywell International, Inc., have entered into an Order on Consent (Consent Order) with New York State Department of Environmental Conservation (NYDEC), and the EPA should leave the Site in the State of New York cleanup program.
- SGPP asserted that placing the Site on the NPL is unnecessary and will delay ongoing remedial activities. SGPP stated that the presence of PFOA at the Site is already being addressed without intervention by the EPA.
- SGPP commented that the Site does not pose risk to the public. SGPP indicated that listing this Site on the NPL is based on such little evidence of hazardous substances at the Site that the listing in and of itself is unprecedented.
- SGPP commented that PFOA is not a CERCLA hazardous substance, and the EPA has not promulgated any binding drinking water standards for it.

- SGPP also commented that TCE or any other CERCLA hazardous substances have not been detected above any applicable standards in any drinking water supply well.
- SGPP commented that vinyl chloride in PSW 6 is not attributable to alleged historical releases of TCE at the SGPP site. SGPP asserted that the EPA has not presented sufficient evidence to support the degradation of TCE at the Site in MW-6 at the facility to the vinyl chloride detected in PSW 6. SGPP contended that the claim that a single detection of vinyl chloride at a concentration of 1.3 µg/L in PSW 6 is attributable to low levels of TCE in ground water at the Site is not supported by the scientific data. SGPP surmised that the EPA's analysis of the migration of vinyl chloride in the aquifer is flawed and is inconsistent with claims made in the HRS documentation record at proposal.
- SGPP commented that the EPA should not have assigned a pathway hazardous waste quantity of 100 to the ground water migration pathway. SGPP asserted that the EPA acknowledged the actual calculated hazardous waste quantity for the ground water pathway at the Site is 1, not 100.
- SGPP also commented that the EPA should not have assigned a toxicity factor value of 10,000 to PFOA because the reference dose (RfD) for PFOA is premised upon inappropriate assumptions such as the developmental effects upon which the reference dose is based are transient developmental effects that do not alter the well-being of the mice. SGPP also claimed that there are inconsistencies in the data from the experimental animal study; the EPA incorporated inappropriate uncertainty factors into its derivation of the reference dose; the EPA has not found adequate evidence to assign a regulatory classification to PFOA as a likely carcinogen, so there is no basis that a maximum toxicity factor of 10,000 should be applied to PFOA as is applied to known carcinogens; and the EPA has not identified any epidemiological studies regarding PFOA and potential adverse human health effects that it believes are sufficiently reliable to develop regulatory ground water or drinking water standards.
- SGPP additionally contended that there are no Level I concentrations (concentrations meeting observed release criteria and above HRS benchmarks) attributable to the Site in any target well, and the status and pumping capacity of Well PSW 6 was inaccurately represented in the HRS scoring of the Site. SGPP stated that PSW 6 is an emergency back up well, and the population associated with PSW 6 was inaccurately apportioned and should be value of 0 not 13,330.

The commenters' specific challenges to the listing are detailed in the following sections of this support document along with the EPA's responses demonstrating the SGPP site qualifies for placement on the NPL.

### 3.1 Support for Listing

Comment: The Acting Commissioner of the Office of the Commissioner, New York State Department of Environmental Conservation; State Senator, Kathy Marchione of the 43<sup>rd</sup> District of New York; Mayor David B. Borge of the Village of Hoosick Falls; Stan Brownell, Chairman, and Lester Goodermote, Legislator, of the Office of the Majority, Rensselaer County Legislature, New York; and five additional commenters supported the placement of the Site on the NPL.

Acting Commissioner Basil Seggos, Office of the Commissioner, New York State Department of Environmental Conservation, also commented that the government agencies charged with protecting public health and the environment must work together on a full investigation of the nature and extent of the PFOA contamination and any necessary cleanup. The Acting Commissioner stated that the Department of Health will remain responsible for all matters related to public health regarding the Site, and he looks forward to continuing collaboration at all levels of the government to address the PFOA contamination.

Kathy Marchione, State Senator, 43rd District, State of New York commented that an NPL designation will support necessary site investigations, empower the EPA to assess the nature and extent of public health and environmental risks associated with the Site, and make the site eligible for long-term cleanup. The State Senator



noted that continued cooperation with Federal, State and local government must be part of the long term solution to address the PFOA contamination in the community.

Mayor David B. Borge of the Village of Hoosick Falls stated that the community showed support for the placement of the Site on the NPL at the October 24, 2016 joint public hearing. He added that during that public forum the EPA representatives and New York State Department of Environmental Conservation (NYDEC) assured the community that the collaborative efforts and resources from both the EPA and NYDEC would continue, and the community would benefit from a full cleanup at no financial cost to the community.

Stan Brownell, Chairman, and Lester Goodermote, Legislator, of the Office of the Majority, Rensselaer County Legislature, New York, also expressed that they look forward to working with the EPA. Mr. Brownell and Mr. Goodermote commented that they expect inclusion of the Site on the NPL will allow contamination at the Site to be addressed and the community to thrive in coming years. Mr. Brownell and Mr. Goodermote stated that, as residents, they recognize the crucial situation the Village currently faces as the discovery of PFOAs has affected the image of the Village, disrupted quality of life in the community and possibly impacted property values. However, they stated that an effective remediation effort can do a great deal to restore the standing of the Village and to address the reasonable concerns regarding health and safety of their fellow residents. Mr. Brownell and Mr. Goodermote added that the resources and compliance powers of the EPA are necessary to investigate and remediate the Site, and a full investigation of the PFOA contamination, including water, air, and soil migrations, is necessary.

Mr. James Donovan, a resident of Hoosick Falls, supported the listing but also requested that the Hoosick Falls landfill be added to the Superfund list. He said his health has been adversely impacted by exposure to PFOA in the Village water supply. Similarly, an anonymous commenter expressed concerns that the former landfill is being overlooked by the EPA. The commenter explained that she lives 2.7 miles from the SGPP site but 0.7 mile from the landfill, and her private well has 70 part per trillion (ppt) of PFOA. The commenter requested that all areas of Hoosick Falls be investigated to ensure safety and security of her family.

An anonymous commenter, while supporting the listing, also requested there be continued investigations at “other pollution sites in Hoosick Falls” including the Village landfill.

Another anonymous commenter also requested that the Federal government continue to investigate other pollution in Hoosick Falls to ensure future generations will not have to address medical and financial impacts due to contaminated soil and water. The commenter indicated that his/her health has been adversely impacted since living in Hoosick Falls, and his/her home is not worth anything.

Mr. John Bozeman stated that Superfund will provide the necessary resources to clean up the Site and guarantee the safety of the Village’s drinking water supply. He also commented that the EPA can investigate to determine who the polluters are and hold them accountable. He noted that the American Cancer Society reported that PFOA is a B2 carcinogen. He cited the following document: *American Cancer Society. Teflon and Perfluorooctanoic Acid (PFOA)*. (2016). Retrieved from <http://www.cancer.org/cancer/cancercauses/othercarcinogens/athome/teflon-and-perfluorooctanoicacid--Pfoa>.

Response: The EPA is adding the Saint-Gobain Performance Plastics Site to the NPL. Listing makes a site eligible for remedial action funding under CERCLA, and the EPA will examine the site to determine what response, if any, is appropriate. The EPA will determine the need for using Superfund monies for remedial activities on a site-by-site basis, taking into account the NPL ranking, State priorities, further site investigation, other response alternatives and other factors as appropriate.

Regarding the request for continued investigations at other sites in Hoosick Falls, this listing addresses releases from the SGPP site.

### 3.2 Scope of the HRS Evaluation

Comment: SGPP commented that the EPA should include the results of the EPA's soil sampling in the Village in the HRS documentation record. It explained that although the EPA did not calculate a soil exposure pathway score for the Site, the EPA should include the results of its soil sampling in the Village to complete the record.

SGPP further stated that the soil sampling is relevant to evaluating whether the Site should be listed on the NPL as one of the EPA's top priorities. SGPP contended that off-site sampling results performed by the EPA to determine whether a cleanup action is needed showed PFOA levels from non-detected to 0.02 parts per million (ppm) which is well below the EPA's soil screening level and from which the EPA then concluded that no-offsite soil cleanup work is required. SGPP cited to SGPP Exhibit 20<sup>1</sup> to support its comment. SGPP noted the following soil sampling event which supported the EPA's conclusion and which it noted is relevant to evaluating whether the Site should be placed on the NPL:

- In the February 2016 soil samples in ball fields and park areas along Waterworks Road and in the Athletic Field near the local ice rink and community pool, PFOA levels in soils ranged from non-detected to 0.0277 ppm, well-below the EPA soil screening level. (SGPP Exhibit 20).
- In the May 2016 soil samples at 33 additional locations including residential properties in the vicinity of the Site, PFOA levels ranged from non-detected to 0.0277 ppm.

Response: The information contained in the SGPP site HRS documentation package was sufficient to document that the Site qualifies for the NPL; none of the additional information regarding a possible threat via the soil exposure pathway suggested by SGPP contradicts the HRS documentation record characterization of the Site, source, observed releases, or targets. If SGPP is suggesting that additional preliminary soils sampling indicate that the Site poses no risk via the soil exposure pathway, a subsequent stage of the Superfund process, the remedial investigation (RI), will characterize conditions and hazards at the Site more comprehensively. This site has been placed on the NPL because it has an HRS score greater than 28.50 and meets all CERCLA and NCP listing criteria.

Regarding SGPP's comment that the Site should be listed on the NPL as one of the EPA's top priorities, the EPA places eligible sites on the NPL pursuant to the Agency's authorities under CERCLA and its associated regulations. CERCLA § 105(a)(8)(a) requires the EPA to determine NPL priorities based on the "relative risk or danger to public health or welfare, or the environment." Consistent with CERCLA, the SGPP site is being placed on the NPL based on an HRS evaluation of the risk relative to other sites being considered for the NPL resulting from the release at this site of hazardous substances to a ground water aquifer and the resulting threat the release poses to the City's drinking water supply. The EPA must balance the need to fully characterize a site with the limited resources available to collect and analyze site data. However, any additional data that characterizes site conditions could provide useful information during the RI. Additionally, the subsequent Superfund remedial investigation and risk assessment will include extensive processes to establish the threat posed via additional migration and exposure pathways.

---

<sup>1</sup> Exhibit 20 of SGPP comment document (available at EPA docket ID: EPA-HQ-OLEM-2016-0434-0015) is: *Hoosick Falls Update: EPA Soil Sampling at Ballfields, Community Update No. 1* (February 2016). *Hoosick Falls Update: EPA Soil Sampling at Hoosick Falls Athletic Field, Community Update No. 2* (February 2016). *Hoosick Falls Update: EPA Results Show Ballfields & Athletic Field OK to Use, Community Update No. 3* (Spring 2016). *Hoosick Falls Update: EPA Expands Sampling Program in Areas Near McCaffrey Street Facility, Community Update No. 4* (Spring 2016). *Hoosick Falls Update: EPA Expands Sampling Program in Areas Near McCaffrey Street Facility, Community Update No. 4-V2* (Spring 2016). *Hoosick Falls Update: Results from 34 Locations Show No Soil Cleanup Needed at Residential Properties, Football & Recreational Fields, Community Update No. 5* (September 2016).

Further, the HRS does not require scoring all four pathways if scoring those pathways does not change the listing decision. For some sites, data for scoring a pathway are unavailable and obtaining these data would be time-consuming or costly. In other cases, data for scoring some pathways are available, but would only have a minimal effect on the site score. In still other cases, data on other pathways could substantially add to a site score, but would not affect the listing decision. The HRS is a screening model that uses limited resources to determine whether a site should be placed on the NPL for possible Superfund response. A subsequent stage of the Superfund process, the RI, characterizes conditions and hazards at the site more comprehensively.

To the extent practicable, the EPA attempts to score all pathways that pose significant threats. If the contribution of a pathway is minimal to the overall score, in general, that pathway will not be scored. In these cases, the HRS documentation record may include a brief qualitative discussion to present a more complete picture of the conditions and hazards at the site. As a matter of policy, the EPA does not delay listing a site to incorporate new data or score new pathways if the listing decision is not affected.

The HRS is intended to be a “rough list” of prioritized hazardous sites; a “first step in a process--nothing more, nothing less.” *Eagle Picher Indus. v. EPA*, 759 F.2d 922, 932 (D.C. Cir. 1985) (*Eagle Picher II*). The EPA would like to investigate each possible site completely and thoroughly prior to evaluating them for proposal for the NPL, but it must reconcile the need for certainty before action with the need for inexpensive, expeditious procedures to identify potentially hazardous sites. The D.C. Circuit Court of Appeals has found the EPA's approach to solving this conundrum to be “reasonable and fully in accord with Congressional intent.” *Eagle Picher Industries, Inc. v. EPA*, (759 F.2d 905 (D.C. Cir. 1985) *Eagle Picher I*).

Further, the decisions made regarding soil sampling under the EPA Removal program to date, addressed only the acute direct human contact risk to contaminated surface soils. Therefore, because the EPA Removal Program was focused on the direct contact risk, these actions did not necessarily address the impacts to ground water drinking water supplies due to migration from the contaminated soils. Placing this site on the NPL allows the EPA to investigate and address this risk in separate phases of the Superfund process as necessary.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.3 Alternative to Listing/Defer to State

Comment: SGPP stated that it and the prior owner of the facility, Honeywell International, Inc., have entered into an Order on Consent (Consent Order) with New York State Department of Environmental Conservation (NYDEC). SGPP stated it and Honeywell are in the process of remediating the Site and potentially impacted wells and have implemented various remediation measures. SGPP asserted that Federal involvement is not necessary. SGPP requested that the EPA leave the site in the New York State cleanup program and withdraw the listing.

SGPP asked a variety of questions regarding oversight at the Site. It questioned if the National Contingency Plan (NCP) and other Federal regulations apply to the cleanup and if so how will they apply since there are no Federal standards for PFOA? Will the existing Consent Order between SGPP, Honeywell and the NYDEC be superseded by some other agreement and if so what will take its place and how long will it take to finalize? Will the EPA perform work at the Site and if so which portion and why? SGPP contended that uncertainty and confusion can be avoided by leaving the Site in the New York State cleanup program.

Response: Adding the SGPP site to the NPL is an appropriate next step in the Superfund process. The HRS site score of above 28.50 represents the EPA's assessment that the relative risk posed by the Site demonstrates that the Site qualifies for placement on the NPL and warrants further investigation under the Superfund program.

The State of New York has requested the Site be placed on the NPL. In a letter dated January 14, 2016, (docket ID EPA-HQ-QLEM-2016-0434-0007), prior to the placement of the Site on the NPL, Acting Commissioner Mr. Basil Seggos, Office of the Commissioner, New York State Department of Environmental Conservation, stated:

The detection of perfluorooctanoic acid (PFOA) in the public water supply of the Village of Hoosick Falls (Village) in Rensselaer County, New York is deeply concerning.....

As the government agencies charged with protecting public health and the environment, it is imperative that DOH, the New York State Department of Environmental Conservation (DEC), and the EPA work together on a full investigation of the nature and extent of PFOA contamination and, then, on any necessary cleanup. DEC and DOH stand ready to assist in this investigation by the EPA.

I am proposing that EPA, after conducting an investigation, nominate for inclusion on the National Priorities List the Saint-Gobain Performance Plastics Corp. McCaffrey Street Plant Site in the Village of Hoosick Falls (EPA facility No. NYD000829598), where high levels of PFOA in groundwater have been observed, and any other source of a release of PFOA in the Village or Town of Hoosick Falls that may be identified during the course of the investigation.

On May 3, 1995, the EPA issued its “Guidance on Deferral of NPL Listing Determinations While States Oversee Response Actions.” The EPA developed the guidance in an effort to enhance the State role in addressing sites. The deferral program is an administrative tool to enable States and Tribes, under their own laws, to respond at sites that the EPA would otherwise not soon address. Because of the great differences in State and Tribal capabilities; however, the EPA implements the guidance in a flexible manner. Hence, Regions may act at variance from certain provisions of the guidance.

Pursuant to guidance and the request by the State of New York, the EPA has decided that deferral to the State of New York is not appropriate in this case.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### **3.4 Need for Listing and Resulting Delay**

Comment: SGPP submitted comments questioning the need for and purpose of placing the SGPP site on the NPL and indicated that placement of this site on the NPL will serve to delay cleanup. SGPP commented that listing is unnecessary and would impede already ongoing remedial activities.

SGPP stated that the presence of PFOA at the Site is already being addressed without intervention by the EPA. It claimed that it has spent nearly the last two years working cooperatively with the Village and State officials to reduce or eliminate PFOA at the Site and in the local water supply without any direction or action from the EPA.

SGPP further claimed that “on March 30, 2016, NYDOH announced that the Village’s water was non-detect for PFOA as of March 13, 2016, and determined that Village residents ‘may use the water for any and all uses, including drinking and cooking.’” (SGPP cited to Exhibits 4 through 8 of its comment document available at EPA docket ID: EPA-HQ-OLEM-2016-0434-0015.)<sup>2</sup>

---

<sup>2</sup>Exhibit 4 of SGPP comment document is: The Village of Hoosick Falls Municipal Water public release statements  
Exhibit 5 of SGPP comment document is: Confidential, Calgon Carbon Corporation, Pittsburgh, PA, technical service Report No. 20150420, prepared for Hoosick falls, Hoosick, NY, May 22, 2015.  
Exhibit 6 of SGPP comment document is: Department of Environmental Conservation, New York State Department of

SGPP added that it and Honeywell are already performing a RI/FS at the Site under the direct oversight of the NYDEC pursuant to a Consent Order that was entered in June 2016. (SGPP cites Reference 18<sup>3</sup> of the HRS documentation record at proposal.)

Response: The need for placing this site on the NPL has not been negated by the actions taken by SGPP and is consistent with the purpose of the NPL. In addition, the act of placing this site on the NPL need not delay any ongoing or planned site remediation. As discussed below, SGPP can work with the EPA and the State of New York to avoid unnecessary delays.

First, the EPA considers that the promulgation of this site to the NPL fulfills the purpose of the NPL. The primary purpose of the NPL is stated in the legislative history of CERCLA (Report of the Committee on Environment and Public Works, Senate Report No. 96-848, 96th Cong., 2d Sess. 60 [1980]), as follows (in relevant part): “The priority list serves primarily informational purposes, identifying for the States and the public those facilities and sites or other releases which appear to warrant remedial actions.” The EPA has clearly, via this listing, identified for the States and the public the release that is currently scored using the HRS. Listing also is a necessary step to enable the use of CERCLA funds as needed to ensure that Site cleanup moves forward.

Second, regarding the need for placing this site on the NPL, the response actions taken to remove the immediate risks to the public do not eliminate this site from NPL consideration because these actions do not show that the contaminated drinking water supply (contaminated aquifer) does not still exist. The drinking water samples show no detection of PFOA were collected after being treated by the granular activated carbon filtration system at the water treatment facility, from within the drinking water distribution system holding tanks, and from taps at homes on several street locations. (See Exhibits 4 and 8 of SGPP comments available at EPA docket ID: EPA-HQ-OLEM-2016-0434-0015.) However, sampling of water from the aquifer, at a point prior to filtration to remove PFOA, has not confirmed that the aquifer is not contaminated with PFOA. As long as the aquifer remains contaminated, a risk exists that warrants further investigation. Further, the extent of contamination of PFOA, TCE, 1,2-DCE and vinyl chloride, known to be present in the aquifer, will be more fully determined at a subsequent stage of the Superfund process, the remedial investigation (RI).

Third, placement of the Site on the NPL does not necessarily lead to delay of planned response actions or associated negotiations. These actions can be considered in other steps of the Superfund process. Consistent with CERCLA, the EPA has in place an orderly procedure for identifying sites where releases of substances addressed under CERCLA have occurred or may occur, placing such sites on the NPL, evaluating the nature and extent of the threats at such sites, responding to those threats, and deleting sites from the NPL. The purpose of the initial two steps is to develop the NPL, which identifies for the States and the public those sites that appear to warrant remedial action (56 FR 35842, July 29, 1991). The evaluation or RI/FS phase involves on-site testing to assess the nature and extent of the public health and environmental risks associated with the site and to determine what CERCLA-funded remedial actions, if any, may be appropriate. After a period of public comment, the EPA responds to those threats by issuing a Record of Decision which selects the most appropriate alternative. The

---

Environmental Conservation Secures Agreement that holds Saint Gobain & Honeywell Responsible for PFOA Contamination in Hoosick Falls Area, June 3, 2016.

Exhibit 7 of SGPP comment document is: EPA Statement on Private Wells in the Town of Hoosick and Village of Hoosick Falls, NY, January 28, 2016.

Exhibit 8 of SGPP comment document is: Letter dated March 30, 2016 from Commissioner Howard A. Zuker, M.D., J.D., New York Department of Health, to The Honorable David B. Borge, Village of Hoosick Falls.

<sup>3</sup> Reference 18 of the HRS documentation record at proposal is: New York State Department of Environmental Conservation (NYSDEC) State Superfund Program (ECL §27-1301 et seq.). Order on Consent and Administrative Settlement, Index No. CO 4-20160212-18, In the Matter a Remedial Program for PFOA impacting the Village of Hoosick Falls Municipal Water Supply, private drinking water wells in the Town of Hoosick, and Saint-Gobain McCaffrey Street (DEC Site No. 442046) and Saint-Gobain Liberty Street Site (DEC Site No. 442048). June 3, 2016.

selected remedy is implemented during the remedial design/remedial action phase. Finally, the site may be deleted from the NPL when the EPA determines that no further response is appropriate.

Therefore, any site investigation work, as well as any remediation undertaken by SGPP and other potentially responsible parties (PRPs) performed to date and that which is currently proceeding can be considered in other steps of the Superfund remediation process, such as when performing a remedial investigation or a Superfund risk assessment for the Site. Then, based on the findings of the risk assessment, a determination of what further remedial actions, if any, are necessary will be made. If SGPP or any designated PRP wishes to expedite cleanup efforts, it may continue negotiations with the EPA and undertake removal actions under supervision of the EPA and pursuant to appropriate agreements with governmental authorities (under enforcement authorities of CERCLA or those of other statutes). Further, as stated in section 3.3, Alternative to Listing/Defer to State, of this support document, the State of New York supports the placement of the Site on the NPL as is evident in a correspondence dated January 14, 2016, from Acting Commissioner Mr. Basil Seggos, Office of the Commissioner, New York State Department of Environmental Conservation (docket ID EPA-HQ-QLEM-2016-0434-0007).

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.5 Risk

Comment: SGPP asserted that the Site does not pose risk to the public or the environment. SGPP indicated that listing this Site on the NPL is based on such little evidence of hazardous substances at the Site that the listing in and of itself is unprecedented. SGPP made the following claims:

- With the exception of one ground water monitoring well in which TCE was detected at 13 parts per billion (ppb) in May 2016, there is not a single CERCLA hazardous substance present above applicable ground water or drinking water standards anywhere at the Site.
- Only vinyl chloride was detected in a single well (PSW 6) at a concentration of 1.3 ppb which is approximately ½ of the applicable maximum contaminant level (MCL) and it has not been detected by the Village in any of its supply wells during its annual monitoring between 2004 and 2009, in 2011, or in 2014, 2016.
- PFOA at the Site does not present any risk to health or the environment.
- There is no need for further investigation or remedial action of the PFOA by the EPA and therefore no sound basis for listing the Site on the NPL. On March 30, 2016, NYDOH announced that the Village's water was non-detect for PFOA as of March 13, 2016, and Village residents 'may use the water for any and all uses, including drinking and cooking.'

Response: The HRS site score above 28.50 demonstrates that the Site poses a sufficient relative risk to warrant placement on the NPL. SGPP has not documented that all unacceptable risk posed by the release from the SGPP facility has been eliminated by their actions. Listing makes a site eligible for remedial action funding under CERCLA, and the EPA will examine the site to determine site-specific risk and what response, if any, is appropriate as part of a separate stage of the Superfund process. The NPL is intended primarily to guide the EPA in determining which sites warrant further investigation to assess the nature and extent of public health and environmental risks associated with a release of hazardous substances, pollutants or contaminants. See, 81 FR 62428-62433 (Proposed Rule for Saint-Gobain Performance Plastics, September 9, 2016); see also 55 FR 51532 (Final Rule, Hazard Ranking System, December 14, 1990). CERCLA § 105(a)(8)(a) requires the EPA to determine NPL priorities among sites based on the "relative risk or danger to public health or welfare, or the environment." The criteria the EPA applies to determine this relative risk or danger is codified in the HRS, and it is the Agency's primary tool for deriving a site score based on the factors identified in CERCLA.

The HRS evaluation and a score above 28.50 represent the EPA's determination that the Site may pose a relative risk or danger to human health and the environment and warrants further investigation under CERCLA.

As part of the standard Superfund process and once the Site is on the NPL, the investigations performed to date to characterize the Site will be evaluated for completeness. Further information will be collected if deemed necessary to adequately characterize the risks posed by the Site, and based on this information, a risk assessment decision will be made determining what, if any, remedial action is necessary to protect human health and the environment.

The HRS documentation record at proposal establishes that the SGPP site poses sufficient relative risk to human health to warrant inclusion on the NPL, and it establishes that there could be unacceptable site specific risk associated with the Site. Contaminated soil and ground water have been documented at the Site, and drinking water target wells are contaminated with vinyl chloride above the cancer risk screening concentration and with PFOA at a level associated with unacceptable health effects. (See Figure 2 and pages 19-28 and 33-44 of the HRS documentation record at proposal.)

Regarding other released hazardous substances, TCE, vinyl chloride, PFOA, 1,2-DCE and PCBs were documented in sources and/or the observed release at the Site. (See pages 23 to 26, 33 to 49 of the HRS documentation record at proposal; see sections 3.7, Eligibility of PFOA for HRS Evaluation, and 3.8, Releases Below Regulatory Limits, of this support document).

In addition, a release of vinyl chloride was detected in PSW 6 above the cancer risk screening concentration (pages 38, 39 and 50 of the HRS documentation record at proposal). Also, PFOA was found in release concentrations in PSW 7 (pages 42, 43 and 51 of the HRS documentation record at proposal; page 9 of Exhibit 15<sup>4</sup> of SGPP's comment document, EPA docket ID: EPA-HQ-OLEM-2016-0434-0015). PFOA was detected at a level in this well that could lead to exposures above that associated with health effects. PSW 3 was also found to be contaminated with PFOA. (See sections 3.4, Need for Listing and Resulting Delay, and 3.9, Observed Releases, of this support document for additional information.)

Regarding the need for further investigation, the EPA's actions to evaluate the Site using the HRS and list the SGPP site are consistent with the requirements of CERCLA and the statutory purpose of the NPL. That the granular activated carbon (GAC) filtration system installed at the municipal water supply is currently removing PFOA from drinking water prior to water being distributed for use to residents does not negate that a release of hazardous substances, both PFOA and vinyl chloride in the aquifer has been documented. (See section 3.4, Need for Listing and Resulting Delay, of this support document for additional information.) Until the contamination in the aquifer has been permanently removed, the risk associated with the release to the aquifer has not been eliminated.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### **3.6 Economic Impact-Stigma of Listing**

Comment: Mr. Brownell and Mr. Goodermote stated that the discovery of PFOAs has affected the image of the Village, disrupted quality of life in the Community and possibly impacted property values, but that an effective remediation effort can do a great deal to restore the standing of the Village and address the reasonable concerns regarding health and safety of their fellow residents. An anonymous commenter indicated that his/her home is not worth anything.

---

<sup>4</sup> Health Advisory for Perfluorooctanoic Acid (PFOA) (USEPA, May 2016) [also available at: [https://www.epa.gov/sites/production/files/2016-05/documents/pfoa\\_health\\_advisory\\_final-plain.pdf](https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final-plain.pdf)]

Response: Inclusion of a site or facility on the NPL reflects the EPA's judgment that a significant release or threat of release has occurred and that the site is a priority for further investigation under CERCLA. The EPA notes that there are both costs and benefits that can be associated with listing a site. Among the benefits are increased health and environmental protection as a result of increased public awareness of potential hazards. In addition to the potential for Federally financed remedial actions, the addition of a site to the NPL could accelerate privately financed, voluntary cleanup efforts. Listing sites as national priority targets also may give States increased support for funding responses at particular sites. As a result of the additional CERCLA remedies, there will be lower human exposure to high-risk chemicals and higher quality surface water, ground water, soil, and air. Therefore, it is possible that any perceived or actual negative fluctuations in property values or development opportunities that may result from contamination may also be countered by positive fluctuations when a CERCLA investigation and any necessary cleanup are completed.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.7 Eligibility of PFOA for HRS Evaluation

Comment: SGPP asserted that per 42 U.S.C. § 9602(a), PFOA is not a CERCLA hazardous substance. It explained that despite having studied PFOA for years, the EPA has not designated PFOA as a hazardous substance under CERCLA or any other federal laws, nor has the EPA promulgated any binding ground water or drinking water standards for PFOA. SGPP then asserted that the EPA should not be listing the Site on the NPL based upon the presence of PFOA in ground water at the Site.

Response: PFOA was correctly identified as qualifying as a CERCLA pollutant or contaminant at the SGPP site, not a CERCLA hazardous substance, and, therefore, can be considered in the HRS site evaluation, as explained below. Furthermore, there is no requirement that a drinking water standard must be promulgated for a substance for it to be included in an HRS evaluation, only that it meet the CERCLA definition of a pollutant or contaminant.

CERCLA Section 101(33) defines "pollutant or contaminant" as including but not limited to,

any element, substance, compound, or mixture, including disease-causing agents, which after release into the environment and upon exposure, ingestion, inhalation, or assimilation into any organism, either directly from the environment or indirectly by ingestion through food chains, will or may reasonably be anticipated to cause death, disease, behavioral abnormalities, cancer, genetic mutation, physiological malfunctions (including malfunctions in reproduction) or physical deformations, in such organisms or their offspring.

Hazardous substances are defined for HRS purposes in HRS Section 1.1, *Definitions*, as,

CERCLA hazardous substances, pollutants, and contaminants as defined in CERCLA sections 101(14) and 101(33), except where otherwise specifically noted in the HRS. [55 FR 51586, December 14, 1990].

Therefore, while a substance may not be a CERCLA hazardous substance, it can be considered a HRS hazardous substance because the HRS defines pollutants and contaminants to be HRS hazardous substances.

PFOA can be considered a pollutant or contaminant at this site because it is at a concentration at the Site that could cause increase total cholesterol, thyroid disease, decreased response to vaccines, and pregnancy-related hypertension or preeclampsia (pages 241 to 242, 253 to 257 of Reference 13, *Health Effects Support Document*



for Perfluorooctanoic Acid (PFOA) (EPA, 2016)<sup>5</sup>). PFOA is clearly in the release from the SGPP facility. It was found in quantifiable levels in 2 of the 3 drinking water wells evaluated in the scoring of the Site. The PFOA concentration in a sample from PSW 7 was found to be 520 ng/L (0.52 µg/L), and the PFOA concentration in a sample from PSW 3 was found to be 140 ng/L (0.14 µg/L). PFOA has also been documented in monitoring wells at the Site at concentrations ranging from 570 ng/L to 18,000 ng/L (0.57 µg/L to 18 µg/L) (pages 41 – 43 of the HRS documentation record at proposal).

On pages 11 and 12 of the HRS documentation record at proposal, the EPA documented that the PFOA concentration in the sample from PSW 7 and in other samples from the Site are at levels that can cause adverse health effects, and, therefore, PFOA can be used in HRS scoring. It states:

The May 2016 Health Effects Support Document for PFOA established a Reference Dose (RfD) value of 0.00002 milligrams per kilogram per day (mg/kg/day) [Ref. 13, p. 256]. The calculated PFOA dose in Village Well 7 is 0.000025 mg/kg/day [Ref. 59, pp. 1–4]. The calculated PFOA dose in ground water can be up to 0.000897 mg/kg/day [Ref. 59, pp. 1–4]. Both calculated dose values exceed the RfD [Ref. 59, pp. 1–4]. Therefore, the TSCA submittal by SGPP documents an observed release by direct observation of PFOA at a concentration that likely results in harm to any organism following exposure [Ref. 59, pp. 1–4]. The exceedances of the RfD establishes PFOA as a Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) pollutant or contaminant (i.e., any element, substance, compound, or mixture, including disease-causing agents, which after release into the environment and upon exposure, ingestion, inhalation, or assimilation into any organism, either directly from the environment or indirectly by ingestion through food chains, will or may reasonably be anticipated to cause death, disease, behavioral abnormalities, cancer, genetic mutation, physiological malfunctions [including malfunctions in reproduction] or physical deformations, in such organisms or their offspring) [Ref. 1, Section 3.1.1; 46, pp. 14–15; 59, pp. 1–4].

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.8 Releases Below Regulatory Limits

Comment: SGPP stated that TCE or any other CERCLA hazardous substances have not been detected above any applicable standards in any drinking water supply well.

Response: The identification of PFOA, TCE and vinyl chloride found in soils and in ground water documented in the HRS documentation record at proposal is eligible for HRS evaluation because the identification of a release of these substances is consistent with CERCLA and the HRS. Furthermore, if SGPP is specifically implying that the identification of HRS observed releases of vinyl chloride and PFOA are incorrect because the levels of these substances were below drinking water standards, this challenge is also incorrect.

On July 16, 1982, when responding to public comments on the proposed (original) HRS (47 FR 31188), and again on September 8, 1983 (48 FR 40665), the EPA rejected the idea that releases within regulatory limits should not be considered in HRS scoring of a site in general or specifically when identifying “observed releases” under the HRS. As the EPA noted in 1982:

[E]mission or effluent limits do not necessarily represent levels which cause no harm to public health or the environment. These limitations are frequently established on the basis of economic impacts or achievability.

---

<sup>5</sup> Health Effects Support Document for Perfluorooctanoic Acid (PFOA) (EPA, 2016) is also available at: [https://www.epa.gov/sites/production/files/2016-05/documents/pfoa\\_hesd\\_final-plain.pdf](https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final-plain.pdf).

By contrast, an observed release represents a 100 percent likelihood that substances can migrate from the site (47 FR 31188, July 16, 1982).

Section 2.3 of the revised HRS (55 FR 51589, December 14, 1990) states that an observed release can be established either by direct observation or by chemical analysis. An observed release by chemical analysis has occurred when a contaminant is measured significantly above background level if some portion of the release is attributable to the site. Although contaminant levels may be lower than regulatory limits, an observed release has nevertheless occurred if the measured levels are significantly higher than background levels. The HRS does, however, consider whether releases are above regulatory limits in evaluating target populations, increasing by a factor of 10 the weight assigned populations exposed to contaminants above regulatory limits.

Of course, the observed release factor alone is not intended to reflect the hazard presented by the particular release. Instead, the hazard of the site is approximated by the total HRS score, which incorporates the observed release factors with other factors such as waste characteristics (including waste quantity, toxicity, and mobility) and targets. This total HRS score reflects the hazard of the site relative only to the other sites that have been scored. The actual degree of contamination and its effects are more fully determined during the remedial investigation that typically follows listing.

Furthermore, vinyl chloride was detected in a drinking water well above an HRS health based benchmark. Vinyl chloride was documented in PSW 6 at a concentration above the HRS cancer risk screening level for drinking water. Vinyl chloride in PSW 6 was documented at a concentration of 1.3 µg/L, and the HRS cancer risk screening concentration for vinyl chloride is  $2.1 \times 10^{-2}$  µg/L (or 0.021 µg/L) (page 50 of the HRS documentation record at proposal). See section 3.11.1, Level I Concentration, of this support document for additional information.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### **3.9 Observed Releases**

SGPP comments on the observed release to ground water are discussed below in the following subsections:

- 3.9.1 Observed Releases –Applicable Standards
- 3.9.2 Observed Releases –Attribution

#### **3.9.1 Observed Releases – Applicable Standards**

Comment: SGPP stated that TCE or any other CERCLA hazardous substances have not been detected above any applicable standards in any drinking water supply well.

Response: The EPA identified observed releases of TCE, vinyl chloride and PFOA to ground water according to the criteria in the HRS. As identified above in section 3.8, Releases Below Regulatory Limits, of this support document, neither CERCLA nor the HRS requires that the concentration establishing significant increases be above any applicable standards for an observed release to ground water to be eligible for evaluation at a Site. See section 3.9.2, Observed Releases - Attribution, of this support document for discussion of attribution of the releases to the Site.

The directions for establishing observed releases to ground water are in HRS Sections 3.1, 3.1.1 and 2.3. None of these sections require the concentration in the observed release samples to be above regulatory limits.

In evaluating the likelihood of release factor, HRS Section 3.1, *Likelihood of release*, states:

For an aquifer, evaluate the likelihood of release factor category in terms of an observed release factor or a potential to release factor.

In establishing an observed release, HRS Section 3.1.1, *Observed release*, states:

Establish an observed release to an aquifer by demonstrating that the site has released a hazardous substance to the aquifer. Base this demonstration on either:

- Direct observation—a material that contains one or more hazardous substances has been deposited into or has been observed entering the aquifer.
- Chemical analysis—an analysis of ground water samples from the aquifer indicates that the concentration of hazardous substance(s) **has increased significantly above the background concentration for the site** (see section 2.3). Some portion of the significant increase must be attributable to the site to establish the observed release, except: when the source itself consists of a ground water plume with no identified source, no separate attribution is required. [Emphasis added].

As referenced in HRS Section 3.1.1, quoted above, HRS Section 2.3, *Likelihood of release*, further directs to:

Establish an observed release either by **direct observation of the release of a hazardous substance into the media being evaluated** (for example, surface water) **or by chemical analysis** of samples appropriate to the pathway being evaluated (see sections 3, 4, and 6). **The minimum standard to establish an observed release by chemical analysis is analytical evidence of a hazardous substance in the media significantly above the background level. Further, some portion of the release must be attributable to the site. Use the criteria in Table 2–3 as the standard for determining analytical significance....** [Emphasis added].

HRS Table 2-3 outlines the criteria to determine analytical significance when establishing a significant increase. It states:

**TABLE 2–3—OBSERVED RELEASE CRITERIA FOR CHEMICAL ANALYSIS**

<b>Sample Measurement &lt; Sample Quantitation Limit<sup>a</sup></b>
No observed release is established.
<b>Sample Measurement ≥ Sample Quantitation Limit<sup>a</sup></b>
An observed release is established as follows:
<ul style="list-style-type: none"> <li>• If the background concentration is not detected (or is less than the detection limit), an observed release is established when the sample measurement equals or exceeds the sample quantitation limit.<sup>a</sup></li> <li>• If the background concentration equals or exceeds the detection limit, an observed release is established when the sample measurement is 3 times or more above the background concentration.</li> </ul>

<sup>a</sup> If the sample quantitation limit (SQL) cannot be established, determine [sic] if there is an observed release as follows:  
 —If the sample analysis was performed under the EPA Contract Laboratory Program, use the EPA contract-required quantitation limit (CRQL) in place of the SQL.  
 —If the sample analysis is not performed under the EPA Contract Laboratory Program, use the detection limit (DL) in place of the SQL.

In the HRS documentation record at proposal, the EPA identified both observed releases by direct observation and by chemical analyses from the SGPP facility according to the HRS requirements cited above.

### Observed release by direct observation

Page 33 of the HRS documentation record at proposal documents an observed release of PFOA by direct observation to the aquifer based on the finding that a material that contains one or more hazardous substances has been deposited into the aquifer at the Site. Pages 33 of the HRS documentation record at proposal states:

Information provided to EPA by SGPP documents an observed release by direct observation to the aquifer being evaluated. On December 12, 2014, SGPP became aware of the presence of PFOA in the [V]illage [of Hoosick Falls] drinking water supply and obtained the analytical results on December 15, 2014 [Ref. 19, p. 1]. On December 30, 2014, counsel for SGPP submitted notification to EPA under the Section 8(e) of TSCA (15 U.S.C. § 2601 *et seq.*) regarding the presence of PFOA in the Village public drinking water supply; PFOA analytical results for the [V]illage wells were attached to the notification [Ref. 19, pp. 1–10]. The notification acknowledges that SGPP processed fluoropolymers that were made with PFOA at a facility within the [V]illage [Ref. 19, p. 1]. Section 8(e) of TSCA requires any person who manufactures, processes, or distributes in commerce a chemical substance or mixture and who obtains information which reasonably supports the conclusion that such substance or mixture presents a substantial risk of injury to health or the environment to immediately notify EPA of such information [Ref. 31, pp. 32, 33].

The May 2016 Health Effects Support Document for PFOA established an RfD value of 0.00002 mg/kg/day [Ref. 13, p. 256]. The calculated PFOA dose in the Village Well 7 is 0.000025 mg/kg/day [Ref. 59, pp. 1–4]. The calculated PFOA dose in ground water can be up to 0.000897 mg/kg/day [Ref. 59, pp. 1–4]. Both calculated dose values exceed the RfD [Ref. 59, pp. 1–4]. Therefore, the TSCA submittal by SGPP documents an observed release by direct observation of PFOA at a concentration that likely results in harm to any organism following exposure [Ref. 59, pp. 1–4]. The exceedances of the RfD establishes PFOA as a CERCLA pollutant or contaminant [Ref. 1, Section 3.1.1; 46, pp. 14–15; 59, pp. 1–4].

In June 2016, SGPP and NYSDEC State Superfund Program entered into an Order on Consent and Administrative Settlement [Ref. 18, pp. 1–31]. The Order designates the McCaffrey Street facility SGPP [the location of the Saint-Gobain Performance Plastics site] as a “significant threat to public health or the environment” [Ref. 18, p. 4]. Therefore, the Order directs SGPP to prepare and submit an RI/FS work plan for the McCaffrey Street facility to NYSDEC that includes a study and assessment of alternatives to eliminate or reduce PFOA in the [municipal water supply] MWS [Ref. 18, p. 4].

### Observed release by chemical analysis

An observed release by chemical analysis was identified based on a significant increase in PFOA, TCE and vinyl chloride (VC) levels and that at least part of the significant increase was due to a release from the Site. Pages 33 through 48 of the HRS documentation record at proposal document an observed release of PFOA, TCE and vinyl chloride by chemical analysis to the aquifer. The concentration of these substances were found to be significantly increased above background levels established for the Site on pages 33 to 44 of the HRS documentation record at proposal. Figures 2 and 3 on pages 13 and 14 of the HRS documentation record at proposal show the sample locations. See also Figures 1 and 2 of this support document. A summary table showing the background levels and observed release concentrations for TCE, vinyl chloride and PFOA extracted from pages 35 to 44 of the HRS documentation record at proposal is provided below:

BACKGROUND SAMPLE RESULTS – TCE						
Field Sample ID	CLP Sample ID	Hazardous Substance	Date Sampled	Result (µg/L)	RDL* (µg/L)	Reference(s)
SGPP-MW05	BD3E9	TCE	5/11/16	5.0 U	5.0	22, p. 33; 23, p. 133; 33, p. 8; 35, pp. 6–10, 50, 140; 47, pp. 5, 325
SGPP-MW06 (Duplicate of SGPP-MW05)	BD3F0	TCE	5/11/16	5.0 U	5.0	22, p. 33; 23, p. 133; 33, p. 8; 35, pp. 6–10, 58, 141; 47, pp. 5, 335
µg/L = micrograms per liter RDL = reporting detection limit U = The analyte was analyzed for, but was not detected at a level greater than or equal to the level of the adjusted CRQL for sample and method. *The RDL for each result is the CRQL adjusted for sample and method [Ref. 33, p. 8]. Since the samples were analyzed through CLP, these adjusted CRQLs are used in place of the HRS-defined SQL [Ref. 1, Sections 1.1 and 2.3].						
OBSERVED RELEASE SAMPLE RESULTS – TCE						
Field Sample ID	CLP Sample ID	Hazardous Substance	Date Sampled	Result (µg/L)	RDL* (µg/L)	Reference(s)
SGPP-MW03	BD3E7	TCE	5/11/2016	13	5.0	22, p. 33; 23, p. 134; 33, p. 8; 35, pp. 6–10, 36, 138; 47, pp. 4, 304
µg/L = micrograms per liter RDL = reporting detection limit *The RDL for each result is the CRQL adjusted for sample and method [Ref. 33, p. 8]. Since the samples were analyzed through CLP, these adjusted CRQLs are used in place of the HRS-defined SQL [Ref. 1, Sections 1.1 and 2.3].						
<b>Notes on samples</b> • Release sample concentration is compared to the maximum RDL for non-detect background samples. • Sampling Methods: The background and release samples were all collected by EPA from monitoring wells installed by SGPP at the McCaffrey Street facility that are screened in the same hydrologic unit, using an EPA SOP, during the same sampling event in May 2016 [Figure 2; Ref. 7, pp. 204, 206, 211, 213; 22, pp. 31–33; 23, pp. 47–50, 133–134; 30, pp. 46–50, 56–58]. • Analytical Procedures: The background and release samples were all analyzed for Organic TAL VOC parameters via EPA CLP SOW SOM02.3 (low/medium concentration) by the same laboratory (Chemtech Consulting Group of Mountainside, New Jersey) [Ref. 23, pp. 1, 3–4, 133–134; 47, pp. 1, 304, 325]. The chemical analyses were coordinated through the EPA CLP; EPA validated the data according to EPA Region 2 data validation guidelines (SDG: BD3E5) [Ref. 35, pp. 1, 6–10].						

BACKGROUND SAMPLE RESULTS – VC						
Field Sample ID	CLP Sample ID	Hazardous Substance	Date Sampled	Result (µg/L)	RDL* (µg/L)	Reference(s)
SGPP-DW02	BD3G2	VC	5/16/2016	0.50 U	0.50	22, p. 37; 23, p. 148; 33, p. 8; 43, pp. 2–6, 33, 116; 48, pp. 4, 58
SGPP-DW04*	BD3G4	VC	5/16/2016	0.50 U	0.50	22, p. 37; 23, p. 148; 33, p. 8; 43, pp. 2–6, 49, 118; 48, pp. 4, 79
SGPP-DW01	BD3G1	VC	5/16/2016	0.50 U	0.50	22, p. 37; 23, p. 147; 33, p. 8; 43, pp. 2–6, 28, 115; 48, pp. 3, 48
<p>* Environmental duplicate of SGPP-DW02</p> <p>µg/L = micrograms per liter</p> <p>RDL = reporting detection limit</p> <p>U = The analyte was analyzed for, but was not detected at a level greater than or equal to the level of the adjusted CRQL for sample and method.</p> <p>*The RDL for each result is the CRQL adjusted for sample and method [Ref. 33, p. 8]. Since the samples were analyzed through CLP, these adjusted CRQLs are used in place of the HRS-defined SQL [Ref. 1, Sections 1.1 and 2.3].</p>						
OBSERVED RELEASE SAMPLE RESULTS – VC						
Field Sample ID	CLP Sample ID	Hazardous Substance	Date Sampled	Result (µg/L)	RDL* (µg/L)	Reference(s)
SGPP-DW03	BD3G3	VC	5/17/2016	1.3	0.50	22, p. 38; 23, p. 152; 43, pp. 3–6, 39, 117; 48, pp. 7, 68
<p>µg/L = micrograms per liter</p> <p>RDL = reporting detection limit</p> <p>*The RDL for each result is the CRQL adjusted for sample and method [Ref. 33, p. 8]. Since the samples were analyzed through CLP, these adjusted CRQLs are used in place of the HRS-defined SQL [Ref. 1, Sections 1.1 and 2.3].</p> <p><i>Notes on samples</i></p> <ul style="list-style-type: none"> <li>• Release sample concentration is compared to the RDLs reported for the non-detect background samples.</li> <li>• Sampling Methods: The background and release samples were all collected by EPA from the three active village wells via the raw water sampling spigot within the Hoosick Falls water treatment plant, that withdraw water from the same hydrologic unit, using an EPA SOP, during the same sample event in May 2015 [Figure 3; Ref. 6, pp. 12–13, 53–54; 8, p. 2; 22, pp. 37–38, 58; 23, pp. 147–148, 152; 28, pp. 1, 8, 13, 24–25].</li> <li>• Analytical Procedures: The background and release samples were all analyzed for Organic TAL VOC parameters via EPA CLP SOW SOM02.3 (trace concentration) by the same laboratory (Chemtech Consulting Group of Mountainside, New Jersey) [Ref. 23, pp. 1, 147–148, 152; 47, pp. 1, 48, 58, 68, 79]. The chemical analyses were coordinated through the EPA CLP; EPA validated the data according to EPA Region 2 data validation guidelines (SDG: BD3F5) [Ref. 35, pp. 1, 3–6].</li> </ul>						

SGPP FACILITY BACKGROUND SAMPLE RESULTS – PFOA						
Field Sample ID	Laboratory Sample ID	Hazardous Substance	Date Sampled	Result (ng/L)	MDL* (ng/L)	Reference(s)
SGPP-MW01D	K1605066-004	PFOA	5/11/16	40	0.27	22, p. 33; 23, p. 143; 55, pp. 9, 16
ng/L = nanograms per liter MDL = method detection limit * For HRS purposes, the DL used is the MDL, which is the lowest concentration of analyte that a method can detect reliably in either a sample or blank [Ref. 1, Section 1.1]. Since the sample analysis was not performed under the CLP, the MDL is used in place of the HRS-defined SQL [Ref. 1, Section 2.3].						
SGPP FACILITY OBSERVED RELEASE SAMPLE RESULTS – PFOA						
Field Sample ID	Laboratory Sample ID	Hazardous Substance	Date Sampled	Result (ng/L)	MDL** (ng/L)	Reference(s)
SGPP-MW02D	K1605066-006	PFOA	5/10/2016	18,000	14	22, p. 32; 23, p. 143; 55, pp. 9, 18
SGPP-MW03	K1605066-008	PFOA	5/11/2016	7,200	14	22, p. 33; 23, p. 143; 55, pp. 9, 20
SGPP-MW04	K1605066-009	PFOA	5/10/2016	2,100	5.4	22, p. 32; 23, p. 143; 55, pp. 9, 21
SGPP-MW05	K1605066-010	PFOA	5/11/2016	590	0.27	22, p. 33; 23, p. 143; 55, pp. 9, 22
SGPP-MW06*	K1605066-011	PFOA	5/11/2016	570	0.27	22, p. 33; 23, p. 144; 55, pp. 10, 23
ng/L = nanograms per liter MDL = method detection limit * environmental duplicate of SGPP-MW05 ** For HRS purposes, the DL used is the MDL, which is the lowest concentration of analyte that a method can detect reliably in either a sample or blank [Ref. 1, Section 1.1]. Since the sample analysis was not performed under the CLP, the MDL is used in place of the HRS-defined SQL [Ref. 1, Section 2.3].  <i>Notes on samples</i> <ul style="list-style-type: none"> <li>• Release sample concentrations are compared to the most upgradient deep well sample concentration.</li> <li>• Sampling Methods: The background and release samples were all collected by EPA from monitoring wells installed by SGPP at the McCaffrey Street facility that are screened in the same hydrologic unit, using an EPA SOP, during the same sampling event in May 2016 [Figure 2; Ref. 7, pp. 200, 202–206, 208, 210–213; 22, pp. 31–33; 23, pp. 41–45, 48–51, 143–144; 30, pp. 46–50, 56–58].</li> <li>• Analytical Procedures: The background and release samples were all analyzed for PFCs by a single EPA-subcontracted laboratory using standard operating procedures for extraction, analysis (high performance liquid chromatography/mass spectrometry), and quality control [Ref. 55, pp. 77, 80; 57, pp. 3, 10–18, 23]. The data were validated by EPA according to EPA Region 2 data validation guidelines [Ref. 58, pp. 1–22].</li> <li>• The behavior and fate of PFCs in sandy aquifer sediment is affected by pore water pH, which impacts their adsorptive properties. As pH decreases the potential of PFCs to adsorb to aquifer sediment increases [Ref. 53, pp. 2, 7]. Background ground water sample SGPP-MW01D showed a higher pH than the release samples, suggesting that the PFOA exhibited greater mobility near the background well than near the release wells.</li> </ul>						

VILLAGE WELLS BACKGROUND SAMPLE RESULTS – PFOA						
Field Sample ID	Laboratory Sample ID	Hazardous Substance	Date Sampled	Result (ng/L)	MDL** (ng/L)	Reference(s)
SGPP-DW02	K1605268-002	PFOA	5/16/2016	140	0.27	22, p. 37; 23, p. 158; 56, pp. 9, 14
SGPP-DW04*	K1605268-004	PFOA	5/16/2016	150	0.27	22, p. 37; 23, p. 158; 56, pp. 9, 16
* Environmental duplicate of SGPP-DW02 ng/L = nanograms per liter MDL = method detection limit ** For HRS purposes, the DL used is the MDL, which is the lowest concentration of analyte that a method can detect reliably in either a sample or blank [Ref. 1, Section 1.1]. Since the sample analysis was not performed under the CLP, the MDL is used in place of the HRS-defined SQL [Ref. 1, Section 2.3].						
VILLAGE WELL OBSERVED RELEASE SAMPLE RESULTS – PFOA						
Field Sample ID	Laboratory Sample ID	Hazardous Substance	Date Sampled	Result (ng/L)	MDL* (ng/L)	Reference(s)
SGPP-DW01	K1605268-001	PFOA	5/16/2016	520	0.27	22, p. 37; 23, p. 158; 56, pp. 9, 13
ng/L = nanograms per liter MDL = method detection limit * For HRS purposes, the DL used is the MDL, which is the lowest concentration of analyte that a method can detect reliably in either a sample or blank [Ref. 1, Section 1.1]. Since the sample analysis was not performed under the CLP, the MDL is used in place of the HRS-defined SQL [Ref. 1, Section 2.3].						

That at least part of the significant increase in the release concentrations of PFOA, TCE and vinyl chloride is attributable to the SGPP site is documented on pages 45 to 48 of the HRS documentation record at proposal. In summary, the EPA showed that TCE and PFOA are associated with the Site sources, and vinyl chloride is a degradation product of TCE. In addition, the EPA documented that there are no known upgradient (in terms of ground water flow) alternative sources of these contaminants in the vicinity of the Site. Section 3.9.2, Observed Releases - Attribution, of this support document further discusses the attribution of vinyl chloride to the Site.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.9.2 Observed Releases – Attribution

Comment: SGPP contested the attribution of the observed release of vinyl chloride to the Site specifically stating that attribution of the vinyl chloride in PSW 6 to alleged historic releases of TCE at Saint-Gobain Performance Plastics Corporation is flawed; the single detection of vinyl chloride at a concentration of 1.3 ppb in PSW 6 is attributable to low levels of TCE in ground water at the Site is not supported by the scientific data; the EPA has not presented sufficient evidence to support the degradation of TCE at the Site in MW-6 to the vinyl chloride detected in PSW 6; and the EPA's analysis of the migration of vinyl chloride in the aquifer is flawed and is inconsistent with claims made in the HRS documentation record at proposal.

SGPP commented that the EPA's assumption that the single detection of vinyl chloride at a concentration of 1.3 ppb in PSW 6 is attributable to low levels of TCE in ground water at the Site is not supported by the scientific data. It explained that although vinyl chloride is a breakdown product of TCE, the EPA has not presented any degradation rate calculations or other ground water data to adequately explain how the 13 ppb of TCE detected in MW-3 at the Site may be the source of the 1.3 ppb of vinyl chloride detected in PSW 6. It, thus, claimed that the available data suggest the contrary.

SGPP also commented that the EPA's explanation of the absence of TCE or vinyl chloride in any of the downgradient monitoring wells by theorizing that the vinyl chloride is 'traveling horizontally' in the upper aquifer



before being drawn down into the lower aquifer by the pumping of PSW 6 is unavailing (see page 47 of the HRS documentation record). SGPP contended that there is no data to support this assumption, and in fact, the EPA rejected the same theory when evaluating whether the vinyl chloride in PSW 6 might be attributable to the nearby laundromat, stating that the silt and clay layer that separated the upper and lower aquifers ‘would likely form a barrier to a solvent release.’ Additionally, contended SGPP, this theory fails to account for the fact that vinyl chloride has historically not been detected in the Village’s wells (SGPP Exhibits 1, 2, and 12).

SGPP commented that there is no basis to conclude that vinyl chloride in PSW 6 is attributable to conditions at the Site. SGPP made the following claims to support its comments:

- Vinyl chloride is not present in any monitoring well at the Site or any of the downgradient or off-site monitoring wells located between the Site and PSW 6 (References 23 and 35 of the HRS documentation record at proposal). Available ground water sampling data from the Site and the monitoring wells installed by the EPA between the Site and the Village wells demonstrate that the single detection of 1.33 ppb of vinyl chloride in PSW 6 is not attributable to releases at the Site. (References 23 and 35 of the HRS documentation record at proposal.)
- Vinyl chloride was not detected by the Village in any of its supply wells during its annual monitoring between 2004 and 2009, in 2011, or in 2014, as would be expected if the vinyl chloride detected by the EPA in 2016 were attributable to historic releases of TCE from past operations at the Site. (SGPP Exhibits 1, 2, 3, and 12.)<sup>6</sup>
- TCE was not detected by the EPA in any of the ground water monitoring wells located downgradient of MW-3 (including MW-4 and MW-5 at the Site and EPA offsite well GW-03 and GW-04). (References 23 and 35 of the HRS documentation record at proposal.)
- TCE was not detected by the EPA in any of the Village’s supply wells between 2004 and 2009, or in 2011, 2014, or 2015 (SGPP Exhibits 1-3, 12) (References 23 and 35 of the HRS documentation record at proposal). If TCE were migrating from the vicinity of MW-3 at the Site towards the Village’s wells, one would expect to find appreciable amounts of TCE downgradient from MW-3. Similarly, one would expect there to be some historic detections of TCE in the Village’s wells. The absence of such data undermines the EPA’s conclusion that the vinyl chloride in PSW 6 is associated with the low levels of TCE detected at the Site.

Response: The significant increase in the vinyl chloride concentration in well PSW 6 was correctly attributed to the SGPP site consistent with the HRS. In establishing attribution of a release of vinyl chloride to this Site, the EPA documented that there are parent substances of vinyl chloride associated with the Site sources and in observed releases attributable to the Site, which the commenter did not challenge. Further, the EPA documented that the conditions do not prevent the parent substances from degrading to the daughter substance vinyl chloride and that the substances could migrate to the location of well PSW 6. The EPA also documented that there is no evidence suggesting that the significant increase in vinyl chloride concentrations could have come from other sources in the vicinity of the Site.

The HRS does not establish specific requirements for establishing attribution. HRS Section 3.1.1, *Observed release*, which provides specific instructions for establishing the observed release to the aquifer, states:

Establish an observed release to an aquifer by demonstrating that the site has released a hazardous substance to the aquifer. Base this demonstration on either:

---

<sup>6</sup> Exhibit 1 of SGPP comment document is: Annual Drinking Water Quality Report for 2011, Village of Hoosick Falls.  
Exhibit 2 of SGPP comment document is: Annual Drinking Water Quality Report for 2014, Village of Hoosick Falls.  
Exhibit 3 of SGPP comment document is: Annual Drinking Water Quality Report for 2015, Village of Hoosick Falls.  
Exhibit 12 of SGPP comment document is: National drinking Water Database, Hoosick Falls (V) Pws – Troy, NY.

- Direct observation—a material that contains one or more hazardous substances has been deposited into or has been observed entering the aquifer.
- Chemical analysis—an analysis of ground water samples from the aquifer indicates that the concentration of hazardous substance(s) has increased significantly above the background concentration for the site (see section 2.3). **Some portion of the significant increase must be attributable to the site to establish the observed release**, except: when the source itself consists of a ground water plume with no identified source, no separate attribution is required. [Emphasis added].

HRS Section 2.3, *Likelihood of release*, presents the basic requirements for establishing an observed release including attribution to the site in relevant part, as follows:

Establish an observed release either by direct observation of the release of a hazardous substance into the media being evaluated (for example, surface water) or by chemical analysis of samples appropriate to the pathway being evaluated (see sections 3, 4, and 6). The minimum standard to establish an observed release by chemical analysis is analytical evidence of a hazardous substance in the media significantly above the background level. **Further, some portion of the release must be attributable to the site.** [Emphasis added].

The HRS documentation record at proposal clearly established attribution of the significant increase in vinyl chloride concentrations in well PSW 6 to the Site. First, on pages 23 to 26 of the HRS documentation record at proposal, the EPA established that the TCE and cis-1,2-DCE are associated with the source at the site. In addition, the EPA documented observed releases of TCE. These substances are parent substances for vinyl chloride, as documented below. In characterizing the contaminated soil source at the Site, section 2.4.1 of the HRS documentation record at proposal provides sampling analytical results documenting TCE, and cis-1,2-DCE in soil samples on Site.

Page 19 of the HRS documentation record at proposal documents that chlorinated solvents were found in source samples:

Analysis of soil and ground water samples collected as part of a May 1996 [Environmental Site Assessment] ESA prepared for a former facility occupant, Furon Company, reported the presence of TCE at an estimated concentration of 4.0 µg/kg at soil sample location MW-1M-0 and in ground water in two monitoring wells, MW-2M (13 µg/L) and MW-5M [6 µg/L (estimated) and duplicate result 7 µg/L (estimated)] [Ref. 40, pp. 36, 40, 42, 44]. The compound 1,2-DCE, which the Phase II noted is a breakdown product of TCE, was detected in MW-5M and its duplicate MW-15M at 2.0 µg/L each [Ref. 40, p. 42]. The Phase II ESA noted that the facility maintains floor drains and a sump, and concluded that the TCE source may be related to the facility sump pit [Ref. 40, p. 46].

In addition, pages 36 and 37 of the HRS documentation record at proposal document a significant increase in TCE associated with the Site. Page 36 documents the background level for TCE:

<b>TABLE 10. BACKGROUND SAMPLE RESULTS – TCE</b>						
<b>Field Sample ID</b>	<b>CLP Sample ID</b>	<b>Hazardous Substance</b>	<b>Date Sampled</b>	<b>Result (µg/L)</b>	<b>RDL* (µg/L)</b>	<b>Reference(s)</b>
SGPP-MW05	BD3E9	TCE	5/11/16	5.0 U	5.0	22, p. 33; 23, p. 133; 33, p. 8; 35, pp. 6–10, 50, 140; 47, pp. 5, 325
SGPP-MW06 (Duplicate of SGPP-MW05)	BD3F0	TCE	5/11/16	5.0 U	5.0	22, p. 33; 23, p. 133; 33, p. 8; 35, pp. 6–10, 58, 141; 47, pp. 5, 335

µg/L = micrograms per liter

RDL = reporting detection limit

U = The analyte was analyzed for, but was not detected at a level greater than or equal to the level of the adjusted CRQL for sample and method.

\*The RDL for each result is the CRQL adjusted for sample and method [Ref. 33, p. 8]. Since the samples were analyzed through CLP, these adjusted CRQLs are used in place of the HRS-defined SQL [Ref. 1, Sections 1.1 and 2.3].

#### **Contaminated Samples – TCE**

On May 11, 2016, EPA collected ground water sample SGPP-MW03 from SGPP facility monitoring well MW-3. Analysis reported the presence of TCE at a concentration of 13 µg/L. This result is compared to the TCE results reported for designated background monitoring well, MW-5.

Page 37 of the HRS documentation record at proposal documents observed release levels of TCE:

<b>TABLE 12. OBSERVED RELEASE SAMPLE RESULTS – TCE</b>						
<b>Field Sample ID</b>	<b>CLP Sample ID</b>	<b>Hazardous Substance</b>	<b>Date Sampled</b>	<b>Result (µg/L)</b>	<b>RDL* (µg/L)</b>	<b>Reference(s)</b>
SGPP-MW03	BD3E7	TCE	5/11/2016	13	5.0	22, p. 33; 23, p. 134; 33, p. 8; 35, pp. 6–10, 36, 138; 47, pp. 4, 304

µg/L = micrograms per liter

RDL = reporting detection limit

\*The RDL for each result is the CRQL adjusted for sample and method [Ref. 33, p. 8]. Since the samples were analyzed through CLP, these adjusted CRQLs are used in place of the HRS-defined SQL [Ref. 1, Sections 1.1 and 2.3].

#### *Notes on samples*

- Release sample concentration is compared to the maximum RDL for non-detect background samples.
- Sampling Methods: The background and release samples were all collected by EPA from monitoring wells installed by SGPP at the McCaffrey Street facility that are screened in the same hydrologic unit, using an EPA SOP, during the same sampling event in May 2016 [Figure 2; Ref. 7, pp. 204, 206, 211, 213; 22, pp. 31–33; 23, pp. 47–50, 133–134; 30, pp. 46–50, 56–58].

- Analytical Procedures: The background and release samples were all analyzed for Organic TAL VOC parameters via EPA CLP SOW SOM02.3 (low/medium concentration) by the same laboratory (Chemtech Consulting Group of Mountainside, New Jersey) [Ref. 23, pp. 1, 3-4, 133–134; 47, pp. 1, 304, 325]. The chemical analyses were coordinated through the EPA CLP; EPA validated the data according to EPA Region 2 data validation guidelines (SDG: BD3E5) [Ref. 35, pp. 1, 6–10].

In addition, the HRS documentation record at proposal identifies activities at the SGPP commonly associated with chlorinated solvents. Page 15 of the HRS documentation record at proposal identifies that historical facility operations related to the manufacture of circuit board laminates and electronics were conducted at the SGPP facility from the early 1960s to 1987 (i.e., approximately 26 years). Also as discussed on page 34 of the HRS documentation record at proposal, chlorinated solvents can be associated with the Site based on a March 1996 Phase I Environmental Site Assessment (ESA) prepared for a former site occupant, Allied Signal Fluorglas. This document indicates that past uses of the facility included activities related to circuit board and electronics manufacturing. Further, on pages 19, 36, 41 and 42 of the HRS documentation record at proposal TCE, cis-1,2-DCE and PFOA were also documented in ground water samples collected in monitoring wells located on the SGPP facility.

Second, on pages 18, 35, 46 and 47 of the HRS documentation record at proposal, a rationale for why vinyl chloride is a possible degradation product of TCE at this site was provided to document this degradation could occur. An explanation of the degradation process of TCE to vinyl chloride provided in the HRS documentation record at proposal explains on pages 18, 35 and 47 that subsurface microorganisms can degrade chlorinated solvents via a variety of chemical processes. “The most important process for the natural biodegradation of chlorinated solvents is reductive dechlorination” (see page 35 of the HRS documentation record at proposal and pages 15-17 of Reference 38 of the HRS documentation record at proposal). The discussion of the degradation of TCE to its daughter substances (cis-1,2-DCE and vinyl chloride) found in releases attributable to the Site is supported by Reference 38<sup>7</sup> of the HRS documentation record at proposal. Page 16 of Reference 38 of the HRS documentation record at proposal illustrates the transformation of chlorinated ethenes, such as TCE, via reductive dechlorination. In general, reductive dechlorination occurs by sequential dechlorination from tetrachloroethylene (PCE) to TCE to DCE to vinyl chloride to ethene. Page 16 of Reference 38 of the HRS documentation record at proposal provides a figure illustrating this degradation:

---

<sup>7</sup> Reference 38 of the HRS documentation record at proposal: EPA. Technical Protocol for Evaluating Natural Attenuation of Chlorinated Solvents in Ground Water (EPA/600/R-98/128 (excerpts). September 1998.

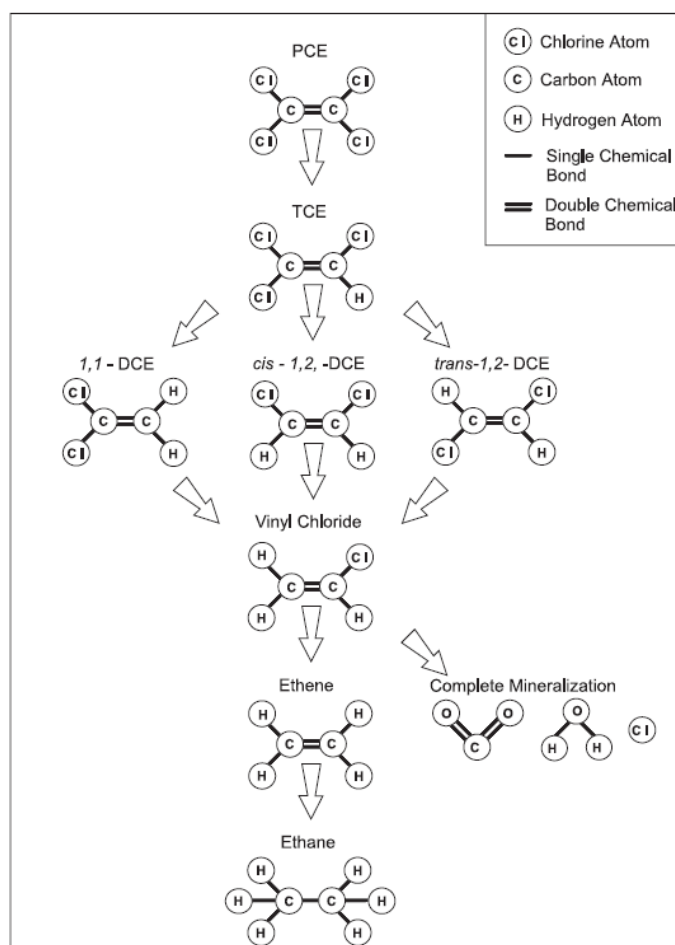


Figure 2.2 Reductive dehalogenation of chlorinated ethenes.

This information illustrates how TCE, detected in the source at the Site, can degrade to cis-1,2-DCE (also detected in a source at the Site) and vinyl chloride detected in a ground water observed release sample. This information is sufficient to attribute the release of solvents, including vinyl chloride to sources at the SGPP site. Further, SGPP has not provided evidence of another source of the chlorinated solvent including vinyl chloride documented at the Site.

Third, on pages 11 and 30 of the HRS documentation record at proposal the EPA identified that there is a possible migration pathway from the Site source to ground water. It did this by showing the geologic structure at the Site does not prevent contamination from migrating from the facility to the contaminated wells. Page 11 of the HRS documentation describes that the geologic features of the sand and gravel aquifer makes it conducive for contaminants to migrate from the sources to the wells.

Page 11 of the HRS documentation record at proposal states:

The municipal wells withdraw water from the lower sand and gravel aquifer that overlies bedrock [see Section 3.0.1 of this HRS documentation record]. The lower aquifer was deposited by glacial meltwater [Ref. 6, pp. 12–13, 17–18; 27, p. 3]. The deep gravel deposit is as much as 25 feet thick and is generally overlain by approximately 12 feet of fine sand that is part of the aquifer [Ref. 27, p. 3]. The areal extent of the sand and gravel aquifer is generally limited to the river valley areas, including the Hoosic River and its tributaries [Ref. 10, p. 1; 11, p. 21]. The lower aquifer is overlain by approximately 8 feet of poorly permeable clay and silt, which can be a barrier to water flow and separates the deep aquifer from the shallow aquifer [Ref. 6, pp. 12–13; 27, p. 3]. However, the lower aquifer is described as exhibiting “leaky artesian conditions” and there is evidence of site-attributable hazardous substance migration across the silt and clay layer; therefore, an aquifer interconnection occurs within 2 miles of sources at the site and, for Hazard Ranking System (HRS) scoring purposes, the upper and lower aquifers are evaluated together as a single hydrologic unit [Figure 3; see Section 3.1.1 of this HRS documentation record; Ref. 1, Section 3.0.1.2.1; 6, p. 18].

Page 30 of the HRS documentation record at proposal states:

The municipal wells withdraw water from the lower of two sand and gravel aquifers that overlie bedrock, as evidenced by available background information that indicates that Village Well 3, which has a total depth of 55 feet and a pump suction flange depth of 53 feet, withdraws water from the lower aquifer and that the total well depths and pump suction flange depths of Village Wells 6 and 7 are of similar or greater depth; therefore it is reasonable to conclude that Village Wells 6 and 7 also withdraw water from the lower aquifer [Ref. 27, pp. 7, 18; 28, pp. 1, 8, 13, 24–25, 27, 31, 37]...

The sand and gravel aquifer extends north of the well field along the valleys of the Hoosic River and its tributaries and underlies the SGPP facility [Ref. 10, p. 1]. Surficial deposits outside the valley areas consist primarily of glacial till, a heterogeneous mixture of grain sizes ranging from clay and silt to cobbles and boulders [Ref. 11, pp. 17, 20]. The thickness of the glacial till is variable and may exceed 100 feet; ground water yields are generally small and are considered sufficient for domestic use [Ref. 11, pp. 17, 20]....

...

The lower sand and gravel aquifer is described as exhibiting “leaky artesian conditions” [Ref. 6, p. 18]. In addition, the detection of VC in Village Well 6 documents that contamination has migrated between the upper and lower aquifers [see Section 3.1.1 of this HRS documentation record].

Pages 11 and 47 of the HRS documentation record at proposal also document that if there is a transport route from the Site source to the wells, the Site source would be within the radius of influence of the city wells, identifying that any ground water beneath the facility would be drawn to the city wells. Regarding the radius of influence of the city wells, the HRS documentation record states the following:

Page 11 of the HRS documentation record at proposal states:

[T]he pumping of the [V]illage wells has created a radius of influence that extends out as far as 0.67 mile and encompasses the SGPP facility [Ref. 7, pp. 22–23; 29, pp. 1–3; 42, p. 1]. Shallow

ground water flow beneath the SGPP facility is northwest to southeast toward the village wells [Ref. 7, pp. 22-23; 42, p. 1].

Page 47 of the HRS documentation record at proposal states:

EPA calculated the estimated radius of influence for the Village of Hoosick Falls water supply wells [Ref. 29, pp. 1–3]. Based on this calculation, the maximum radius of influence for the Village of Hoosick Falls water supply wells is estimated to be 3,530 feet (0.67 mile) [Ref. 29, pp. 2–3]. Based on this radius of influence, and the absence of VC in Village Wells 3 and 7, it is unlikely that any potential sources to the south, southeast, or southwest are contributing contamination to ground water beneath the SGPP facility or Village Well 6 [Ref. 43, pp. 28, 33, 49].

Fourth, pages 33 through 49 of the HRS documentation record at proposal present the EPA's rational for asserting that the significant increase in vinyl chloride or the parent substance TCE did not come from other sites. The background locations in ground water and soil samples screen out other upgradient and cross-gradient sources. Also, the EPA could not identify another site that used chlorinated solvents.

Regarding background wells location, page 34 of the HRS documentation record at proposal states:

SGPP facility monitoring well MW-5 is evaluated as representing background conditions. Based on the direction of ground water flow beneath the facility at the time of sampling, MW-5 is side-gradient to MW-3 [Figure 2; Ref. 7, pp. 20, 208, 210–213; 23, pp. 41–42, 44, 47, 49; 42, pp. 1, 6]. .... Analysis of ground water sample SGPP-MW05 and duplicate sample SGPP-MW06 reported non-detect values for TCE with an RDL of 5.0 µg/L [Ref. 22, p. 33; 23, p. 133; 33, p. 8; 35, pp. 2, 6–10, 50, 58, 140–141; 47, pp. 325, 335]. .... Ground water samples collected from SGPP facility monitoring wells MW-1 (Sample No SGPP-MW01D) and MW-2 (Sample No. SGPP-MW02D), which are situated upgradient of MW-3, reported non-detect values for TCE, documenting that the contamination has not migrated onto the SGPP facility from an upgradient off-site source to the north-northwest [Figure 2; Ref. 7, pp. 20, 200, 203, 208, 210; 22, p. 32–33; 23, pp. 41, 45, 48, 130, 134; 35, pp. 2, 6–10, 21, 29; 42, p. 1; 47, pp. 272, 294]. (Page 34 of the HRS documentation record at proposal)

Regarding the EPA investigation of other possible sources of solvents in the vicinity of the Site, page 47 of the HRS documentation record at proposal states:

EPA identified a laundromat located approximately 0.5 mile north-northeast of the SGPP facility [Ref. 44, pp. 1, 3, 6–7]. Information obtained from an employee indicates that dry cleaning has not been conducted historically or currently at the facility [Ref. 44, p. 2]. In addition, an extensive silt and clay layer (112 feet thick) was encountered during the April 2016 monitoring well installation activities approximately midway between the laundromat and the SGPP facility that would likely form a barrier to a solvent release from the laundromat or any other potential sources to the north-northeast [Ref. 44, pp. 1, 7–15]. In April 2016, EPA installed a monitoring well (EPA MW-5) at the intersection of Waterworks Road and Carey Avenue, east-northeast of the SGPP facility [Figure 3; Ref. 22, p. 14; 24, pp. 12–16]. The well is screened<sup>8</sup> in the sand and gravel

---

<sup>8</sup> EPA MW-5 is screened in the lower sand and gravel aquifer at an interval of 427.5 – 412.5 feet above mean sea level, the same relative elevations that MW-3 and PSW 6 are screened. MW-3 is screened at 432.33–417.33 feet above mean sea level; is located on the SGPP facility; and a release of TCE has been documented in MW-3. PSW 6 is screened at 380 feet above mean sea level, and a release of vinyl chloride is documented in PSW 6. (See pages 35, 36, 38 and Figure 3 of the HRS documentation record at proposal.)

aquifer beneath the silt and clay [Ref. 24, pp. 12–16]. Analysis of the ground water sample (SGPP-EPA-GW05) collected by EPA from this well reported a non-detect value for TCE, as well other chlorinated solvents [Ref. 43, pp. 2, 19–20; 44, p. 1; 48, pp. 383–384].

Regarding vinyl chloride not being detected in any monitoring wells at the Site, the rate of migration of vinyl chloride or degradation of parent substances to vinyl chloride in the aquifer could have influenced the lack of detection in these wells. Further, the HRS does not require multiple observed releases of a substance for a release of that substance to be eligible for evaluation. See section 3.9.1, Observed Releases-Applicable Standards, of this support document for discussion of observed release criteria. Also, regarding vinyl chloride not being detected in the Village supply wells during its annual monitoring between 2004 and 2009, in 2011, or in 2014, it is possible that the chlorinated solvent contamination had not yet migrated to those locations at concentrations above detection during those time periods. SGPP does not dispute that vinyl chloride has been found in PSW 6 in ground water sampling performed in 2015 and 2016. (See discussion above regarding 2016 sampling event documenting vinyl chloride in PSW6. See page 5 of Reference 8 of the HRS documentation record at proposal that includes a copy of The Village of Hoosick Falls *Annual Drinking Water Quality Report for 2015*<sup>9</sup>, which shows vinyl chloride being found in PSW 6 in sampling performed in 2015.)

Regarding TCE not being detected in monitoring wells located downgradient of MW-3 or in the Village supply wells during its annual monitoring between 2004 and 2009, in 2011, or in 2014, it is possible that this contamination had not yet migrated to those locations.

Regarding SGPP's claim that the EPA is theorizing that the vinyl chloride is 'traveling horizontally' in the upper aquifer before being drawn down into the lower aquifer by the pumping of PSW 6, finding of vinyl chloride in PSW 6 is sufficient evidence to document that there is some existing migration route, and vinyl chloride is not naturally occurring. This finding supports the conclusion that the clay layer present in the aquifer is not a barrier to migration of hazardous substances. Additionally, a cross section of subsurface geologic conditions included on pages 12 and 13 of Reference 6 of the HRS documentation record at proposal<sup>10</sup> shows the silt and clay layer is not continuous in the aquifer between the SGPP facility and the location of well PSW-6.

These comments result in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.10 Waste Characteristics

Comment: SGPP challenged the waste characteristics assigned value used to score the Site, stating that the waste characteristic value is inflated due to inaccurate hazardous waste quantity and a flawed PFOA toxicity factor value.

According to SGPP, the EPA assigned a hazardous waste quantity value of 100 to the ground water pathway and the maximum toxicity value of 10,000 to PFOA, which resulted in a total waste characteristic score of 32 for the ground water pathway. However, according to SGPP, both the ground water pathway hazardous waste quantity value of 100 and the toxicity value of 10,000 were not appropriate and therefore, the total waste characteristic value should not have been 32.

Response: The waste characteristic factor value, 32, assigned as part of the HRS scoring of the Site is consistent with HRS Sections 2.4, *Waste Characteristics*, (and its subsections), and 3.2, *Waste Characteristics* (and its subsections). As documented on page 49 of the HRS documentation record at proposal, both vinyl chloride and

---

<sup>9</sup> The Village of Hoosick Falls *Annual Drinking Water Quality Report for 2015* is also available at: <http://www.villageofhoosickfalls.com/Media/PDF/WaterQualityReport2015.pdf>.

<sup>10</sup> Reference 6 of the HRS documentation record at proposal: Hanson, Eric L., Dunn Geoscience Corporation. *Hydrogeologic Evaluation of the Hoosick Falls Aquifer, Village of Hoosick Falls, New York*. May 14, 1981.



PFOA were correctly assigned a toxicity factor value of 10,000 and a mobility value of 1 for HRS purposes, and when combined with the pathway hazardous waste quantity of 100, a waste characteristic factor value of 32 was appropriately assigned using HRS Table 2-7, *Waste Characteristics Factor Category Values*. Below is a summary of the specific factor values assigned and the calculated waste characteristics category value presented on page 49 of the HRS documentation record at proposal:

- Both vinyl chloride and PFOA are assigned a toxicity factor value of 10,000.
- Both vinyl chloride and PFOA are assigned mobility value of 1.
- The toxicity mobility value for vinyl chloride and for PFOA is:  $10,000 \times 1 = 10,000$ .
- The pathway hazardous waste quantity is assigned a value of 100<sup>11</sup>
- Toxicity/mobility value x pathway hazardous waste quantity:
  - $10,000 \times 100 = 1,000,000$  (or  $1 \times 10^6$ )

Based on the above assignments and using HRS Table 2-7, *Waste Characteristics Factor Category Values*, a waste characteristic product of  $1 \times 10^6$  is assigned a waste characteristic factor value of 32, the value assigned in the HRS score at proposal (page 49 of the HRS documentation record at proposal).

SGPP's specific comments and the EPA's responses supporting the pathway hazardous waste quantity value and the PFOA toxicity factor value are discussed in the following sections:

- 3.10.1 Ground Water Pathway Hazardous Waste Quantity Value
- 3.10.2 PFOA Toxicity

### 3.10.1 Ground Water Pathway Hazardous Waste Quantity Value

Comment: SGPP commented that the EPA should not have assigned a pathway hazardous waste quantity of 100 to the ground water migration pathway.

SGPP stated that the EPA acknowledged the actual calculated hazardous waste quantity for the ground water pathway at the Site is 1, not 100, yet, "EPA assigned a hazardous waste quantity of 100 based on its conclusion that there are Level I and Level II Concentrations in target wells that may be attributed to the groundwater pathway." SGPP then explained that because the only Level I concentration present in any target wells is the 1.3 ppb of vinyl chloride that was detected in PSW 6 and vinyl chloride is not associated with or its release attributable to the Site, the hazardous waste quantity value assigned to the ground water pathway should have been 1, not 100, which, in turn, would have resulted in a lower total waste characteristic value.

Response: The ground water pathway hazardous waste quantity factor value of 100 was correctly assigned consistent with the HRS because the estimated pathway waste quantity was correctly based on a source waste quantity greater than zero but exact amount unknown; because the constituent waste quantity is not known with reasonable confidence; and, contrary to SGPP's assertions, because targets at the Site are subject to actual contamination at Level I and Level II concentrations.

HRS Section 3.2.2, *Hazardous waste quantity*, explains the assignment of the hazardous waste quantity for the ground water migration pathway. It states:

---

<sup>11</sup> The pathway waste quantity factor value was assigned consistent with HRS Sections 3.2.2, *Hazardous waste quantity*, and 2.4.2.2, *Calculation of hazardous waste quantity factor value*, and this documentation is shown on pages 27-28 and 49-52 of the HRS documentation record at proposal. See discussion below in section 3.10.1, Ground Water Pathway Hazardous Waste Quantity Value, of this support document.

Assign a hazardous waste quantity factor value for the ground water pathway (or aquifer) as specified in section 2.4.2. Enter this value in table 3-1.

HRS Section 2.4.2.2, *Calculation of hazardous waste quantity factor value*, explains the selection of the hazardous waste quantity factor value for a pathway considering all of the sources affecting that pathway: Sum the source hazardous waste quantity values assigned to all sources (including the unallocated source) or areas of observed contamination for the pathway being evaluated and round this sum to the nearest integer, except: if the sum is greater than 0, but less than 1, round it to 1. Based on this value, select a hazardous waste quantity factor value for the pathway from table 2-6.

**TABLE 2-6—HAZARDOUS WASTE QUANTITY FACTOR VALUES**

Hazardous waste quantity value	Assigned value
0	0
1 <sup>a</sup> to 100	1 <sup>b</sup>
Greater than 100 to 10,000	100
Greater than 10,000 to 1,000,000	10,000
Greater than 1,000,000	1,000,000

<sup>a</sup> If the hazardous waste quantity value is greater than 0, but less than 1, round it to 1 as specified in text.

<sup>b</sup> For the pathway, if hazardous constituent quantity is not adequately determined, assign a value as specified in text; do not assign the value of 1.

HRS Section 2.4.2.2, *Calculation of hazardous waste quantity factor value*, then provides additional instructions corresponding to footnote “b” of HRS Table 2-6 (in relevant part):

For a migration pathway, if the hazardous constituent quantity is adequately determined (see section 2.4.2.1.1) for all sources (or all portions of sources and releases remaining after a removal action), assign the value from table 2-6 as the hazardous waste quantity factor value for the pathway. **If the hazardous constituent quantity is not adequately determined** for one or more sources (or one or more portions of sources or releases remaining after a removal action) assign a factor value as follows:

- **If any target for that migration pathway is subject to Level I or Level II concentrations (see section 2.5), assign either the value from table 2-6 or a value of 100, whichever is greater, as the hazardous waste quantity factor value for that pathway.** [Emphasis added].

...

HRS Section 2.4.2.1.1, *Hazardous constituent quantity*, provides the conditions for when the hazardous waste quantity is adequately determined. It states, in relevant part:

If the hazardous constituent quantity for the source (or area of observed contamination) is adequately determined [that is the total mass of all CERCLA hazardous substances is known or estimated with reasonable confidence],...

Pages 19 through 29 of the HRS documentation record at proposal evaluated one source, Source 1, a contaminated soil source, at the Site. The EPA did not estimate the source hazardous constituent quantity because of the lack of sufficient information to do so, as explained on page 27 of the HRS documentation record at proposal:

The hazardous constituent quantity for Source 1 could not be adequately determined according to the HRS requirements; that is, the total mass of all Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) hazardous substances in the source and releases from the source is not known and cannot be estimated with reasonable confidence [Ref. 1, Section 2.4.2.1.1]. There are insufficient historical and current data [manifests, potentially responsible party (PRP) records, State records, permits, waste concentration data, etc.] available to adequately calculate the total or partial mass of all CERCLA hazardous substances in the source and the associated releases from the source. Therefore, there is insufficient information to evaluate the associated releases from the source to calculate the hazardous constituent quantity for Source 1 with reasonable confidence.

As directed in HRS Section 2.4.2, *Hazardous Waste Quantity*, and its subsections, when the hazardous constituent quantity, the hazardous wastestream quantity and the volume of the hazardous waste quantity are not known and could not be adequately estimated with reasonable confidence, the scoring of the hazardous waste quantity proceeds through Tiers A, B and C to Tier D, Area. On pages 27-28 of the HRS documentation record at proposal, the EPA documented a source waste quantity of greater than zero for Source 1 based on an area (Tier D) estimate using the instructions in HRS Section 2.4.2.1.4, *Area*. This HRS Section directs that the area value be based on the area of the source. The EPA explains on page 27 of the HRS documentation record at proposal that the area measure is appropriately assigned a value of >0:

Contaminated soil has been documented at the site; however, as contamination has been documented (e.g., SGPP-S07, SG1-MW04S-00.0) a definitive area of contamination has not been determined. Because the information available is insufficient to estimate the area and measure with reasonable confidence [as required in Section 2.4.2.1.4 of Reference 1], a value of greater than zero (>0) is established as the source hazardous waste quantity (HWQ) value for Tier D – area. The source type is "Contaminated Soil," so the area value is divided by 34,000 to obtain the assigned value of >0, as shown below [Ref. 1, p. 51591, Section 2.4.2.1.3, Table 2-5].

$$\begin{aligned}\text{Area of source in ft}^2 &= >0 \\ \text{Area (A) Assigned Value: } & >0/34,000 = >0\end{aligned}$$

The EPA notes that the commenter did not challenge this estimate.

On page 28 of the HRS documentation record at proposal, the EPA then documents the determination of the source waste quantity value as value greater than zero using the instructions in HRS Section 2.4.2.1.5, *Calculation of source hazardous waste quantity value*. This HRS Section directs the scorer to use the highest waste quantity estimate from any Tier. In this case, Tier D is the only tier scored and therefore the Tier D value was assigned as the source hazardous waste quantity value.

#### 2.4.2.1.5 Source Hazardous Waste Quantity Value

The source hazardous waste quantity value for Source No. 1 is >0 for Tier D – Area [Ref. 1, p. 51591].

$$\text{Source Hazardous Waste Quantity Value: } >0$$

Page 49 of the HRS documentation record at proposal explains the sum of the source waste quantity, the application of HRS Section 2.4.2 and the assignment of a ground water pathway hazardous waste quantity of 100. It states on that page:

### 3.2.2 Hazardous Waste Quantity

<b>TABLE 26. HAZARDOUS WASTE QUANTITY – GROUND WATER PATHWAY</b>		
<b>Source Number</b>	<b>Source Hazardous Waste Quantity (HWQ) Value (Section 2.4.2.1.5)</b>	<b>Is source hazardous constituent quantity data complete? (yes/no)</b>
1	>0	No
Sum of Values:	1 (rounded to 1 as specified in HRS Section 2.4.2.2)	

Therefore, because the sum of the source waste quantity was greater than zero, the sum of the source waste quantity was rounded to 1 per the instructions in footnote “a” to HRS Table 2-6, *Hazardous Waste Quantity Factor Values*, quoted above.

Page 49 of the HRS documentation record at proposal further explains that as required in HRS Section 2.4.2.2, *Calculation of hazardous waste quantity factor value*, and in footnote “b” to HRS Table 2-6, *Hazardous Waste Quantity Factor Values*, quoted above, the EPA assigned the hazardous waste quantity factor value of 100:

The sum corresponds to a hazardous waste quantity factor value of 1 in Table 2-6 of the HRS [Ref. 1, p. 51591]. However, based on the fact that targets are subject to Level I and Level II concentrations (see Section 3.3.2.3), a hazardous waste quantity factor value of 100 is assigned if it is greater than the hazardous waste quantity value from Table 2-6 of the HRS (i.e., 1) [Ref. 1, pp 51591-51592]. Therefore, a hazardous waste quantity factor value of 100 is assigned for the ground water pathway [Ref. 1, pp 51591-51592].

Hazardous Waste Quantity Factor Value: 100

The HRS documentation record at proposal and at promulgation documented that targets are subject to vinyl chloride at Level I concentrations in PSW 6, and targets are subject to Level II concentrations of PFOA in PSW 7 (pages 50, 51 and 52 of the HRS documentation record at proposal and at promulgation). Either of the Level I or Level II concentrations in the target wells PSW 6 or PSW 7, respectively, would support the pathway hazardous waste quantity value assigned.

As discussed in section 3.11.1, Level I Concentrations, of this support document, the EPA correctly established both Level I and Level II targets at the Site based on vinyl chloride in an observed release at a level above an HRS benchmark and an observed release of PFOAs in drinking water wells, respectively, and assigned a pathway waste quantity of 100.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.10.2 **PFOA Toxicity**

Comment: SGPP challenged the HRS toxicity factor value, 10,000, assigned to PFOA stating that the reference dose that is used as its basis is based on inappropriate assumptions. SGPP concluded that, ultimately, the EPA reference dose<sup>12</sup> for PFOA is not based upon sound scientific data or established regulatory principles; use of that reference dose to assign a toxicity value for the purpose of establishing a HRS score for the Site is fundamentally flawed; and use of a more appropriate regulatory toxicity value for PFOA would have resulted in a lower and more appropriate total waste characteristic value for the ground water pathway at the Site resulting in a lower HRS score.

<sup>12</sup> Reference dose (RfD). HRS Section 1.1, *Definitions*, defines an RfD as an, “[e]stimate of a daily exposure level of a substance to a human population below which adverse noncancer health effects are not anticipated. [milligrams toxicant per kilogram body weight per day (mg/kg-day)].”

**Response:** The EPA correctly assigned an HRS toxicity factor value of 10,000 to PFOA according to the directions contained in HRS Section 2.4.1.1, *Toxicity factor*, and HRS Table 2-4, *Toxicity Factor Evaluation*, based on its reference dose of 0.00002 mg/kg/day (or  $2 \times 10^{-5}$  mg/kg/day). This reference dose was obtained from *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016) and was determined using sound scientific information and standard accepted procedures.

HRS Section 3.2.1.1, *Toxicity*, of the ground water migration pathway directs how to determine the correct toxicity factor value for specific substances for the ground water migration pathway. It states:

Assign a toxicity factor value to each hazardous substance as specified in Section 2.4.1.1.

HRS Section 2.4.1.1, *Toxicity factor*, states in relevant part:

Evaluate toxicity for those **hazardous substances at the site** that are available to the pathway being scored. For all pathways and threats, except the surface water environmental threat, **evaluate human toxicity** as specified below... [Emphasis added].

**Establish human toxicity factor values based on quantitative dose-response parameters for the following three types of toxicity:** [Emphasis added].

- Cancer-Use slope factors (also referred to as cancer potency factors] combined with weight-of-evidence ratings for carcinogenicity. If a slope factor is not available for a substance, use its ED<sub>10</sub> value to estimate a slope factor as follows:

$$\text{Slope factor} = \frac{1}{6(\text{ED}_{10})}$$

- Noncancer toxicological responses of chronic exposure-use reference dose (RfD) values.
- Noncancer toxicological responses of acute exposure-use acute toxicity parameters, such as the LD<sub>50</sub>.

Assign human toxicity factor values to a hazardous substance using Table 2-4 as follows:

- **If RfD and slope factor values are both available for the hazardous substance, assign the substance a value from Table 2-4 for each. Select the higher of the two values assigned and use it as the overall toxicity factor value for the hazardous substance.** [Emphasis added].
- **If either an RfD or slope factor value is available, but not both, assign the hazardous substance an overall toxicity factor value from Table 2-4 based solely on the available value (RfD or slope factor).** [Emphasis added].
- If neither an RfD nor slope factor value is available, assign the hazardous substance an overall toxicity factor value from Table 2-4 based solely on acute toxicity. That is, consider acute toxicity in Table 2-4 only when both RfD and slope factor values are not available.
- If neither an RfD, nor slope factor, nor acute toxicity value is available, assign the hazardous substance an overall toxicity factor value of 0 and use other hazardous substances for which information is available in evaluating the pathway.

**TABLE 2-4—TOXICITY FACTOR EVALUATION**

<b>Chronic Toxicity (Human)</b>	
Reference dose (RfD) (mg/kg-day)	Assigned value
RfD < 0.0005.....	10,000
0.0005 ≤ RfD < 0.005 .....	1,000
0.005 ≤ RfD < 0.05 .....	100
0.05 ≤ RfD < 0.5 .....	10
0.5 ≤ RfD .....	1
RfD not available .....	0

<b>Carcinogenicity (Human)</b>			
<b>Weight-of-evidence<sup>a</sup> /slope factor (mg/kg-day)<sup>-1</sup></b>			Assigned value
A	B	C	
0.5 ≤ SF <sup>b</sup>	5 ≤ SF	50 ≤ SF	10,000
0.05 ≤ SF < 0.5	0.5 ≤ SF < 5	5 ≤ SF < 50	1,000
SF < 0.05	0.05 ≤ SF < 0.5	0.5 ≤ SF < 5	100
- -	SF < 0.05	SF < 0.5	10
Slope factor not available	Slope factor not available	Slope factor not available	0
<sup>a</sup> A, B, and C refer to weight-of-evidence categories. Assign substances with a weight-of-evidence category of D (inadequate evidence of carcinogenicity) or E (evidence of lack of carcinogenicity) a value of 0 for carcinogenicity. <sup>b</sup> SF = Slope factor.			

Page 49 of the HRS documentation record at proposal lists a human toxicity factor value of 10,000 for PFOA.

HRS Section 2.4.1.1, *Toxicity factor*, directs the use of the PFOA RfD in assigning a HRS human toxicity factor value. The PFOA RfD of 0.00002 mg/kg/day (or  $2.0 \times 10^{-5}$  mg/kg/day) is documented on page 22 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), of the HRS documentation record at proposal. When the PFOA RfD of 0.00002 mg/kg/day is applied to the “Chronic Toxicity (Human)” section of HRS Table 2-4, *Toxicity Factor Evaluation*, it falls in the category of “RfD < 0.0005” mg/kg/day and the assigned human toxicity factor value for that category is 10,000. Thus, the HRS documentation record at proposal and at promulgation correctly assigned a human toxicity factor value of 10,000 for PFOA based on an oral RfD of 0.00002 mg/kg/day (or  $2.0 \times 10^{-5}$  mg/kg/day). (See page 49 of HRS documentation record at proposal; page 22 of Reference 13<sup>13</sup> of the HRS documentation record at proposal; pages 1-2 of Reference 34<sup>14</sup> of the HRS documentation record at proposal.)

Regarding SGPP’s assertion that replacing the PFOA toxicity factor value with what they consider a more appropriate value would lower the HRS site score, this is not the case. Even if the PFOA HRS toxicity factor value of 10,000 was removed from the HRS documentation record, the Site score would not change because the toxicity and mobility values associated with vinyl chloride would continue to support the toxicity/mobility component of the waste characteristics factor category value component of the Site score. Vinyl chloride is correctly identified in an observed release to ground water from the Site as explained in section 3.9.1, Observed Releases-Applicable Standards, of this support document. This makes it eligible for inclusion in determining the

<sup>13</sup> *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016).

<sup>14</sup> Snyder, Scott, WESTON. Project Note to Saint-Gobain Performance Plastics File, Subject: Toxicity and Mobility Factor Values for PFOA. June 8, 2016.

combined HRS toxicity/mobility factor value as directed in HRS Sections 3.2, *Waste characteristics*, and 3.2.1, *Toxicity /mobility*. The toxicity/mobility value for vinyl chloride is also 10,000 (see page 49 of the HRS documentation record at proposal), which the commenter did not challenge. Then, per HRS Section 3.2.1.3, *Calculation of Toxicity/mobility factor value*, the value assigned for the pathway scoring is the highest value for any substance associated with the pathway, and, thus, the value would be 10,000, which is the same value assigned at proposal. As no other HRS values would be impacted by lowering the PFOA toxicity, the Site score would, therefore, remain the same as at proposal.

The following subsections address SGPP's specific comments on the assigned PFOA human toxicity factor value and the adequacy of the studies used to develop the RfD used in this determination:

- 3.10.2.1 PFOA Reference Dose
- 3.10.2.2 PFOA Carcinogenicity
- 3.10.2.3 PFOA Human Epidemiology Studies

### **3.10.2.1 PFOA Reference Dose**

Comment: SGPP stated that the reference dose identified for PFOA which is used to assign a toxicity factor value for this substance is based on inappropriate assumptions. SGPP's comments on the EPA methodology used to derive the PFOA reference dose are discussed in the following subsections:

- 3.10.2.1.1 Selection of Critical Effects
- 3.10.2.1.2 Use of Uncertainty Factors in Calculation of Reference Dose

#### **3.10.2.1.1 Selection of Critical Effects**

Comment: SGPP asserted that the PFOA RfD used in the assignment of an HRS human toxicity factor is premised on inappropriate assumptions that resulted in the improper selection of critical effects used in the RfD calculation.

SGPP claimed that the developmental effects upon which the reference dose is based (reduced ossification in the proximal phalanges of newborn mice and accelerated puberty in male mice pups) are transient developmental effects that do not alter the well-being of the mice (SGPP cited Exhibit 15<sup>15</sup> of its comment document). SGPP added that the EPA authors of the study upon which the reference dose is based, state in the abstract of their report that 'no significant increase in malformations was noted in any treatment group' (SGPP cited to page 1 of Exhibit 16<sup>16</sup> of its comment document). SGPP also commented that the same EPA authors did not identify either of these effects as adverse effects in their subsequent 2007 review paper in which they addressed the potential developmental toxicity of PFOA (SGPP cited Exhibit 17<sup>17</sup> of its comment document.). Hence, SGPP commented that, "it is not clear why USEPA selected those endpoints as the critical effects from a protective regulatory policy perspective, for what it considered to be the 'most protective' endpoints in the most 'sensitive' population, from which it developed its reference dose for PFOA."

---

<sup>15</sup>Exhibit 15 of SGPP comment document (available at EPA docket ID: EPA-HQ-OLEM-2016-0434-0015) is: *Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA)* (EPA, 2016).

<sup>16</sup> Exhibit 16 of SGPP comment document (available at EPA docket ID: EPA-HQ-OLEM-2016-0434-0015) is: Lau, Christopher, et. al. (2006). "Effects of Perfluorooctanoic Acid Exposure during Pregnancy in the Mouse", *Toxicological Sciences*, 90(2): 510-518.

<sup>17</sup> Exhibit 17 of SGPP comment document (available at EPA docket ID: EPA-HQ-OLEM-2016-0434-0015) is: Lau, Christopher, et.al. (2007). "Review, Perfluoroalkyl Acids: A Review of Monitoring and Toxicological Findings", *Toxicological Sciences*, 99(2): 366-394.

SGPP also claimed that as well as the effects being transient, there are also “inconsistencies in the data from the experimental animal study that the reference dose is based upon, which calls into question whether there is any relationship between PFOA exposure and the purported developmental effects upon which the reference dose was derived.” SGPP explained that, for example, the reduction in ossification of forelimb and hind limb proximal phalanges observed in the Lau et al. (2006) study was greater at the lowest and highest doses, but statistically significant decreased proximal phalangeal ossification was not consistently observed in the mid-doses from the study as would be expected if the effect were actually related to PFOA exposure levels (SGPP Exhibit 16 at Table 2).

In addition, SGPP also raised issues with the effect of PFOA on sexual maturation in general. It stated that the sexual maturation data indicated that the greatest effect (an earlier attainment of sexual maturation by four days) occurred at the lowest PFOA dose, with the effect becoming less and approaching the control value as the dose increased, which is entirely inconsistent with what would be expected if the effect were caused by exposure to PFOA (SGPP Exhibit 16 at Table 5). Moreover, per SGPP, the sexual maturation data from Lau et al. (2006) was also inconsistent with other experimental animal studies involving PFOA that have reported that PFOA delays, rather than accelerates, sexual maturity in male rats (SGPP Exhibit 18<sup>18</sup>).

SGPP summarized that ultimately, the data from the Lau et al. (2006) study is highly suspect and should not have formed the basis for the derivation of a reference dose for PFOA.

Response: For HRS scoring purposes, the RfD used to assign PFOA a human toxicity factor value of 10,000 meet the HRS definition of an RfD. It was obtained from the EPA document titled, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), which was subjected to a notice and comment period that closed on April 29, 2014. The EPA considers the studies supporting the PFOA RfD were correctly interpreted and used to assign an RfD. A summary of the studies and the derivation of the PFOA RfD is provided in the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016) document included as Reference 13 of the HRS documentation record at proposal. The adverse effects upon which the RfD for PFOA was derived are consistent with the EPA’s *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991). The *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* document and the RfD for PFOA derived within were subject to an extensive review process. Therefore, the use of the RfD from this study for PFOA was appropriate for use in the development of a human toxicity factor value, for HRS scoring purposes.

The following discussion is presented in the following order:

- HRS requirements for selection of an RfD
- Overview of the peer review process for the RfD
- Summary of the development process for the RfD
- Overview of the peer review charge questions
- Response to SGPP’s specific comments

Further, the EPA points out that even if the PFOA HRS toxicity factor value of 10,000, which was assigned based on its RfD, was removed from the HRS documentation record, the Site score would not change because the association of vinyl chloride with the Site would continue to support the toxicity/mobility component of the waste characteristics factor category value component of the Site score. (See section 3.10.2 of this support document for further explanation of this alternative scoring.)

### **HRS Requirements for Selection of an RfD**

While HRS Section 1.1, *Definitions*, defines an RfD as an “[e]stimate of a daily exposure level of a substance to a human population below which adverse noncancer health effects are not anticipated. [milligrams toxicant per

---

<sup>18</sup> Exhibit 18 of SGPP comment document is: Butenhoff, John L, et. al. (2004). “Characterization of Risk for General Population Exposure to Perfluorooctanoate”, *Regulatory Toxicology and Pharmacology*, 39: 363-380.



kilogram body weight per day (mg/kg-day)],” the HRS contains no directions on how to calculate this value or what would be an acceptable source of the RfDs.

The EPA selected the value from the most recent EPA study in which an RfD was calculated, the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* document. This document and specifically the derivation of the PFOA RfD by the EPA was subjected to a peer and public review. The notice for public comments was posted in the *Federal Register* on February 28, 2014 (<https://www.gpo.gov/fdsys/pkg/FR-2014-02-28/pdf/2014-04455.pdf>). The draft *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* document was made available in the EPA docket at <http://www.regulations.gov> (Docket ID No. EPA-HQ-OW-2014-0138) and on an EPA contractor’s website (<http://peerreview.versar.com/epa/pfoa/>). The *Federal Register* notification requested nominations for peer reviewers and public comments. The nomination period for scientific experts began on February 28, 2014, and ended on March 21, 2014. The public comment period began on February 28, 2014, and ended on April 29, 2014. Thus, the RfD underwent a public notice and comment process before being issued. At this time, the EPA is not accepting additional comments as the study has been completed. The PFOA health assessment was initiated by the EPA Office of Water, Office of Science and Technology in 2009. The draft *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* was completed in 2013 and released for public comment in February 2014. An external peer-review panel meeting was held on August 21 and 22, 2014. The final document reflects input from the panel as well as public comments received on the draft document. Both the peer-reviewed draft and the final document include only the sections of a health effects support document (HESD) that cover the toxicokinetics and health effects of PFOA. (See page 3 of Reference 13 of HRS documentation record at proposal, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016)).

#### **Overview of the Peer Review Process for the RfD**

The peer review covered technical issues through the use of independent experts. The information discussed in the peer review process formulated revisions to the draft document. The final document reflects sound technical information and analyses subjected to the peer review. This information is publicly available in the peer review summary. (See Appendix A: *EPA Response to External Peer Review Comments on EPA Draft Documents: Health Effects Support Document for Perfluorooctanoic Acid (PFOA) and Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)* (May 2016) [herein referred to as *EPA Response to External Peer Review Comments*]).

In the August 2014 external peer review, the peer reviewers were asked to evaluate the scientific and technical merit of the draft document and provide their responses to 12 charge questions. This included evaluating the appropriateness of the quality, accuracy, and relevance of the data in the documents and included the studies, the selection of the studies and the procedures used in the assignment of the RfD. In addition to being provided the draft documents and charge questions, comments submitted to the EPA’s public docket (Docket ID number EPA–HQ–OW–2014–0138) during each document’s 60-day public comment period were provided to the peer reviewers ahead of the meeting for their consideration. Also, a brief summary of the public comments was provided to the reviewers. (See pages 4–6 of Appendix A: *EPA Response to External Peer Review Comments*.) The EPA responses to the peer reviewers address the peer reviewers’ general impression; the 12 charge questions topic areas; and editorial and other technical comments.

### Summary of the Development Process for the RfD

The development of the RfD was consistent with accepted standard procedures set forth by the National Research Council and the EPA, and it was thoroughly peer reviewed. As stated on page 4 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), of the HRS documentation record at proposal, the studies included in the final *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* were determined to provide the most current and comprehensive description of the toxicological properties of PFOA and the risk it poses to humans exposed to it in their drinking water. Appendix B of the final draft summarizes the studies evaluated for inclusion in the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* following the August 2014 peer review and identifies those selected for inclusion in the final assessment. Appendix B of the final draft includes epidemiology data that provide a high-level summary of the outcomes across the studies evaluated. (See page 4 of Reference 13 of the HRS documentation record at proposal.)

As stated on page 4 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), of the HRS documentation record at proposal, the development of the hazard identification and dose-response assessment for PFOA followed the general guidelines for risk assessment set forth by the National Research Council (1983) and EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* (EPA, 2014). Other EPA guidelines used in the development of this assessment include the following:

- *Guidelines for the Health Risk Assessment of Chemical Mixtures* (EPA, 1986)
- *Guidelines for Mutagenicity Risk Assessment* (EPA, 1986)
- *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (EPA, 1988)
- *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991)
- *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity Studies* (EPA, 1994)
- *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA, 1994)
- *Use of the Benchmark Dose Approach in Health Risk Assessment* (EPA, 1995)
- *Guidelines for Reproductive Toxicity Risk Assessment* (EPA, 1996)
- *Guidelines for Neurotoxicity Risk Assessment* (EPA, 1998)
- *Science Policy Council Handbook: Peer Review (2nd edition)* (EPA, 2000)
- *Supplemental Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (EPA, 2000)
- *A Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002)<sup>19</sup>
- *Guidelines for Carcinogen Risk Assessment* (EPA, 2005)
- *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA, 2005)
- *Science Policy Council Handbook: Peer Review (3rd edition)* (EPA, 2006)
- *A Framework for Assessing Health Risks of Environmental Exposures to Children* (EPA, 2006)
- *Exposure Factors Handbook* (EPA, 2011)
- *Benchmark Dose Technical Guidance Document* (EPA, 2012)
- *Child-Specific Exposure Scenarios Examples* (EPA, 2014)

In the process of developing the RfD, the EPA reviewed and presented numerous studies and several candidate RfDs. This RfD assessment was not isolated to just “a” single study showing adverse effects at low doses of PFOA. Rather, several studies document adverse effects at low doses of PFOA. From these studies, the summary of candidate RfDs presented in Table 4-9 of the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016) (Reference 13 of the HRS documentation record at proposal) were derived from several points of departure with differing critical effects, and the resulting candidate RfDs differ by about an order of magnitude (0.00002–0.00015 mg/kg/day) as do the uncertainty factor values applied to the points of departure.

<sup>19</sup> See <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>

From the candidate RfDs presented on page 255 of the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), the EPA selected the RfD of 0.00002 mg/kg/day based on effects observed in a developmental toxicity study in mice for PFOA (Lau et al., 2006) and explained that the PFOA toxicity studies demonstrate that the developing fetus is particularly sensitive to PFOA-induced toxicity.

Page 255 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016) of the HRS documentation record at proposal provides the candidate RfDs:

**Table 4-9. The Impact of Quantification Approach on the RfD Outcomes for the HEDs from the PK Model Average Serum Values**

POD	Value 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> Perkins rats; ↑liver weight/necrosis	0.0044	10	3	-	-	-	30	0.00015
PK-HED <sub>LOAEL</sub> Wolf GD 1-17 mice; ↓pup body weight	0.0109	10	3	10	-	-	300	0.00004
PK-HED <sub>LOAEL</sub> Wolf GD 7-17 mice; ↓pup body weight <sup>a</sup>	0.0123	10	3	10	-	-	300	0.00004
PK-HED <sub>NOAEL</sub> DeWitt mice; ↓IgM response to SRBC	0.0053	10	3	-	10	-	300	0.00002
PK-HED <sub>LOAEL</sub> Lau mice reduced pup ossification (m, f), accelerated male puberty	0.0053	10	3	10	-	-	300	0.00002
PK-HED <sub>LOAEL</sub> Butenhoff □ ↓F0 body weight/↑ absolute and relative kidney weight	0.0064	10	3	10	-	-	300	0.00002

Notes: m = male; f = female; SRBC = Sheep Red Blood Cell

<sup>a</sup>serum from pups on PND<sup>20</sup> 22

As stated on page 22 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), of the HRS documentation record at proposal:

EPA used a peer-reviewed **PK [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 to calculate corresponding human equivalent doses (HEDs) for the derivation of candidate reference doses (RfDs). Overall, the **toxicity studies available for PFOA demonstrate that the developing fetus is particularly sensitive to PFOA-induced toxicity**. In addition to the critical developmental effects described above, other adverse effects include decreased survival, delays in eye opening and ossification, skeletal defects, delayed vaginal opening in females, and altered mammary gland development. [Emphasis added].

The **EPA Office of Water (OW) selected an RfD of 0.00002 mg/kg/day** based on effects observed in a developmental toxicity study in mice for PFOA (Lau et al. 2006). **The RfD is**

<sup>20</sup> PND = postnatal data

**based on reduced ossification and accelerated puberty (in males).** The total uncertainty factor (UF) applied to the HED LOAEL from Lau et al. (2006) is 300 and includes a UF of 10 for intrahuman variability, a UF of 3 to account for toxicodynamic differences between animals and humans, and a UF of 10 to account for use of a LOAEL as the point of departure (POD<sup>21</sup>). [Emphasis added].

### Overview of the Peer Review Charge Questions

In the external panel review, the 12 charge questions posed to the peer reviewer panel addressed topic areas that include: 1. Studies used for quantification; 2. Additional references; 3. Use of epidemiological data; 4. Characterization of epidemiological data; 5. Cancer classifications; 6. Use of pharmacokinetic model; 7. Selected parameters of pharmacokinetic model; 8. Volume of distribution and half-life values; 9. Candidate RfD; 10. Duration; 11. Interspecies uncertainty factor; and 12. Other suggestions. Based on the reviewer panel comments, the EPA reanalyzed its assessment and included clearly defined adverse effects. The final assessment of the candidate RfDs include adverse effects identified in the animal studies such as increased liver weight accompanied by some necrosis, decreased pup body weight, decreased immunoglobulin response, reduced ossification in pups, accelerated puberty in male pups, and decrease in body weight accompanied by an increase in relative kidney weight. (See pages 254-255 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* of the HRS documentation record at proposal; pages 7 and 8 of Appendix A: *EPA Response to External Peer Review Comments*.)

The selection of critical effects was addressed in charge question 9<sup>22</sup> posed to external panel reviewers as well as in the peer reviewer general impressions comments. Based on peer reviewer panel comments that when identifying LOAELs that the EPA should select endpoints that represents a defined adverse effect, the EPA made some revisions to its assessment in the selection of adverse effects originally presented in the draft RfD document. Among the adverse effects selected as points of departure, the EPA included reduced ossification and accelerated puberty in male mice as critical effects and the LOAELs associated with these effects as appropriate points of departure for determining the final RfD supported in the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* document. These points of departure are also supported by several other candidate RfDs which together presented a narrow range of RfDs, 0.00002–0.00015 mg/kg/day. (See page 59 of Appendix A: *EPA Response to External Peer Review Comments*; see Table 4-9 on page 255 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, of the HRS documentation record at proposal, cited above.) The selection of the reduced ossification and accelerated puberty in male mice as critical effects (and the human equivalent dose derived from these endpoints as the points of departure to derive the RfD) are intended to be protective of the human population including sensitive subpopulations, which in this case are the developing fetus and newborn. (See pages 59 -62 of Appendix A: *EPA Response to External Peer Review Comments*.) Deriving an RfD from a dose that presents significant adverse or overt toxicity as a point of departure would not be protective of human health.

---

<sup>21</sup> Point of departure (POD): “The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response.” *A Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002). <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>

<sup>22</sup> Charge Question 9 - Candidate RfDs: A variety of endpoints and studies were used to compare points of departure and the resultant RfDs for both PFOA and PFOS. In addition, comparisons were provided across RfD outcomes based on the model outputs compared to those for the NOAEL, LOAEL and BMDL points of departure. The range of candidate RfDs derived from the different points of departure is fairly narrow. Please comment on the strengths, weaknesses and transparency of this analysis.

The duration of studies as it impacts assessing short term and long term exposures and their association with diverse effects, are addressed in charge question 10<sup>23</sup> posed to the external panel reviewers. Based on peer reviewer panel comments, the EPA revised the selection of critical effects presented in the draft RfD document and included among its selection reduced ossification and accelerated puberty in male mice because the RfD should be protective against adverse developmental effects on the developing fetus and offspring resulting from exposures that occur during gestation. “Because the developing organism is changing rapidly and is vulnerable at a number of various stages in development, a single exposure at a critical time in development can produce an adverse effect (USEPA 1991).” (See page 63 of Appendix A: *EPA Response to External Peer Review Comments*.)

The use of a pharmacokinetic (PK) model to derive the human equivalent dose is addressed in charge questions 6<sup>24</sup>, 7<sup>25</sup>, and 8<sup>26</sup> posed to the external panel reviewers. (See pages 45-58 of *EPA Response to External Peer Review Comments*.) In addressing their comments, the EPA agreed that further refinement of the model will eventually be ideal when the state of the science permits it. However, the model is empirical and has shown to give results that agree with observed data. The EPA noted in its response, “A unique feature of the Wambaugh et al. (2013) approach was to use a single model for all species in the toxicological studies to examine the consistency in the average serum values associated with effects and with no effects from nine animal studies of PFOA.” (See page 47 of the Appendix A: *EPA Response to External Peer Review Comments*.) The panel reviewers noted in their comments that the August 2014 face to-face peer review meeting had extensive discussion regarding modeling and whether the clarifications of Dr. Wambaugh, who was also present at that meeting, were adequate. In response to the discussions and the panel reviewer comments, the EPA also clarified in the final *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* that a single PK model was used to reanalyze all available data, and “[t]he tables containing the new PK parameter estimates have been retitled ‘Pharmacokinetic parameters from Wambaugh et al. (2013) meta-analysis of literature data’ to further indicate that this reanalysis occurred.” (See page 49 of Appendix A: *EPA Response to External Peer Review Comments*; page 72 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, of the HRS documentation record at proposal.)

Hence, the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* and the *EPA Response to External Peer Review Comments* provide sufficient technical justification for the acceptability of the RfD for HRS purposes.

---

<sup>23</sup> Charge Question 10 - Duration: The RfDs for PFOS and PFOA are derived from the modeled steady state serum concentrations and their association with effects that include short term and longer term exposures with associated diverse effects. The studies considered included effects due to exposure durations that ranged from 11 to 182 days and occur at comparable human equivalent dose (HED) levels. The current draft RfDs do not include an uncertainty factor for study duration because of the apparent concordance HEDs despite duration differences. Given this pattern of response, is it appropriate to conclude that the candidate RfDs are applicable to both short-term and lifetime exposures?

<sup>24</sup> Charge Question 6 - Use of Pharmacokinetic Model: Significant interspecies differences in pharmacokinetics exist for both PFOA and PFOS. Adjusting for interspecies differences was an important step in developing candidate RfDs given the totality of the human and animal data. Please comment on the strengths and weaknesses of the pharmacokinetic model adjustments to accommodate the impact of albumin binding and renal tubule transporters in determining average serum values.

<sup>25</sup> Charge Question 7 - Selected Parameters of Pharmacokinetic Model: Table 5-5 in the PFOA document and Table 5-7 in PFOS document list the parameters used for the ORD pharmacokinetic models that provide the final serum and AUC values for calculating the internal dose point of departure for the RfD calculation. Please comment on the strengths and weaknesses of the selected parameters.

<sup>26</sup> Charge Question 8 - Volume of Distribution and Half-life Values: The volume of distribution (Vd) and half-life values are critical in the derivation of the interspecies uncertainty factor applied in derivation of candidate RfDs from a NOAEL, LOAEL or a BMDL. The available data for both values are provided in Section 3.5.2 and 3.5.3 of both documents. Please comment the strengths and weaknesses of the values selected.

### Response to SGPP's Specific Comments

The EPA considers the studies supporting the PFOA RfD acceptable and has provided a summary of the studies and the derivation of the PFOA RfD in the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016) document included as Reference 13 of the HRS documentation record at proposal. Responses to SGPP's comments that the PFOA reference dose is premised on inappropriate assumptions are as follows:

First, regarding two of SGPP's claims: (1) that developmental effects upon which the RfD is based (reduced ossification and accelerated puberty in male mice pups) are transient developmental effects that do not alter the well-being of the mice, and (2) why the EPA selected those endpoints as the critical effects from a protective regulatory policy perspective, for what it considered to be the 'most protective' endpoints in the most 'sensitive' population, from which it developed its reference dose for PFOA, the evaluation of reduced ossification as well as accelerated puberty as critical effects (i.e., adverse effects) is consistent with standard developmental toxicity assessment procedures as presented in the EPA *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991)<sup>27</sup>. Page 4 of this document states:

The four major manifestations of developmental toxicity are death, structural abnormality, altered growth, and functional deficit. The relationship among these manifestations may vary with increasing dose and, especially at higher doses, death of the conceptus may preclude expression of other manifestations. Of these, all four manifestations have been evaluated in human studies, but only the first three are traditionally measured in laboratory animals using the conventional developmental toxicity (also called teratogenicity or Segment II) testing protocol as well as in other study protocols, such as the multigeneration study or the continuous breeding study.

Thus, consistent with the EPA *Guidelines for Developmental Toxicity Risk Assessment*, the Lau et al. (2006) study correctly identified reduced ossification as a critical developmental toxicity effect or endpoint. (See Section 3.1.1.2, Endpoints of Developmental Toxicity: Altered Survival, Growth, and Morphological Development, and Section 3.1.1.4, Overall Evaluation of Maternal and Developmental Toxicity, of EPA's *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991).) In the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, the EPA further explains that the developmental studies are important in quantification of dose-response because the exposures occur during critical windows of development and predicate effects that can occur later in life (page 244 of Reference 13 of the HRS documentation record at proposal).

Second, regarding SGPP's claim that authors of the study upon which the reference dose is based, state in the abstract of their report that "no significant increase in malformations was noted in any treatment group", this statement has been presented out of context by the commenter. It must be read within context of the results summarized for all the treatment groups in the study. The authors, did *not* state that no malformations were observed, only that there was no significant increase in one group than in another. At the 1 mg/kg dose and other doses, the study documented an increase in malformations over the control. That is, in assessing the **number of ossified proximal phalanges** (forelimbs and hindlimbs) impacted at the 1 mg/kg/day dosing level, Table 2 of the Lau et al. (2006) study document that the **control exhibited**  $4.8 \pm 0.8$  sites for ossified forelimbs and  $3.9 \pm 0.9$  ossified hindlimbs. **In contrast, the 1 mg/kg PFOA dose group exhibited**  $1.8 \pm 1.0$  sites for ossified forelimbs and  $0.4 \pm 0.3$  ossified hindlimbs. This marked reduction in the number of ossified proximal phalanges (forelimbs and hindlimbs) was noted by the authors who indicated that these results show significant differences ( $p < 0.05$ ) from controls, meaning that there is a less than 0.05 probability that these results are inaccurate. Similarly, the data also showed that the percent of reduced ossification for other skeletal sites were also markedly increased over control. Table 2 of the Lau et al. (2006) study reports these findings as shown below.

---

<sup>27</sup> <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23162>

Table 2 of Lau et al. (2006) study:

<b>Table 2</b> <b>Mouse Reproductive Outcome and Fetal Teratology, Examined at Term</b>							
	PFOA dosage (mg/kg)						
	0	1	3	5	10	20	40
Dams examined (#)	45	17	17	27	26	42	9
Dams with FLR (#)	3	2	1	7	12	37	9
Dams with FLR (%)	6.7	11.8	5.9	25.9*	46.1*	88.1*	100*
Implants (# per litter with FLR)	7.0 ± 4.0	10.0 ± 3.0	13.0	11.6 ± 1.2	10.8 ± 1.2	11.5 ± 0.6	11.9 ± 0.5
Implants (# per live litter)	12.9 ± 0.4	13.1 ± 0.4	11.6 ± 0.9	11.5 ± 0.5	12.6 ± 0.6	10.2 ± 2.1	—
Live fetuses (# per live litter)	12.5 ± 0.4	13.0 ± 0.4	10.8 ± 0.9	11.1 ± 0.4	11.7 ± 0.8	7.2 ± 2.0*	—
Prenatal loss (% per live litter)	4.1 ± 1.4	1.0 ± 0.7	7.4 ± 2.5	2.4 ± 0.8	7.7 ± 3.3	25.9 ± 11.7*	—
Fetal body weight (g)	1.05 ± 0.02	0.98 ± 0.03	1.03 ± 0.04	1.03 ± 0.04	0.98 ± 0.05	0.86 ± 0.11*	—
Notable skeletal findings (n)	13	6	7	11	5	5	—
<b>Ossification (number of sites):</b>							
Sternebrae	5.9 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	5.5 ± 0.3	5.7 ± 0.2	4.0 ± 1.1*	—
Caudal vertebrae	4.3 ± 0.3	4.1 ± 0.1	4.0 ± 0.2	4.3 ± 0.3	3.7 ± 0.2	2.1 ± 0.7*	—
Metacarpals	7.7 ± 0.2	7.3 ± 0.3	7.6 ± 0.2	6.6 ± 0.5	6.8 ± 0.4	5.2 ± 1.4*	—
Metatarsals	9.3 ± 0.3	8.9 ± 0.4	9.1 ± 0.3	8.2 ± 0.6	8.6 ± 0.4	6.2 ± 1.6*	—
Proximal phalanges (forelimb)	4.8 ± 0.8	1.8 ± 1.0*	2.2 ± 0.9*	2.9 ± 0.9	1.0 ± 0.6*	0.0 ± 0.0*	—
Proximal phalanges (hindlimb)	3.9 ± 0.9	0.4 ± 0.3*	1.5 ± 1.0	2.8 ± 0.9	1.0 ± 0.6*	0.0 ± 0.0*	—
<b>Reduced ossification(%):</b>							
Calvaria	13.5 ± 9.2	62.5 ± 15.5*	66.7 ± 13.0*	22.7 ± 10.4	35.0 ± 12.7	55.0 ± 20.0*	—
Supraoccipital	14.7 ± 4.0	33.3 ± 10.5	28.6 ± 8.5	27.3 ± 9.2	45.0 ± 9.4*	90.0 ± 10.0*	—
Unossified hyoid	0	0	0	0	0	26.7 ± 19.4*	—
Enlarged fontanel	17.3 ± 9.1	66.7 ± 21.1*	53.6 ± 15.8*	18.2 ± 9.6	45.0 ± 20.0	95.0 ± 5.0*	—
Notable visceral findings (n)	10	6	6	11	5	5	—
Tail defects (curly, bent) (%)	0	0	0	20.5 ± 5.7*	5.0 ± 5.0*	11.7 ± 7.3*	—
Limb defects (club, bent) (%)	0	0	0	5.7 ± 2.8*	0	5.8 ± 3.9*	—
Microcardia (%)	0	0	0	0	5.0 ± 5.0*	30.0 ± 18.3*	—
<i>Note.</i> Data represent means ± SE of litters examined as indicated. One-way ANOVA indicates significant differences ( $p < 0.05$ ) in number of live fetuses and prenatal loss. Asterisks denote significant differences from controls ( $p < 0.05$ ) by Fisher's exact test for full litter resorptions (FLR) and by Dunnett's t-test for other parameters.							

Hence, while the authors did state no significant increase in malformations was detected in the lower PFOA dose groups, they did not conclude that no adverse effects were observed at the 1 mg/kg dose level. Further, in selecting a lowest concentration corresponding to an observed adverse effect level as a point of departure (a dose-response point that marks the beginning of a low-dose extrapolation) to base the RfD on, a level corresponding to



significant overt toxicity would not be protective of human population including sensitive subpopulations, which in this case are the developing fetus and newborn.

The abstract of the Lau et al. (2006) study states:

Perfluorooctanoic acid (PFOA), a member of the perfluoroalkyl acids that have wide commercial applications, has recently been detected in humans and wildlife. The current study characterizes the developmental toxicity of PFOA in the mouse. **Timed pregnant CD-1 mice were given 1, 3, 5, 10, 20, or 40 mg/kg PFOA** by oral gavage daily from gestational day (GD) 1 to 17; controls received an equivalent volume (10 ml/kg) of water. PFOA treatment produced dose-dependent full-litter resorptions<sup>28</sup>; all dams in the 40-mg/kg group resorbed their litters. Weight gain in dams<sup>29</sup> that carried pregnancy to term was significantly lower in the 20-mg/kg group. At GD 18, some dams were sacrificed for maternal and fetal examinations (group A), and the rest were treated once more with PFOA and allowed to give birth (group B). Postnatal survival, growth, and development of the offspring were monitored. PFOA induced enlarged liver in group A dams at all dosages, but did not alter the number of implantations. The percent of live fetuses was lower only in the 20-mg/kg group (74 vs. 94% in controls), and fetal weight was also significantly lower in this group. However, no **significant** increase in malformations was noted in any treatment group. The incidence of live birth in group B mice was significantly lowered by PFOA: ca. 70% for the 10- and 20-mg/kg groups compared to 96% for controls. Postnatal survival was severely compromised at 10 or 20 mg/kg, and moderately so at 5 mg/kg. Dose-dependent growth deficits were detected in all PFOA treated litters except the 1-mg/kg group. Significant delays in eye-opening (up to 2–3 days) were noted at 5 mg/kg and higher dosages. Accelerated sexual maturation was observed in male offspring, but not in females. **These data indicate maternal and developmental toxicity of PFOA in the mouse, leading to early pregnancy loss, compromised postnatal survival, delays in general growth and development, and sex-specific alterations in pubertal maturation.** [Emphasis added].

In the discussion of the Lau et al. (2006) study, the authors stated:

**In contrast, the onset of puberty** for the male pups was markedly advanced by PFOA, such that the prepuce<sup>30</sup> was separable in the **1-mg/kg dose** group almost 4 days earlier than in the controls. It is noteworthy that this accelerated pubertal maturation took place despite a body weight deficit of 25–30%. [Emphasis added].

...

Teratological<sup>31</sup> findings (such as reduced ossification) typically reflected delays of fetal development, although a few incidences of malformed limbs and tail, and microcardia were detected at 5 mg/kg and higher dose groups. On the other hand, the BMD<sub>5</sub> **estimates for phalangeal ossification were less than 1 mg/kg (Table 6)**<sup>32</sup>, indicating the sensitivity of this PFOA effect. **That reduced ossification was observed at such low doses without affecting**

<sup>28</sup> Resorption is early pregnancy loss; early embryonic or fetal death.

<sup>29</sup> Dams referred to here are the female parent mice.

<sup>30</sup> Genitalia

<sup>31</sup> Teratological - abnormal in growth or structure; of or relating to teratology.

Teratology-the study of malformations or deviations from the normal types in developing organisms.

<sup>32</sup> The EPA notes that Table 6, *Benchmark Dose Estimates for Various Parameters of PFOA, Maternal and Developmental Toxicity in the Mouse*, of the Lau et al. (2006) study contains the BMD<sub>5</sub> and BMDL<sub>5</sub> extrapolated from the administered dose. However, Table 2, *Mouse Reproductive Outcome and Fetal Teratology, Examined at Term*, of the Lau et al. (2006) study contains the administered dose. The lowest administered dose showing reduced ossification is Table 2 of the Lau et al. (2006) study is 1 mg/kg.



**fetal weight suggests the possibility that effects on ossification may not be a simple developmental delay.** Regardless, these findings are generally comparable to those reported for two related PFAA chemicals, perfluorodecanoic acid (Harris and Birnbaum, 1989) and PFOS (Thibodeaux et al., 2003). [Emphasis added].

The Lau et al. (2007) study where it states, ‘no significant increase in malformations was noted in any treatment group’, the authors stated the following:

Accordingly, Lau et al. (2006) carried out a reproductive toxicity study with PFOA in CD-1 mice using daily **doses of 1–40 mg/kg throughout gestation**. Full-litter resorptions were noted at 40 mg/kg. At 20 mg/kg, the percent of live fetuses and fetal weight were reduced and some structural abnormalities were seen in the fetuses. However, **no significant** increase in malformations was detected in the lower PFOA dose groups. The lack of significant teratological findings in mice was consistent with previous studies using rats and rabbits (Gortner, 1981, 1982; Staples et al., 1984). However, when neonatal survival was evaluated in this study, a pattern of neonatal mortality mirroring that obtained with PFOS (Lau et al., 2003) was observed. Postnatal survival was severely compromised at 10 or 20 mg/kg and moderately affected at 5 mg/kg. **Postnatal growth impairment and developmental delays were noted among the survivors in these same dose groups.** [Emphasis added].

Third, regarding SGPP’s claim that the authors did not identify either reduced ossification or accelerated puberty in male mice as adverse effects in their subsequent 2007 review paper in which they addressed the potential developmental toxicity of PFOA, the Lau et al. (2006) and Lau et al. (2007) studies do not actually refute each other. The Lau et al. (2007) study is not a dosing study but is a review of previous literature of perfluoroalkyl acids and does not include all the detailed observations documented in the Lau et al. (2006) study at the various doses of PFOA administered to mice. The Lau et al. (2006) study characterized developmental toxicity of PFOA in pregnant mice and provides detailed dosing and responses observed at the various dosing levels (1–40 mg/kg), whereas the Lau et al. (2007) study is a review of the monitoring and toxicological findings of perfluoroalkyl acids (including PFOA). In addition in the Lau et al. (2007) study, the authors specifically noted that, “[t]his review provides an **overview** of the recent advances in the toxicology and mode of action for PFAAs<sup>33</sup>, and of the monitoring data now available for the environment, wildlife, and humans. Several avenues of research are proposed that would further our understanding of this class of compounds” [emphasis added].

Fourth, regarding SGPP’s claim that there are inconsistencies in the data and that reduced ossification was greater at the lowest and highest doses but a statistically significant decrease was not observed at the mid-doses from the study, insufficient information is provided to assess these results. However, there are a number of factors such as differences in pharmacokinetic handling of PFOA in the mice and immature pups that can influence the observed adverse effects. Regardless, the conclusion that there was an adverse effect from the doses is not in doubt.

Fifth, regarding SGPP’s claim that the sexual maturation data are entirely inconsistent with what would be expected of exposure to PFOA as well as with the results of other experimental animal studies involving PFOA shown in SGPP Exhibit 18<sup>34</sup>, these data do not show inconsistency but rather show that pharmacokinetics differences between species and even within species during development impact the adverse effect outcomes. The data in Table 2 of Exhibit 18 of SGPP’s comment document that SGPP referred to as being contradictory is from a study performed on rats, not mice as was used in the Lau et al (2006) study. These differences were noted in the Lau et al. (2006) study of which an excerpt is provided below.

---

<sup>33</sup> PFAA= perfluoroalkyl acids

<sup>34</sup> Exhibit 18 of SGPP comment document (available at EPA docket ID: EPA-HQ-OLEM-2016-0434-0015) is: Butenhoff et al. (2004). “Characterization of risk for general population exposure to perfluorooctanoate,” *Regulatory Toxicology and Pharmacology*. 39 (2004) 363–380.

Lau et al. (2006) states:

Results from the current study that evaluated the **developmental toxicity of PFOA in the CD-1 mouse are strikingly different than those described previously with the rat model.** Butenhoff et al. (2004b) conducted a comprehensive two generation reproductive toxicity study on PFOA with Sprague- Dawley rats and reported little toxicity; small postnatal weight gain deficits, **slight delays of sexual maturation**, and postweaning mortality (likely related to immaturity) were noted only in the F1-generation animals of the highest dose group (30 mg/kg). **In contrast, here we report** a significant increase in the incidence of full-litter resorptions and neonatal mortality in the CD-1 mouse at 5 mg/kg (Table 2), with BMD<sub>5</sub> and BMDL<sub>5</sub> estimated at 2.84 mg/kg and 1.09 mg/kg, respectively for neonatal mortality (determined by survival to weaning) (Table 6). **Significant alterations of postnatal growth and development were seen at even lower doses** (1 and 3 mg/kg, Fig. 5), with BMD<sub>5</sub> and BMDL<sub>5</sub> estimates of 1.07 mg/kg and 0.86 mg/kg respectively, for pup weight at weaning, and 2.64 mg/kg and 2.10 mg/kg respectively, for eye-opening (Table 6). **These disparate findings in rats and mice are likely due, at least in part, to the differential pharmacokinetic disposition of PFOA.** [Emphasis added].

Table 2 of Exhibit 18 of SGPP comment document shows the result in question (when compared to the Lau et al. (2006) study which used mice) is based on a study performed using rats (see emphasized text):

Table 2 Endpoints and source studies used in evaluating dose–response		
Endpoint	Source study	Source data table
<b>Post-natal development in rats<sup>a</sup></b>	Two-generation reproduction study (Butenhoff et al., 2004)	Table 3
Liver-to-brain-weight ratio in rats <sup>b</sup>	Two-generation reproduction study (Butenhoff et al., 2004)	Table 3
Body-weight change in rats <sup>c</sup>	Two-generation reproduction study (Butenhoff et al., 2004)	Table 3
Liver-to-brain-weight ratio in rats <sup>d</sup>	13-week dietary study (Palazzolo, 1993)	Table 4
Body-weight change	13-week dietary study (Palazzolo, 1993)	Table 4
Liver-to-brain-weight ratio in monkeys <sup>c</sup>	6-month oral toxicity study (Butenhoff et al., 2002b)	Table 5
Body-weight change in monkeys <sup>f</sup>	6-month oral toxicity study (Butenhoff et al., 2002b)	Table 5
Leydig cell tumors in rats <sup>e</sup>	Two-year cancer bioassay (Sibinski et al., 1983)	Table 6
<p><sup>a</sup> The following endpoints were evaluated separately: (1) pre-weaning mortality (combined sexes); (2) pup body-weight at weaning (combined sexes); (3) post-weaning mortality in males and females (separately); (4) days to preputial separation in males; and (5) days to vaginal patency in females.</p> <p><sup>b</sup> Male liver-weight-to-brain-weight ratio was selected because male rats respond to a greater extent than females to the liver-enlarging effects of PFOA. PFOA affects body weight; therefore, use of liver-weight-to-brain-weight ratio normalizes for body-weight changes, since brain is not responsive to body-weight change from dietary restriction (Feron et al., 1973). F<sub>0</sub> and F<sub>1</sub> data were evaluated separately. The two-generation reproduction study involved oral dosing of male rats in both the F<sub>0</sub> and F<sub>1</sub> generations for more than 90 days, the typical term of a subchronic study, and, therefore, has the advantage of following a subchronic dosing response over two generations and group sizes of approximately 30.</p> <p><sup>c</sup> Body-weight change was evaluated as reduced body-weight gain compared to controls only in male rats, which were more sensitive than female rats to PFOA-induced reductions in weight gain. F<sub>0</sub> and F<sub>1</sub> data were evaluated separately.</p> <p><sup>d</sup> Liver-weight-to-brain-weight ratio was used to minimize effects of body-weight reduction and reduced feed consumption. The 13-week (90-day) subchronic dietary study in male rats (Palazzolo, 1993) is useful in that serum PFOA concentrations were made at all dose levels.</p>		

<sup>e</sup> Since the male monkeys from this study varied in age and weight at the beginning of the study, and dosing with APFO caused significant weight loss among the high-dose-group monkeys, only data from male monkeys dosed until terminal sacrifice were used, which excludes data from three high-dose-group monkeys for whom dosing was suspended.

<sup>f</sup> For male cynomolgus monkeys, body-weight change was represented by the actual percentage change in individual body weight from pre-study baseline weight through weight at or near termination (scheduled or unscheduled) of dosing. Because these were adult monkeys of various ages and weights, and due to the fact that only two of six monkeys were dosed continuously for six months at the high dose, percent change in body weight from baseline was considered more meaningful than comparison of body-weight change or terminal body weight between treated and control groups.

<sup>g</sup> Human epidemiological studies have not shown statistically significant associations of exposure to PFOA with increased cancer mortality risk (Alexander, 2001). Leydig cell adenoma incidence from the two-year cancer bioassay in rats was used.

These comments result in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.10.2.1.2 Use of Uncertainty Factors in Calculation of Reference Dose

Comment: SGPP questioned the use of uncertainty factors of 10 and 3 used by the EPA in deriving the RfD. SGPP claimed that the EPA incorporated an inappropriate uncertainty factor<sup>35</sup> of 10 into its derivation of the reference dose used in the assignment of an HRS toxicity factor because the EPA used the lowest observed adverse effect level (LOAEL) as the point of departure (POD)<sup>36</sup> from which the RfD is based instead of the benchmark dose for a 5 percent response (BMDL<sub>5</sub>)<sup>37</sup> calculated by the authors in the Lau et al. (2006) study. SGPP explained that the EPA's flawed RfD was based on the following calculations: the serum PFOA concentration associated with the LOAEL was estimated (38 mg/L), and a human equivalency dose was derived by multiplying this serum PFOA concentration by the estimated human clearance for PFOA (0.00014 L/kg/day), and this resulted in a human equivalent dose (HED) of 0.0053 mg/kg/day (SGPP Exhibit 15).

SGPP contended that in deriving the reference dose, the EPA used the LOAEL, 1 mg/kg/day, for the two co-critical effects as a point of departure in its reference dose calculations (SGPP Ex. 15 at Table 5-1.), and that because a LOAEL for the co-critical effects was used instead of a no observable adverse effect Level (NOAEL) or benchmark dose, the EPA added an uncertainty factor of 10 into its calculations to account for adverse effects that might theoretically occur at concentrations below the LOAEL (Table 5-2 of SGPP Exhibit 15). However, according to SGPP, in the Lau et al. (2006) study, the authors did derive benchmark doses for the reduced ossification of proximal phalanges (Table 6 of SGPP Exhibit 16 (the Lau et al. (2006) study)).

SGPP stated:

<sup>35</sup> Uncertainty factor value (UF): "One of several, generally 10-fold, factors used in operationally deriving the RfD and RfC from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population (i.e., interhuman or intraspecies variability); (2) the uncertainty in extrapolating animal data to humans (i.e., interspecies variability); (3) the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure (i.e., extrapolating from subchronic to chronic exposure); (4) the uncertainty in extrapolating from a LOAEL rather than from a NOAEL; and (5) the uncertainty associated with extrapolation from animal data when the database is incomplete." *A Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002).

<sup>36</sup> Point of departure (POD): "The dose-response point that marks the beginning of a low-dose extrapolation. This point can be the lower bound on dose for an estimated incidence or a change in response level from a dose-response model (BMD), or a NOAEL or LOAEL for an observed incidence, or change in level of response." *A Review of the Reference Dose and Reference Concentration Processes* (EPA 2002). <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>.

<sup>37</sup> "Benchmark Dose (BMD) or Concentration (BMC): A dose or concentration that produces a predetermined change in response rate of an adverse effect (called the benchmark response or BMR) compared to background." ... "BMDL or BMCL: A statistical lower confidence limit on the dose or concentration at the BMD or BMC, respectively." *A Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002). <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>

For reduced ossification of the proximal phalanges for the forelimb and hind limb, the lower 95 percent confidence limits of the benchmark doses for a 5 percent response (BMDL<sub>5</sub>) were 0.643 and 0.616 mg/kg/day, respectively. ([SGPP Exhibit 16, Table 6]) While these values are slightly lower than the LOAEL of 1 mg/kg used by USEPA, if USEPA had used the BMDL<sub>5</sub> for reduced proximal phalangeal ossification, it would not have needed to add in any uncertainty factor to account for potential effects below the LOAEL, let alone an uncertainty factor of 10. Accordingly, the dose ultimately used to derive the reference dose would have been 30 to 40 percent lower (BMDL<sub>5</sub> values of 0.646 or 0.616 versus the LOAEL of 1 mg/kg); but, the total uncertainty factor would have been 30 instead of 300, which would have resulted in a higher reference dose.

SGPP also commented that the EPA also applied an additional uncertainty factor of 3 to account for species differences between humans and mice even though there are experimental data that suggests that humans are less sensitive to the developmental effects observed in mice rather than more sensitive as the application of this uncertainty factor implies (SGPP Exhibit 19<sup>38</sup>).

Response: For HRS scoring purposes, the RfD used to assign PFOA a human toxicity factor value of 10,000 met all HRS requirements. The use of uncertainty factor value of 10 in deriving the RfD was appropriate and standard procedure when the reported LOAEL is used instead of a level causing NOAEL because the NOAEL has not been established. In addition, in peer review of the EPA study containing RfD derivation, the reviewers did not question the use of this uncertainty factor of 10. The EPA did not apply the portion of the uncertainty factor for interspecies variability (UF<sub>A</sub>) that accounts for toxicokinetic differences because the PK modeling accounted for that difference, but the EPA did retain the portion of that uncertainty factor that accounts for the differences in toxicodynamics between species (i.e., a UF<sub>A</sub> value of 3 for the differences in the way PFOA interacts with tissues in animals versus in humans).

As explained in greater detail in section 3.10.2.1.1, Selection of Critical Effects, of this support document, the RfD was obtained from the EPA document titled, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, (EPA, 2016), which was subject to a notice and comment process that closed on April 29, 2014. The EPA considers the studies supporting the PFOA RfD and the use of uncertainty factor values to derive the RfD appropriate and consistent with standard procedures; the use of the uncertainty factors accounts for limitations and uncertainties in the available data, when arriving at an RfD that is likely to be without an appreciable risk of deleterious effects in humans. The EPA has provided a summary of the studies and the derivation of the PFOA RfD in the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016) document included as Reference 13 of the HRS documentation record at proposal.

Further, as also explained in section 3.10, Waste Characteristics, of this support document, even if the PFOA HRS toxicity factor value of 10,000 was removed from the HRS documentation record, the Site score would not change because vinyl chloride would continue to support the toxicity/mobility component of the waste characteristics factor category value component of the Site score.

The application of the uncertainty factor of 10 to account for a LOAEL to NOAEL extrapolation was appropriate because the point of departure (POD) for the derivation of the RfD for PFOA is the human equivalent dose (HED), which was derived based on serum concentrations corresponding to a lowest observed adverse effect level.

---

<sup>38</sup> Exhibit 19 of SGPP comment document is: Albrecht, Prajakta P. et al. (2012). "A Species Difference in the Peroxisome Proliferator-Activated Receptor  $\alpha$ -Dependent Response to the Developmental Effects of Perfluorooctanoic Acid", *Toxicological Sciences*, 131(2): 568-582.

Section 4.1.1, RfD determination, of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* of the HRS documentation record at proposal provides a detailed summary of the derivation of the RfD for PFOA. The introduction to this section, on page 241, explaining the RfD derivation provides the following statement that explains the need to utilize a pharmacokinetic (PK) model in the dose response assessment:

The derivation of the RfD for PFOA presented a number of challenges due to the toxicokinetic complexity of PFOA, variability in half-life between species, and metabolic inertness of PFOA in living organisms. The toxicokinetic features of PFOA lead to differences in half-lives across species and in the case of rats, and possibly humans, differences between genders. Toxicokinetics also influence intraindividual and lifestage variability in response to dose. Additionally there were inconsistencies across the epidemiology studies and the effects observed in animal studies, and a number of animal studies lacked a NOAEL. Each of these factors highlights the importance of having measures of internal dose for quantification of an RfD and supports the utilization of a PK model as a component of the dose-response assessment.

Section 4.1.2, RfD Selection, of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)*, of the HRS documentation record at proposal explains the selection of the RfD among the candidate studies discussed in that document. It states on pages 256 and 257:

The candidate RfDs in Table 4-9 range 0.00002–0.00015 mg/kg/day. **The RfD of 0.00002 mg/kg/day calculated from HED [human equivalent dose] average serum values from Lau et al. (2006) was selected.** The RfD based on Lau et al. (2006) 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 selected RfD from the Lau et al. study (2006) is supported by the RfD for effects on the response of the immune system (DeWitt et al. 2008) to external challenges as observed following the short-term 15-day exposures to mature mice and effects on organ and body weights in F1 adult males observed following chronic exposure. [Emphasis added].

...

**Using the PK model** of Wambaugh et al. (2013), **average serum PFOA** concentrations were derived from area under the curve (AUC) considering the number of days of exposure before sacrifice. **The predicted serum concentrations were converted** as described above **to oral HEDs in mg/kg/day** for each corresponding serum measurement. **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>**)<sup>39</sup> was applied to the HED LOAEL to derive an RfD of 0.00002 mg/kg/day. [Emphasis added].

The application of uncertainty factor values applied in the range of RfD determinations are explained on pages 255 to 256 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), of the HRS documentation record at proposal which states:

**A UF for interspecies variability (UF<sub>A</sub>) of three was 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

---

<sup>39</sup> UF = uncertainty factor. UF<sub>A</sub> = uncertainty factor to account for interspecies variability. UF<sub>L</sub> = uncertainty factor for extrapolations beginning from a LOAEL. UF<sub>H</sub> = uncertainty factor value to account for intraspecies variability (within the human populations variability). SGGP did not challenge the UF<sub>H</sub> value applied.

HEDs were derived using average serum values from a model to account for PK differences between animals and humans. [Emphasis added].

**A UF for LOAEL to NOAEL extrapolation (UF<sub>L</sub>) of 10 was applied** to all PODs other than the Perkins et al. study (2004) **to account for use of a LOAEL** for the POD. The POD for the Perkins et al. study (2004) is a NOAEL. [Emphasis added].

Therefore, because the human equivalent dose was derived from *serum levels corresponding to a LOAEL*, the application of the uncertainty of 10 for LOAEL to NOAEL extrapolation (UF<sub>L</sub>) was appropriate. The EPA found it necessary to utilize PFOA serum concentrations available in the animal studies because the complexity of toxicokinetics of PFOA between species supported the utilization of a pharmacokinetic model utilizing serum concentrations corresponding to an administered dose. The use of the animal data and the available pharmacokinetic model allowed for the incorporation of species differences in saturable renal resorption, dosing duration, and serum measurements for doses administered to determine human equivalent doses based on average serum concentration and clearance. Pharmacokinetic modeling is a more rigorous approach to determining dosing for an adverse health effect than the BMDL<sub>5</sub>, which is itself a calculation based on the NOAEL or LOAEL. Thus it would be inappropriate to use a BMDL<sub>5</sub> in a pharmacokinetic model.

Further, regarding SGPP's comment that, humans are less sensitive to the developmental effects observed in mice rather than more sensitive as the application of the uncertainty a factor value of 3 implies and regarding SGPP's citation to Exhibit 19 of its comment document, the EPA applied the uncertainty factor value of 3 for interspecies variability to account for differences in how PFOA interacts with tissues in animals versus in humans. The EPA did not apply the portion of the uncertainty factor for interspecies variability that accounts for toxicokinetic differences because the PK modeling accounted for that difference, but the EPA did retain the portion of that uncertainty factor that accounts for the differences in toxicodynamics between species.

Although the reference that SGPP cited (SGPP Exhibit 19<sup>40</sup>) did perform a study on peroxisome proliferator-activated receptor (PPAR $\alpha$ )<sup>41</sup> humanized mice as well as PPAR $\alpha$ -null mice and wild type mice to determine if species differences in receptor activity might influence the developmental effects induced by PFOA, this study made several observations, among which is that the developmental postnatal effects resulting from prenatal PFOA exposure in mice are differentially mediated by mouse and human PPAR $\alpha$ . It also noted that further studies are needed to identify the specific mechanisms accounting for species differences in responses to PFOA exposure. Additionally, the EPA noted the effect of the PPAR pathway in its assessment of PFOA (and discussed it in several areas throughout the PFOA health effects assessment document). The EPA stated on page 22 of Reference 13, *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), of the HRS documentation record at proposal:

PFOA is known to activate PPAR pathways by increasing transcription of mitochondrial and peroxisomal lipid metabolism, sterol, and bile acid biosynthesis and retinol metabolism genes. **Based on PFOA-induced transcriptional activation of many other genes in PPAR $\alpha$ -null mice, however, other receptors** such as the constitutive androstane receptor (CAR), farnesoid receptor (FXR), and pregnane X receptor (PXR) **could be involved in PFOA-induced toxicity.** [Emphasis added].

Therefore, the application of an uncertainty factor value of 3 to account for interspecies variability when deriving an RfD is appropriate. The results of the study in Exhibit 19 of SGPP's comment document are not sufficient to

---

<sup>40</sup> Exhibit 19 of SGPP comment document is: Albrecht, Prajakta P. et al. (2013). "A Species Difference in the Peroxisome Proliferator-Activated Receptor  $\alpha$ -Dependent Response to the Developmental Effects of Perfluorooctanoic Acid", *Toxicological Sciences*, 131(2): 568-582.

<sup>41</sup> Peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ). PFOA binds to the PPAR $\alpha$

show that interspecies mechanisms mediating PFOA toxicity are sufficiently known to eliminate the need for the application of an uncertainty factor to account for the differences in how PFOA interacts with tissues in animals versus in humans.

### Peer Review Charge Questions and the Use of Uncertainty Factors

The application of uncertainty factor values was addressed by the external peer review panel in their general comments as well as their comments on charge questions 8<sup>42</sup>, 9<sup>43</sup> and 11<sup>44</sup>. A panel reviewer noted in his general comments that by adhering to the EPA policies and use of multiple uncertainty factor values, despite the scientifically-credible exercises and deliberations, the end result (the RfD) seems to have been preordained to be extremely low. The EPA addressed this comment as it impacted the selection of the endpoints in the final assessment and provided a response to the use of uncertainty factor values in its response to charge question 11, which is discussed below. (See pages 8 and 68-70 Appendix A: *EPA Response to External Peer Review Comments*.) For charge questions 8 and 9, direct comments against applying an uncertainty factor of 10 to extrapolations derived from a lowest observed adverse effect level were not provided, but rather, peer reviewer comments and the EPA responses and revisions to the proposed RfD addressed the pharmacokinetic model and selection of critical endpoints for the RfD. In responding to charge question 8, a peer reviewer did recommend that the EPA could use Bayesian analysis to support uncertainty factor value development. However, the EPA noted that “[since] there are no agreed upon guidelines for the new approach recommended by the peer reviewer, EPA used the current Agency approach for determining uncertainty factors in the PFOA assessment.” (See page 55 of Appendix A: *EPA Response to External Peer Review Comments*.) Another peer reviewer responding to charge question 8 also requested that the EPA provide a justification for using the uncertainty factor value of 3 to account for species differences and a more thorough discussion regarding this choice given the differences in clearance rates between humans and animals. In responding to this comment, the EPA made revisions to clearance ratios used in the PK model approach but retained the use of the uncertainty factor of 3 and explained:

In cases where the POD for RfD quantification is the product of toxicokinetic modeling, the toxicokinetic portion of the interspecies UF is not applied. In the absence of data regarding toxicodynamic differences between species, the toxicodynamic portion of the UF is retained. The toxicodynamic factor accounts for differences in the way the chemical interacts with tissues in the animals versus humans. The UF applied to account for toxicodynamics in such circumstances is 3 (see section 4.4.5.3 in EPA’s document *A Review of the Reference Dose Reference Concentrations Processes*). (See page 55 of Appendix A: *EPA Response to External Peer Review Comments*.)

---

<sup>42</sup> Charge Question 8 - Volume of Distribution and Half-life Values: The volume of distribution (Vd) and half-life values are critical in the derivation of the interspecies uncertainty factor applied in derivation of candidate RfDs from a NOAEL, LOAEL or a BMDL. The available data for both values are provided in Section 3.5.2 and 3.5.3 of both documents. Please comment the strengths and weaknesses of the values selected.

<sup>43</sup> Charge Question 9 - Candidate RfDs: A variety of endpoints and studies were used to compare points of departure and the resultant RfDs for both PFOA and PFOS. In addition, comparisons were provided across RfD outcomes based on the model outputs compared to those for the NOAEL, LOAEL and BMDL points of departure. The range of candidate RfDs derived from the different points of departure is fairly narrow. Please comment on the strengths, weaknesses and transparency of this analysis.

<sup>44</sup> Charge Question 11 - Interspecies Uncertainty Factor: In addition to using the average serum values from animal studies to calculate internal doses for humans, the animal to human extrapolation can be accomplished by dividing animal average serum values by the human to animal clearance ratios to project a human average serum point of departure in units of mg/L serum. Please provide recommendations for applying uncertainty factors to the extrapolated average human serum values to determine serum-based thresholds that are protective for humans. A NOAEL expressed in average human serum units would be useful in interpreting NHANES population monitoring data.  
NHANES = National Health and Nutrition Examination Survey

Hence, the EPA did not apply the portion of the uncertainty factor for interspecies variability ( $UF_A$ ) that accounts for toxicokinetic differences because the PK modeling accounted for that difference, but the EPA did retain the portion of that uncertainty factor that accounts for the differences in toxicodynamics between species (i.e., a  $UF_A$  value of 3 for the differences in the way PFOA interacts with tissues in animals versus in humans).

For charge question 11, although the panel reviewers commented that use of human data would negate the need to perform animal to human extrapolations, no comments were provided against applying an uncertainty factor of 10 to extrapolations derived from a LOAEL or 3 for interspecies variability. In responding, the EPA noted the use of human equivalent doses derived from the modeled average serum value for the lowest observed adverse effect level (LOAEL) (and/or no observed adverse effect level (NOAELs) in some candidate RfD studies), pharmacokinetically-derived human equivalent doses based from the animal studies, interspecies differences between animals and humans and the application of the EPA policies in deriving reference dose justified the use of uncertainty factor values. (See pages 54 -55 and 68-70 of Appendix A: *EPA Response to External Peer Review Comments*).

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.10.2.2 PFOA Carcinogenicity

Comment: SGPP asserted that the EPA should not have assigned an HRS toxicity factor value of 10,000 to PFOA. SGPP commented that despite having studied the health effects of PFOA for decades, the EPA has not found adequate evidence to assign a regulatory classification to PFOA as a likely carcinogen. SGPP added that in the absence of such evidence, there is no reasonable basis to apply the same maximum toxicity factor that is applied to known carcinogens to PFOA.

Response: The HRS human toxicity factor value of 10,000 was not assigned based on the carcinogenicity of PFOAs, but, rather, was correctly based on the RfD as it resulted in the assignment of the highest factor value possible. As assigned at proposal and explained in section 3.10.2, PFOA Toxicity, of this support document, the HRS instructs if both an RfD and a cancer slope are available, assign the substance a toxicity factor value from HRS Table 2-4, *Toxicity Factor Evaluation*, for each and use the higher of the two values assigned as the overall toxicity factor value. As explained in sections 3.10.2, PFOA Toxicity, and 3.10.2.1, PFOA Reference Dose, of this support document, the HRS toxicity factor value of 10,000 was correctly assigned to PFOA according to the directions of HRS Section 2.4.1.1, *Toxicity factor*, and HRS Table 2-4, *Toxicity Factor Evaluation*, which explain the assignment of an HRS toxicity factor value of 10,000 to PFOA based on its RfD of 0.00002 mg/kg/day (or  $2 \times 10^{-5}$  mg/kg/day). The exclusion or inclusion of a cancer assessment or cancer slope factor does not negate the non-cancer toxicological parameter (RfD, in this case) used to assign a human HRS toxicity factor value for PFOA or the assignment of the 10,000 value.

HRS Section 3.2.1.1, *Toxicity*, of the ground water migration pathway states:

Assign a toxicity factor value to each hazardous substance as specified in section 2.4.1.1.

HRS Section 2.4.1.1, *Toxicity factor*, states:

Evaluate toxicity for those hazardous substances at the site that are available to the pathway being scored. For all pathways and threats, except the surface water environmental threat, evaluate human toxicity as specified below. ...

Establish human toxicity factor values based on quantitative dose-response parameters for the following **three types of toxicity**: [Emphasis added].



- Cancer-Use slope factors (also referred to as cancer potency factors) combined with weight-of-evidence ratings for carcinogenicity. If a slope factor is not available for a substance, use its ED<sub>10</sub> value to estimate a slope factor as follows:

$$\text{Slope factor} = \frac{1}{6(\text{ED}_{10})}$$

- Noncancer toxicological responses of chronic exposure-use reference dose (RfD) values.
- Noncancer toxicological responses of acute exposure-use acute toxicity parameters, such as the LD<sub>50</sub>.

Assign human toxicity factor values to a hazardous substance using Table 2-4 as follows:

- **If RfD and slope factor values are both available for the hazardous substance, assign the substance a value from Table 2-4 for each. Select the higher of the two values assigned and use it as the overall toxicity factor value for the hazardous substance.** [Emphasis added].
- **If either an RfD or slope factor value is available, but not both, assign the hazardous substance an overall toxicity factor value from Table 2-4 based solely on the available value (RfD or slope factor).** [Emphasis added].
- If neither an RfD nor slope factor value is available, assign the hazardous substance an overall toxicity factor value from Table 2-4 based solely on acute toxicity. That is, consider acute toxicity in Table 2-4 only when both RfD and slope factor values are not available.
- If neither an RfD, nor slope factor, nor acute toxicity value is available, assign the hazardous substance an overall toxicity factor value of 0 and use other hazardous substances for which information is available in evaluating the pathway.

Page 49 of the HRS documentation record at proposal lists a human toxicity factor value of 10,000 for PFOA.

As cited above and in section 3.10.2, PFOA Toxicity, of this support document, HRS Section 2.4.1.1, *Toxicity factor*, instructs that if both an RfD and a cancer slope are available, assign the substance a toxicity factor value from HRS Table 2-4 for each and “[s]elect the **higher of the two values assigned and use it as the overall toxicity**” (emphasis added). HRS Section 2.4.1.1, *Toxicity factor*, further instructs that, “If either an RfD or slope factor value is available, but not both, assign the hazardous substance an overall toxicity factor value from Table 2-4 **based solely on the available value (RfD or slope factor)**” (emphasis added).

Hence, even if a cancer slope factor value for PFOA was considered and it would have yielded a lower human toxicity factor value in HRS Table 2-4 than for the RfD, the human toxicity factor assigned for HRS scoring purposes based on the RfD would still be required to be used to support the overall HRS human toxicity value of 10,000 for PFOA because it is the highest value. The HRS specifically instructs to use the highest value. (See section 3.10.2, PFOA Toxicity, of this support document.)

According to the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016) (Reference 13 of the HRS documentation record at proposal), the EPA did assess the carcinogenicity of PFOA. This document states on page 22:

Under EPA's *Guidelines for Carcinogen Risk Assessment* (USEPA 2005a), 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 its ability to be tumorigenic in one or more organs of rats, including the liver, testes, and pancreas. EPA estimated a cancer slope factor (CSF) of  $0.07 \text{ (mg/kg/day)}^{-1}$  based on testicular tumors.

Considering the cancer slope factor of  $0.07 \text{ (mg/kg/day)}^{-1}$  with a weight-of-evidence of "suggestive evidence of carcinogenic potential"<sup>45</sup> in the Carcinogenicity (Human) section of HRS Table 2-4, *Toxicity Factor Value Evaluation*, this slope factor and weight-of-evidence would fall in the "B" column and the " $0.05 \leq \text{SF} < 0.5$ " category and would be assigned an HRS human toxicity factor value of 100, which is lower than the value of 10,000 assigned to PFOA based on its RfD.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.10.2.3 PFOA Human Epidemiology Studies

Comment: SGPP stated that the EPA should not have assigned an HRS toxicity factor value of 10,000 to PFOA because the EPA "has not identified any epidemiological studies regarding PFOA and potential adverse human health effects that it believes are sufficiently reliable to develop regulatory ground water or drinking water standards."

Response: The HRS toxicity factor of 10,000 for PFOA was correctly based on the RfD as directed by the HRS. Human epidemiological studies or ground water or drinking water standards are not required to be used in assigning the HRS human toxicity value for PFOA. Nor are epidemiological studies required to establish an RfD, which is used to assign a toxicity factor. Although the EPA reviewed and considered human epidemiological data in assessing PFOA toxicity, the human serum PFOA concentrations from the epidemiological studies were not utilized to derive the PFOA RfD because the data lacked the necessary quantitative dose information.

The *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), which the EPA used to support the assignment of the HRS human toxicity factor value, did provide a summary of a number of human epidemiological studies used to qualitatively examine PFOA toxicity. The human epidemiological studies were not utilized to derive the PFOA RfD because, as explained below, the data lacked the necessary quantitative dose information required if they were to be used in developing an RfD.

The HRS does not specify that the RfD must be derived from human epidemiological studies when selecting an RfD to assign an HRS human toxicity factor value. It only states in HRS Section 2.4.1.1, *Toxicity factor*, to:

Establish human toxicity factor values based on quantitative dose-response parameters for the following three types of toxicity:

- Cancer-Use slope factors (also referred to as cancer potency factors) combined with weight-of-evidence ratings for carcinogenicity. If a slope factor is not available for a substance, use its ED<sub>10</sub> value to estimate a slope factor as follows:

<sup>45</sup> <https://www.epa.gov/fera/risk-assessment-carcinogens>;  
[https://www.epa.gov/sites/production/files/2013-09/documents/cancer\\_guidelines\\_final\\_3-25-05.pdf](https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf)

$$\text{Slope factor} = \frac{1}{6(\text{ED}_{10})}$$

- Noncancer toxicological responses of chronic exposure-use **reference dose (RfD) values**. [Emphasis added].
- Noncancer toxicological responses of acute exposure-use acute toxicity parameters, such as the LD<sub>50</sub>.

The *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016) discusses the human epidemiological studies in section 3.1, Human Studies, beginning on page 79 of Reference 13 of the HRS documentation record at proposal. With specific regard to use of epidemiological studies in the derivation of the RfD, the document states on page 254:

As explained previously, human data identified significant relationships between serum levels and specific indicators of adverse health effects **but lacked the exposure information for dose-response modeling. For this reason none of the human studies provided an appropriate POD for RfD derivation.** 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. Extrapolation to humans adds a layer of uncertainty that needs to be accommodated in deriving the RfD. [Emphasis added].

In Section 4.1.2, RfD Selection, of the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* (EPA, 2016), it states on page 257:

There are extensive human data from epidemiology studies on the general population, as well as worker cohorts. The epidemiology data provide support for the human relevance of the hazards identified in the laboratory animals. **However, they lack the quantitative information on the human exposures (doses and durations) responsible for the human serum levels.** Although some associations show a relationship between effects and serum measures, the serum measures are lower than the PODs from the animal studies and some associations are confounded by reverse causality. Data supporting a first-order kinetic relationship between dose/duration and serum concentrations are needed before the human data can be used in a manner comparable to the process utilized in the RfD derivation. [Emphasis added].

## Peer Review Charge Questions and Epidemiological Studies

The use of PFOA human serum levels available in epidemiological studies instead of serum levels from animal studies as the data from which the RfD should be derived was addressed in charge questions 1<sup>46</sup>, 2<sup>47</sup>, 3<sup>48</sup> and 4<sup>49</sup> posed to external panel reviewers for the *Health Effects Support Document for Perfluorooctanoic Acid (PFOA)* used by the EPA to establish the RfD. Based on peer reviewer panel comments, that the EPA can in some cases

<sup>46</sup> Charge Question 1 - Studies Used for Quantification: Please comment on the strengths, weaknesses, and characterization of the studies selected as key for quantification.

<sup>47</sup> Charge Question 2- Additional References: Please provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA consider adding to the document. Describe where you suggest these references be incorporated.

<sup>48</sup> Charge Question 3 - Use of Epidemiology Data: The OW [Office of Water] concluded that the human epidemiology data for PFOS/PFOA do not provide adequate quantifiable dose-response information for use as the basis of a candidate RfD because of uncertainty regarding the routes, levels and timing of exposures plus the confounding influences of other PFCs present in serum. Please comment of the OW characterization of the data.

<sup>49</sup> Charge Question 4 - Characterization of Epidemiology Data: Please comment on the transparency and characterization of the epidemiological data.

consider epidemiological data or not consider these studies in cases in which the epidemiological data are not sufficiently robust for quantifying an RfD, the EPA responded by updating its review of human epidemiological data and explained that the human studies are used qualitatively as a line of evidence to support the health effects assessment. (See Appendix A: *EPA Response to External Peer Review Comments*.) As stated previously, the EPA continued to use the animal data that had serum concentrations corresponding to an administered dose to derive the RfD.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.11 Targets

Comment: SGPP raised several issues with the HRS factor values associated with the level of contamination and the number of individuals (Targets) identified as exposed to contamination released from the SGPP facility. SGPP stated that there are no Level I concentrations attributable to the Site and the status and pumping capacity of well PSW 6 was inaccurately represented in the HRS scoring of the Site, thus the resulting population associated with well PSW 6 was not accurately apportioned. SGPP's comments regarding the targets associated with well PSW 6 are discussed in the following subsections:

- 3.11.1 Level I Concentrations
- 3.11.2 Nearest Well
- 3.11.3 PSW 6 Population

#### 3.11.1 Level I Concentrations

Comment: SGPP contended that there are no Level I concentrations attributable to the Site in any target well. SGPP asserted that, the available data do not support the EPA's assumption that the low level of vinyl chloride detected in PSW 6 is attributable to low levels of TCE at the Site.

Response: A Level I concentration of vinyl chloride was correctly identified at the Site in drinking water well PSW 6. As explained below, for HRS purposes Level I contamination occurs when the concentration of an HRS hazardous substance is present, in a sample meeting observed release criteria, and that concentration is above an applicable HRS identified benchmark. An observed release of vinyl chloride was correctly identified occurring at this site, including attribution of the significant increase of the vinyl chloride concentration and the concentration of vinyl chloride establishing this observed release is above the HRS benchmark associated with the cancer risk screening concentration. See section 3.9, Observed Releases, in this support document.

HRS Sections 3.3.2.1, *Level of contamination*, and 2.5, *Targets*, and its subsections contain the requirements for identifying Level I concentrations. HRS Section 3.3.2.1, *Level of contamination*, of the ground water migration pathway gives the general requirement to identify levels of contamination in the ground water migration pathway. It states:

Evaluate the population served by water from a point of withdrawal based on the level of contamination for that point of withdrawal. Use the applicable factor: Level I concentrations, Level II concentrations, or potential contamination. . . . if one or more samples meet the criteria for an observed release for the point of withdrawal, determine which factor (Level I or Level II concentrations) applies to that point of withdrawal as specified in sections 2.5.1 and 2.5.2. Use the health-based benchmarks from Table 3-10 in determining the level of contamination.

Table 3-10 of the HRS lists the screening concentration for cancer as a drinking water health-based benchmark for evaluating Level I concentrations of drinking water. It is as follows:

**TABLE 3-10—HEALTH-BASED BENCHMARKS FOR HAZARDOUS SUBSTANCES IN DRINKING WATER**

<ul style="list-style-type: none"> <li>• Concentration corresponding to Maximum Contaminant Level (MCL).</li> <li>• Concentration corresponding to a nonzero Maximum Contaminant Level Goal (MCLG).</li> <li>• Screening concentration for cancer corresponding to that concentration that corresponds to the <math>10^{-6}</math> individual cancer risk for oral exposures.</li> <li>• Screening concentration for noncancer toxicological responses corresponding to the Reference Dose (RfD) for oral exposures.</li> </ul>
---

HRS Section 2.5, *Targets*, provides the instructions for determining whether targets are subject to actual contamination at Level I and Level II concentrations. It states:

-Level I:

-Media-specific concentrations for the target meet the criteria for an observed release (or observed contamination) for the pathway and are at or above media-specific benchmark values. These benchmark values (see section 2.5.2) include both screening concentrations and concentrations specified in regulatory limits (such as Maximum Contaminant Level (MCL) values), or

...

Level II:

-Media-specific concentrations for the target meet the criteria for an observed release (or observed contamination) for the pathway, but are less than media-specific benchmarks.

...

HRS Section 2.5.1, *Determination of level of actual contamination at a sampling location*, provides instructions for determining whether Level I or Level II concentrations apply at a sampling location. It states:

Determine whether Level I concentrations or Level II concentrations apply at a sampling location (and thus to the associated targets) as follows:

- Select the benchmarks applicable to the pathway (or threat) being evaluated.
- Compare the concentrations of hazardous substances in the sample (or comparable samples) to their benchmark concentrations for the pathway (or threat), as specified in section 2.5.2.
- Determine which level applies based on this comparison.
- If none of the hazardous substances eligible to be evaluated for the sampling location has an applicable benchmark, assign Level II to the actual contamination at that sampling location for the pathway (or threat).

In making the comparison, consider only those samples, and only those hazardous substances in the sample, that meet the criteria for an observed release (or observed contamination) for the pathway, ...

HRS Section 2.5.2, *Comparison to benchmarks*, explains which benchmarks need to be at or exceeded to be considered Level I concentrations. It states:

Use the following media-specific benchmarks for making the comparisons for the indicated pathway (or threat):

- Maximum Contaminant Level Goals (MCLGs)—ground water migration pathway and drinking water threat in surface water migration pathway. Use only MCLG values greater than 0.
- Maximum Contaminant Levels (MCLs)—ground water migration pathway and drinking water threat in surface water migration pathway.
- ....
- Screening concentration for noncancer toxicological responses corresponding to the RfD for inhalation exposures (air migration pathway) or for oral exposures (ground water migration pathway; drinking water and human food chain threats in surface water migration pathway; and soil exposure pathway).

Select the benchmark(s) applicable to the pathway (or threat) being evaluated as specified in sections 3 through 6. Compare the concentration of each hazardous substance from the sampling location to its benchmark concentration(s) for that pathway (or threat). Use only those samples and only those hazardous substances in the sample that meet the criteria for an observed release (or observed contamination) for the pathway. . . . If the concentration of any applicable hazardous substance from any sample equals or exceeds its benchmark concentration, consider the sampling location to be subject to Level I concentrations for that pathway (or threat). If more than one benchmark applies to the hazardous substance, assign Level I if the concentration of the hazardous substance equals or exceeds the lowest applicable benchmark concentration.

As identified in section 3.9, Observed Releases, and its subsections of this support document, the HRS documentation record at proposal established an observed release of vinyl chloride.

Pages 37-38 and 50 of the HRS documentation record at proposal establish that the HRS criteria for identifying Level I concentration in a target well have been met. Pages 37-38 of the HRS documentation record at proposal document that vinyl chloride was found at a concentration of 1.3 µg/L in a sample from well PSW 6. SGPP does not dispute vinyl chloride was present at this concentration.

Page 50 of the HRS documentation record at proposal states:

Applicable benchmarks for the hazardous substance detected in the observed release are as follows; **boldface type** denotes the lowest applicable benchmark concentration for each hazardous substance);

<b>TABLE 28. HRS BENCHMARKS – GROUND WATER PATHWAY</b>				
<b>Substance</b>	<b>MCL</b>	<b>Cancer Risk</b>	<b>Non-Cancer Risk</b>	<b>Reference(s)</b>
VC	2	<b>2.1 x 10<sup>-2</sup></b>	60	2, p. 4
PFOA*	N/A	N/A	N/A	N/A

Concentrations presented in micrograms per liter (µg/L) for consistency with reported analytical data.

\*Superfund Chemical Data Matrix (SCDM) benchmarks for PFOA have not been established.

TABLE 29. LEVEL I CONCENTRATIONS						
Well	Sample	Substance	Conc. (µg/L)	RDL* (µg/L)	Benchmark (µg/L)	Reference(s)
Village Well 6	SGPP-DW03	VC	1.3	0.50	$2.1 \times 10^{-2}$	2, p. 4; 22, p. 38; 23, p. 152; 43, pp. 3–6, 39, 117; 48, pp. 7, 68

µg/L = micrograms per liter

\*The RDL for each result is the CRQL adjusted for sample and method [Ref. 33, p. 8]. Since the samples were analyzed through CLP, these adjusted CRQLs are used in place of the HRS-defined sample quantitation limit SQL [Ref. 1, Sections 1.1 and 2.3].

As identified on page 50 of the HRS documentation record at proposal and page 4 of Reference 2<sup>50</sup> of the HRS documentation record at proposal, the vinyl chloride cancer risk screening concentration for drinking water is  $2.1 \times 10^{-2}$  µg/L (or  $2.1 \times 10^{-5}$  mg/L)). Therefore, the concentration of vinyl chloride in the PSW 6 well sample is above a health-based HRS benchmark and correctly identified as a Level I concentration. SGPP does not dispute the vinyl chloride cancer risk screening concentration for drinking water.

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.11.2 Nearest Well

Comment: In challenging the presence of a Level I concentration, SGPP indirectly challenged the assignment of the HRS Nearest Well factor value, which is based on the presence of Level I concentrations in a drinking water well. SGPP contended that there are no Level I Concentrations attributable to the Site in any target wells because the available data do not support that the low level of vinyl chloride detected in drinking water well PSW 6 is attributable to low levels of TCE at the Site. In addition, SGPP identified that this well is not in regular use and is used for emergency backup purposes only, and SGPP questioned its use in the HRS evaluation.

Response: The EPA correctly assigned a factor value of 50 to the Nearest Well factor value based on the presence of Level I concentration of vinyl chloride in a drinking water well. A Level I concentration of vinyl chloride was correctly based on a sample from drinking water well PSW 6 containing vinyl chloride meeting observed release criteria and being above an HRS benchmark as demonstrated above in section 3.11.1, Level I Concentrations, of this support document.

To determine what qualifies as a target in the ground water pathway, HRS Section 3.3, *Targets*, instructs the scorer to:

[e]valuate the targets factor category for an aquifer based on four factors: nearest well, population, resources, and Wellhead Protection Area. Evaluate these four factors based on targets within the target distance limit specified in section 3.0.1.1 and the aquifer boundaries specified in section 3.0.1.2. Determine the targets to be included in evaluating these factors for an aquifer as specified in section 3.0.

<sup>50</sup> Reference 2 of the HRS documentation record at proposal: EPA. Superfund Chemical Data Matrix (SCDM) Query. Substance: cis-1,2-Dichloroethylene; Factor Values and Benchmarks: Ground Water Pathway; Substance: Polychlorinated biphenyls; Factor Values and Benchmarks: Ground Water Pathway; Substance: Trichloroethylene; Factor Values and Benchmarks: Ground Water Pathway; and VC; Factor Values and Benchmarks: Ground Water Pathway. Query Accessed June 22, 2016. A complete copy of SCDM is available at <http://www.epa.gov/superfund/superfund-chemical-data-matrix-scdm>.

To evaluate targets for assigning the nearest well factor value, HRS Section 3.3.1, *Nearest well*, states that:

[i]n evaluating the nearest well factor, include both the drinking water wells drawing from the aquifer being evaluated and those drawing from overlying aquifers as specified in section 3.0. Include standby wells in this factor only if they are used for drinking water supply at least once every year.

...

Assign a value for the nearest well factor as follows:

- If one or more drinking water wells is subject to Level I concentrations, assign a value of 50.
- If not, but if one or more drinking water wells is subject to Level II concentrations, assign a value of 45.
- If none of the drinking water wells is subject to Level I or Level II concentrations, assign a value as follows:
  - ...
  - If not, determine the shortest distance to any drinking water well, as measured from any source at the site with a ground water containment factor value greater than 0. Select a value from Table 3-11 based on this distance. Assign it as the value for the nearest well factor.

The EPA documented Level I concentrations of vinyl chloride in PSW 6, and this data is shown on page 50 of the HRS documentation record at proposal. A nearest well factor value of 50 was correctly assigned as listed on page 52 of the HRS documentation record at proposal.

Pages 50 of the HRS documentation record at proposal states:

TABLE 29. LEVEL I CONCENTRATIONS						
Well	Sample	Substance	Conc. (µg/L)	RDL* (µg/L)	Benchmark (µg/L)	Reference(s)
Village Well 6	SGPP-DW03	VC	1.3	0.50	$2.1 \times 10^{-2}$	2, p. 4; 22, p. 38; 23, p. 152; 43, pp. 3-6, 39, 117; 48, pp. 7, 68

µg/L = micrograms per liter

\*The RDL for each result is the CRQL adjusted for sample and method [Ref. 33, p. 8]. Since the samples were analyzed through CLP, these adjusted CRQLs are used in place of the HRS-defined sample quantitation limit SQL [Ref. 1, Sections 1.1 and 2.3].

Page 52 of the HRS documentation record at proposal states:

### 3.3.1 Nearest Well

As identified in **Section 3.3**, the active drinking water supply wells, Village Wells 6 and 7, for the Village of Hoosick Falls are subject to Level I and Level II concentrations, respectively. Therefore, a nearest well factor value of 50 is assigned [Ref. 1, pp. 51602, 51603].

---

Nearest Well Factor Value: 50

Regarding SGPP's assertion that well PSW 6 is only an emergency backup well, this does not eliminate this well from being the basis for the nearest well factor value. As quoted above HRS Section 3.3.1, *Nearest well*, standby



wells can be considered in assigning the nearest well value if they are used at least once every year. The EPA has contacted the Village of Hoosick Falls and confirmed that the well is currently used 12 days a year. Appendix B of this support document contains current information from the City on how PSW 6 is used as a standby well. Appendix B of this support document will also be included as Reference 64 of the HRS documentation record at promulgation.

Regarding SGPP's assertions that it finds the TCE and vinyl chloride concentrations "low", these assertions do not refute the observed releases identified at the Site. See sections 3.8, Releases Below Regulatory Limits, and 3.9, Observed Releases, of this support document for further discussion of why the contamination in this well qualifies for consideration. An observed release of vinyl chloride and TCE attributable to the Site has been correctly documented at the Site. (Also, see section 3.11.1, Level I Concentrations, of this support document for discussion of the documentation of Level I concentration of vinyl chloride in PSW 6.)

This comment results in no change to the HRS score and no change in the decision to place the Site on the NPL.

### 3.11.3 PSW 6 Population

Comment: SGPP challenged the apportionment of population to drinking water well PSW 6 in the HRS documentation record at proposal. SGPP claimed that PSW 6 is used by the Village of Hoosick as an emergency backup well. Therefore, SGPP asserted that the EPA's assumption that the well is used to regularly provide water to 1,333 Village residents is incorrect. SGPP cited to page 3 of SGPP Exhibit 13<sup>51</sup> to support its claim that, "As such, PSW 6 should have been treated as a standby well in the HRS scoring and should not have been assigned the same population as the other Village supply wells." SGPP also cited to SGPP Exhibit 14<sup>52</sup> to support its comment.

SGPP argued that the ground water pathway HRS score for the Site is flawed due to the EPA's assumption that PSW 6 serves 1,333 people. SGPP stated that the EPA incorrectly "calculated this figure by simply dividing the total service population (4,000) by the number of supply wells (3) in the Village in accordance with HRS guidance providing that a system population should be apportioned equally among the active system components if no single component contributes more than 40 percent of the total system population." SGPP explained that contrary to the EPA's assumption, the Village does not equally rely upon each of its supply wells, and, therefore, the EPA should not have apportioned the system population evenly between the three Village supply wells. (SGPP cited to Reference 28<sup>53</sup> of the HRS documentation record at proposal and page 3 of SGPP Exhibit 13). According to SGPP, a July 2015 engineering report prepared by the Village's consultant, MRB Group, states that PSW 6 has a significantly lower pumping capacity than the other two supply wells in the Village (see page 3 of SGPP Exhibit 13). Per SGPP, "[a]s set forth in the MRB Report, PSW 6 has a pumping capacity of only 350 gallons per minute ('gpm'), as opposed to the 900 gpm pumping capacity cited by the EPA in the HRS documentation record." (SGPP also cited to Reference 28 of the HRS documentation record at proposal).

SGPP concluded that the targets factor value assigned on line 8a, Level I concentrations, of the ground water pathway score sheet should be zero, not 13,330. SGPP also concluded that the ground water pathway score for the Site is flawed, and the HRS documentation misrepresents the potential threat posed by the Site.

---

<sup>51</sup> Exhibit 13 of SGPP comment document is: MRB Group. (July 2015). *Engineering Report for Water Treatment Plant Improvements, MRG Group Project No. 0825.15004*.

<sup>52</sup> Exhibit 14 of SGPP comment document is: USEPA (November 2012). *Hazard Ranking System Guidance Manual*. Excerpt 7 pages: cover sheet, pages 187, 188, 189, 190, 191, 192.

<sup>53</sup> Reference 28 of the HRS documentation record at proposal is: Snyder, Scott, WESTON. Project Note to Saint-Gobain Performance Plastics File, Subject: Village Well Information; with attached references. June 6, 2016.

Response: The HRS documentation record has been revised at promulgation to include the most recent data available to determine the population subject to actual contamination at Level I concentration associated with PSW 6 ground water contamination based on its use as a standby well. The EPA agrees that PSW 6 operates as a standby well and has revised the HRS score for the Site accordingly. Based on information from the Village of Hoosick Falls this well is in regular use on approximately a monthly basis when regular maintenance is being performed on the other two wells; therefore, PSW 6 qualifies as a standby well. However, this change to well PSW 6 does not impact the listing decision as the Site score remains above 28.50.

The Level I population associated with drinking water well PSW 6 has been revised in the HRS documentation record at promulgation to reflect the use of this well as a standby well consistent with HRS Section 3.3.2, *Population*, which provides directions on evaluating the population factor.

HRS Sections 3.3.2, *Population*, and 3.3.2.2, *Level I concentrations*, are used to assign a population value for the Site. HRS Section 3.3.2, *Population*, states:

In evaluating the population factor, include those persons served by drinking water wells within the target distance limit specified in section 3.0.1.1. .... **When a standby well is maintained on a regular basis so that water can be withdrawn, include it in evaluating the population factor.** [Emphasis added].

...

In determining the population served by a well, if the water from the well is blended with other water (for example, water from other ground water wells or surface water intakes), apportion the total population regularly served by the blended system to the well based on the well's relative contribution to the total blended system. In estimating the well's relative contribution, assume each well and intake contributes equally and apportion the population accordingly, except: if the relative contribution of any one well or intake exceeds 40 percent based on average annual pumpage or capacity, estimate the relative contribution of the wells and intakes considering the following data, if available:

- Average annual pumpage from the ground water wells and surface water intakes in the blended system.
- Capacities of the wells and intakes in the blended system.

For systems with standby ground water wells or standby surface water intakes, apportion the total population regularly served by the blended system as described above, except:

- Exclude standby surface water intakes in apportioning the population.
- **When using pumpage data for a standby ground water well, use average pumpage for the period during which the standby well is used** rather than average annual pumpage. [Emphasis added].
- For that portion of the total population that could be apportioned to a standby ground water well, **assign that portion of the population either to that standby well or to the other ground water well(s) and surface water intake(s) that serve that population; do not assign that portion of the population both to the standby well and to the other well(s) and intake(s) in the blended system. Use the apportioning that results in the highest population factor value.** (Either include all standby well(s) or exclude some or all of the standby well(s) as appropriate to obtain this highest value.) Note that the specific standby well(s) included or excluded and, thus, the specific apportioning may

vary in evaluating different aquifers and in evaluating the surface water pathway.  
[Emphasis added].

HRS Section 3.3.2.2, *Level I concentrations*, provides the instructions for calculating the Level I concentration factor value. It states:

Sum the number of people served by drinking water from points of withdrawal subject to Level I concentrations. Multiply this sum by 10. Assign this product as the value for this factor. Enter this value in Table 3-1.

The EPA has determined the population factor value as follows:

First, the EPA has determined that well PSW 6 is eligible for consideration at this Site. Well PSW 6 meets the requirements for use in assigning the population factor value for this site because it is used 12 days a year. As quoted above, the HRS states that a standby well can be used in assigning a population factor value if “it is maintained on a regular basis so that water can be withdrawn.” Appendix B of this support document, a January 3, 2017, memorandum between Scott Snyder of Weston Solutions, Inc., the EPA’s contractor, and Jim Hurlburt, Superintendent of the Village of Hoosick Falls municipal water supply, clarifies the use of PSW 6 as a standby well and its pumping during the period when it is used. Appendix B states:

Spoke to Jim Hurlburt of Hoosick Falls Water Department. He confirmed that Village Well 6 is used as an emergency backup well. For maintenance purposes Well 6 is used approximately once per month for approximately thirty to forty minutes at a time. The water pumped from Well 6 is pumped to the pretreatment tank, processed through the water plant, pumped to the clear well, then pumped out to the distribution system. Wells 3 and 7 are disconnected while Well 6 is pumping.

Jim stated that currently, the actual pumping rates of the three village wells are as follows:

Well 7 – 700 gallons per minute (gpm); pumps 365 days/year

Well 3 – 700 gpm; pumps 365 days/year

**Well 6 – 300 gpm; pumps 12 days/year** [emphasis in original]

Therefore, given the well is used 12 days a year, it is “maintained” for use according to the HRS. In a given year, well PSW 6 provides approximately 144,000 gallons of drinking water to the drinking water system.

Second, the EPA determined the appropriate population to apportion to the standby well. As also identified above, HRS Section 3.3.2, *Population*, directs that a standby well may or may not be used in determining the population factor value:

For that portion of the total population that could be apportioned to a standby ground water well, **assign that portion of the population either to that standby well** or to the other ground water well(s) and surface water intake(s) that serve that population; **do not assign that portion of the population both to the standby well and to the other well(s)** and intake(s) in the blended system. **Use the apportioning that results in the highest population factor value.** (Either include all standby well(s) or exclude some or all of the standby well(s) as appropriate to obtain this highest value.) [Emphasis added].

The EPA included well PSW 6 in the Site scoring because its use results in the highest population factor value.

Third, to determine the appropriate population to assign to this standby well, the EPA next determined the number of wells that supply the Village of Hoosick Falls water system when the standby well is in use. As quoted above, HRS Section 3.3.2, *Population*, states:

- **When using pumpage data for a standby ground water well, use average pumpage for the period during which the standby well is used** rather than average annual pumpage. [Emphasis added].

Based on information from the Village of Hoosick Falls (documented in Appendix B of this support document), when PSW6 is in use, PSW 3 and 7 are turned off allowing PSW 6 to supply 100% of the drinking water to the Village of Hoosick Falls water supply:

For maintenance purposes Well 6 is used approximately once per month for approximately thirty to forty minutes at a time. The water pumped from Well 6 is pumped to the pretreatment tank, processed through the water plant, pumped to the clear well, then pumped out to the distribution system. Wells 3 and 7 are disconnected while Well 6 is pumping.

Therefore, when this standby well is in use the other two wells that supply the Village of Hoosick Falls water system are turned off and well PSW 6 serves all (100%) of the population associated with the Village of Hoosick Falls water supply.

Fourth, the EPA determined the population to assign to well PSW 6. As quoted above, because well PSW 6 is the only well serving the Village of Hoosick Falls municipal water supply while it is in use, the entire population of the Village of Hoosick Falls municipal water supply of 4,000 is apportioned to this well. According to page 50 of the HRS documentation record at proposal, the Village of Hoosick Falls municipal water supply serves an approximate population of 4,000. This information is supported by Reference 8<sup>54</sup>, Population and service connections served by municipal water system; with attached reference, of the HRS documentation record at proposal.

Fifth, to arrive at the final HRS population value, the HRS then considers the level of contamination in the well and weights the population apportioned to that well accordingly. As documented in section 3.11.1, Level I Concentrations, of this support document, the EPA correctly identified Level I concentrations of vinyl chloride in well PSW 6. HRS Section 3.3.2.2, *Level I concentrations*, states:

Sum the number of people served by drinking water from points of withdrawal subject to Level I concentrations. Multiply this sum by 10.

Thus, the 4,000 count apportioned to well PSW 6 is multiplied by 10 to obtain a total of 40,000. This value of 40,000 is then summed with the Level II concentrations value and the Potential contamination value as directed in HRS Sections 3.3.2.3, *Level II concentrations*, and 3.3.2.4, *Potential contamination*. However, both of these values are assigned a 0 value because the entire population served by the Village of Hoosick Falls municipal water supply is considered exposed to Level I concentrations while well PSW 6 is in use and are not double counted as Level II or as potential contamination. Thus, the target population value in the HRS documentation record at promulgation is 40,000.

---

<sup>54</sup> Reference 8 of the HRS documentation record at proposal: Snyder, Scott, Weston. Telecon Note: Conversation with Jim Hurlburt, Hoosick Falls Water Department. Subject: Population and service connections served by municipal water system; with attached reference. August 3, 2016.

The HRS documentation record at promulgation was revised to include a total Targets factor value of 40,070 on line 11 of Table 3-1 on page 3 of the HRS documentation record. This total value included the original Resources and Wellhead Protection Area factor values of 0 and 20, respectively, as was proposed.

The EPA notes that, if the EPA had chosen the option of not including drinking water well PSW 6 (a standby well) in the apportioning of the population in the Site scoring, the Site score would remain above 28.50 and continue to qualify for the NPL. In this scenario, although the population apportioned to the standby well would be reduced to 0 and the population, instead, apportioned equally to the two wells in regular use (because they have equal pumping capacity as documented above), the overall site score will remain unchanged. The HRS scoring for the targets associated with the ground water migration pathway would be as follows in this alternative scenario:

<p>Nearest Well: 50*</p> <p>Population</p> <p>Level I Concentrations: 0</p> <p>Level II Concentrations: 2,000**</p> <p>Potential Contamination: 101***,†</p> <p>Population: 2,101</p> <p>Resources: 0†</p> <p>Wellhead Protection Area: 20†</p> <p>Targets: 2,171</p>
<p>Aquifer Score: 100†</p> <p>Ground Water Migration Pathway Score: 100†</p> <p>Site Score 50.00†</p>
<p>*As explained in sections 3.11.1, Level I Concentrations, and 3.11.2, Nearest Well, of this support document, PSW 6 is subject to Level I contamination of vinyl chloride.</p> <p>**The pumping capacity of PSW 3 and 7 are 700 gallons per minute (See Appendix B of this support document). Because in this scenario a well contributes more than 40%, to the Village of Hoosick Falls municipal water supply and PSW 3 and PSW 7 each contributes 50%, the population was apportioned evenly between these 2 wells. That is, 2,000 people for PSW 3 and 2,000 people for PSW 7. (See HRS 3.3.2, <i>Population</i>). In this scenario, PSW 7 is evaluated as a well subject to Level II contamination of PFOA. (See HRS Section 2.5, <i>Targets</i>, which states that actual contamination at Level II concentrations is “[m]edia-specific concentrations for the target meet the criteria for an observed release (or observed contamination) for the pathway, but are less than media-specific benchmarks.”) In this scenario, PSW 7 has an observed release of PFOA but the concentration of PFOA is not evaluated as being above an HRS drinking water benchmark.</p> <p>*** In this scenario, PSW 3 is evaluated as a well subject to potential contamination. The population associated with PSW 3 is evaluated in the “Greater than ¼ to ½” mile distance category of the “Other than karst” section of HRS Table 3-12, <i>Distance-Weighted Population Values for Potential Contamination Factor for Ground Water Migration Pathway</i>. The assigned value for a population of 2,000 is 1,013 which when divided by 10 yields a potential population factor value of 101.3 (rounded to 101). (See HRS Section 3.3.2.4, <i>Potential contamination</i>).</p> <p>† Same value as proposed.</p>

This comment results in no change to the overall HRS score and no change in the decision to place the Site on the NPL.

### 3.12 HRS Score

Comment: SGPP commented that the HRS site score was inappropriately evaluated in the HRS documentation record at proposal and should be revised. SGPP commented that the population apportioned to PSW6 is incorrect

because this well is a standby well, and, hence, the targets factor value assigned on line 8a, Level I Concentrations, of the ground water pathway scoresheet should be zero, not 13,330 as was assigned for this well at proposal.

Response: The HRS documentation record has been revised at promulgation to consider SGPP's comments and to revise the population associated with well PSW6 according to the HRS. As SGPP commented, well PSW 6 is a standby well that was not properly identified as a standby well at proposal. As explained in detail in section 3.11.3, PSW 6 Population, of this support document, the HRS directs that the entire population be considered in the apportionment of the population associated with PSW 6 when it is operating as a standby well. Therefore, the entire population of the Village of Hoosick Falls municipal water supply is considered when this standby well is in operation.

As documented in section 3.9, Observed Release, of this support document, the likelihood of release value of 550 was correctly assigned in the HRS documentation record at proposal. As documented in section 3.10, Waste Characteristics, of this support document, both vinyl chloride and PFOA receive a toxicity/mobility factor value of 10,000 and because Level I targets are appropriately evaluated (or, even if PFOA is the only hazardous substance evaluated at the Site, Level II targets are present) the waste quantity remains at 100 and the waste characteristics factor category value remains at 32 at promulgation.

Scoring the Site on either vinyl chloride or PFOA results in the Likelihood of Release and Waste Characteristics factor category values remaining unchanged at promulgation. Scoring well PSW 6 as subject to Level I contamination (see section 3.11.1, Level I Concentrations, of this support document) results in an assigned Level I concentration population value of 40,000. SGPP did not challenge that well PSW6 is located within 1/4-mile of the Site sources and the nearest well remains at 50. SGPP did not comment on the wellhead protection area and the total targets at promulgation have been revised to 40,070. Therefore, as shown in the revised summary scoresheets below, the ground water migration pathway remains scored at 100.00 in the HRS documentation record at promulgation.

However, as discussed in section 3.11.3, PSW 6 Population, above in this support document, even if no population is apportioned to standby well PSW 6, the population subject to Level II and potential contamination in the remaining wells (well PSW 7 and well PSW 3, respectively) is sufficient to score the Site above 28.50 and continue to qualify for the Site for NPL. In this scenario, there is no population subject to Level I contamination, but a population of 2,000 would be subject to Level II contamination in well PSW7 and an additional population using well PSW 3 would be subject to potential contamination. SGPP did not challenge the location of the nearest well or the wellhead protection area, and those values would remain the same at promulgation. As shown in the revised summary scoresheets below, even if a population of 0 is apportioned to well PSW 6 in the HRS evaluation, the ground water migration pathway would remain scored at 100.00 in the HRS documentation record at promulgation.

**Table 3-1, Revised Summary of Ground Water Migration Pathway Scoresheets**

Factor Categories and Factors	Maximum Value	Value Assigned in HRS documentation record at Proposal	Value Assigned in HRS documentation record at promulgation	Value Assigned for the Scenario for when Well PSW6 is Not Considered in the HRS Population Evaluation at Promulgation
<b>Likelihood of Release to an Aquifer:</b>	550	550	550 <sup>(A)</sup>	550 <sup>(A)</sup>
<b>Waste Characteristics:</b>				
4. Toxicity/Mobility	(a)	10,000	10,000 <sup>(B)</sup>	10,000 <sup>(B)</sup>
5. Hazardous Waste Quantity	(a)	100	100 <sup>(B)</sup>	100 <sup>(B)</sup>
6. Waste Characteristics	100	32	32 <sup>(B)</sup>	32 <sup>(B)</sup>
<b>Targets:</b>				
7. Nearest Well	50	50	50 <sup>(C)</sup>	50 <sup>(C)</sup>
8. Population:				
8a. Level I Concentrations	(b)	13,330	40,000 <sup>(D)</sup>	0
8b. Level II Concentrations	(b)	1,333	0 <sup>(E)</sup>	2,000 <sup>(M)</sup>
8c. Potential Contamination	(b)	101	0 <sup>(F)</sup>	101 <sup>(N)</sup>
8d. Population (lines 8a + 8b + 8c)	(b)	14,814	40,000 <sup>(G)</sup>	2,101 <sup>(O)</sup>
9. Resources	5	0	0 <sup>(H)</sup>	0 <sup>(H)</sup>
10. Wellhead Protection Area	20	20	20 <sup>(I)</sup>	20 <sup>(I)</sup>
11. Targets (lines 7 + 8d + 9 + 10)	(b)	14,834	40,070 <sup>(J)</sup>	2,171 <sup>(P)</sup>
<b>Ground water Migration Score for an Aquifer:</b>				
12. Aquifer Score [(lines 3 x 6 x 11)/82,500] <sup>c</sup>	100	100	100 <sup>(K)</sup>	100 <sup>(K, Q)</sup>
<b>Ground water Migration Pathway Score</b>				
13. Pathway Score ( $S_{gw}$ ), (highest $S_{gw}$ value from line 12 for all aquifers evaluated) <sup>c</sup>	100	100	100 <sup>(L)</sup>	100 <sup>(L, R)</sup>

<sup>a</sup> Maximum value applies to waste characteristics category.

<sup>b</sup> Maximum value not applied.

<sup>c</sup> Do not round to nearest integer.

(A) The Likelihood of Release assigned value of 550 remains the same as proposed for both scoring scenarios. (See pages 33 to 48 of the HRS documentation record at proposal and at promulgation. See also section 3.9, Observed Releases, of this support document.)

(B) The Waste Characteristics assigned value of 32 remains the same as proposed for both scoring scenarios. (See page 49 of the HRS documentation record at proposal and at promulgation. See also sections 3.10, Waste Characteristics, and 3.11.1, Level I Concentrations, of this support document.)

(C) The Nearest Well assigned value remains the same as proposed for both scoring scenarios. (See pages 50 and 52 of the HRS documentation record at proposal and at promulgation. See also section 3.11.2, Nearest Well, of this support document.)

(D) The HRS documentation record has been revised at promulgation to include a Level I Concentrations population assigned value of 40,000. Well PSW 6 is a standby well that provides 100% of the drinking water while in operation (that is PSW 3 and PSW 7 are turned off when PSW 6 is being used). Therefore, according to the HRS, the total population associated with the Village of Hoosick Fall municipal water supply (4,000) is apportioned to PSW6 which when multiplied by 10 yields a Level I Concentrations population assigned value of 40,000. (See sections 3.11.1, Level I Concentrations, and 3.11.3, PSW 6 Population, of this support document.)

(E) The HRS documentation record has been revised at promulgation to include a Level II population of 0 to PSW 7 because when well PSW 6 is in operation it provides 100% of the drinking water (i.e., PSW 3 and PSW 7 are turned off when PSW 6 is being used). Therefore, the total population associated with the Village of Hoosick Fall municipal water supply is apportioned to PSW 6. However, it still remains that PSW 7 is contaminated at Level II concentrations, although the scoring at promulgation assigns a population value of 0 to the Level II concentration population to avoid double counting the targets. (See section 3.11.3, PSW 6 Population, of this support document. See also pages 50 and 52 of the HRS documentation record at proposal and at promulgation.)

(F) The HRS documentation record has been revised at promulgation to include a Potential Contamination population assigned value of 0 because when well PSW 6 is in operation it provides 100% of the drinking water (i.e., PSW 3 and PSW 7 are turned off when PSW 6 is being used). Therefore, the total population associated with the Village of Hoosick Fall municipal water supply is apportioned to PSW6. Although the scoring at promulgation assigns a population value of 0 to the Potential Contamination population to avoid double counting targets, well PSW 3 remains subject to potential contamination for HRS scoring purposes. (See section 3.11.3, PSW 6 Population, of this support document. See also pages 50 and 52 of the HRS documentation record at proposal and at promulgation.)

(G) The HRS documentation record has been revised at promulgation to include the sum of the Population as 40,000 (40,000 for Level I + 0 for Level II + 0 for Potential Contamination).

(H) The Resources assigned value remains the same as proposed. (See page 53 of the HRS documentation record at proposal and at promulgation.)

(I) The Wellhead Protection Area assigned value remains the same as proposed. (See page 53 of the HRS documentation record at proposal and at promulgation.)

(J) The HRS documentation record has been revised at promulgation to include the sum of the Targets (40,000 for the Population + 50 for nearest well + 20 for Wellhead Protection Area = 40,070).

(K) The overall ground water migration pathway score for the aquifer remains the same as proposed.

(L) The overall ground water migration pathway score for the Site remains the same as proposed.

(M) In this alternative scenario, PSW 7 is evaluated as a well subject to Level II contamination of PFOA; PSW 7 has an observed release of PFOA, but the concentration of PFOA is not evaluated as being above an HRS drinking water benchmark. The pumping capacity of PSW 3 and 7 is each 700 gallons per minute. (See Appendix B of this support document.) Because in this scenario a well contributes more than 40%, to the Village of Hoosick Falls municipal water supply and PSW 3 and PSW 7 each contributes 50%, the population was apportioned evenly between these 2 wells. That is, the total population of the Village of Hoosick Falls water supply would be apportioned as follows: 2,000 people for PSW 3 and 2,000 people for PSW 7. (See HRS Section 3.3.2, *Population*. See section 3.11.3, PSW 6 Population, of this support document and pages 50 and 52 of the HRS documentation record at proposal.)



(N) In this alternative scenario, even if PSW 3 is evaluated as a well subject to Potential Contamination the pumping capacity of PSW 3 and 7 is each 700 gallons per minute. (See Appendix B of this support document.) In this scenario, a well contributes more than 40% to the Village of Hoosick Falls municipal water supply, and PSW 3 and PSW 7 each contributes 50%, therefore, the population would be apportioned evenly between these 2 wells. That is, the total population of the Village of Hoosick Falls water supply would be apportioned as follows: 2,000 people for PSW 3 and 2,000 people for PSW 7. The population (2,000) associated with PSW 3 is evaluated in the “Greater than  $\frac{1}{4}$  to  $\frac{1}{2}$ ” mile distance category of the “Other than karst” section of HRS Table 3-12, Distance-Weighted Population Values for Potential Contamination Factor for Ground Water Migration Pathway. The assigned value for a population of 2,000 is 1,013 which when divided by 10 yields a potential population factor value of 101.3 (rounded to 101). (See HRS Section 3.3.2.4, *Potential contamination*. See section 3.11.3, PSW 6 Population, of this support document and pages 50 and 52 of the HRS documentation record at proposal.)

(O) In this alternative scenario, the sum of the Population would be 2,101, (0 for Level I + 2,000 for Level II Concentrations + 101 for Potential Contamination). (See section 3.11.3, PSW 6 Population, of this support document.)

(P) In this alternative scenario, the sum of the Targets would be 2,171 (2,101 for Population + 50 for Nearest Well + 20 for Wellhead Protection Area = 2,171). (See section 3.11.3, PSW 6 Population, of this support document.)

(Q) In this alternative scenario, the overall ground water migration pathway score for the aquifer would remain the same as proposed.

(R) In this alternative scenario, the overall ground water migration pathway score for the Site would remain the same as proposed.

These comments result in no change to the overall HRS score and no change in the decision to place the Site on the NPL.

## 4. Conclusion

The original HRS score for this site was 50.00. Based on the above responses to comments, while HRS population factor values have been revised, the overall site score remains unchanged. The final scores for the Saint-Gobain Performance Plastics site are:

Ground Water:	100.00
Surface Water:	Not Scored
Soil Exposure:	Not Scored
Air:	Not Scored
HRS Site Score:	50.00

## Appendix A:

EPA Response to External Peer Review Comments on EPA Draft Documents: Health Effects Support Document for Perfluorooctanoic Acid (PFOA) and Health Effects Support Document for Perfluorooctane Sulfonate (PFOS) (EPA, May 2016). (99 pages)

**EPA Response to External Peer Review Comments on  
EPA Draft Documents:**

***Health Effects Support Document for Perfluorooctanoic Acid (PFOA)***

**and**

***Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)***

**May 2016**

**U.S. Environmental Protection Agency  
Office of Water, Office of Science and Technology  
Health and Ecological Criteria Division  
1200 Pennsylvania Avenue, NW  
Washington, DC 20460**

## **DISCLAIMER**

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## Contents

<b>1. Introduction.....</b>	<b>4</b>
External Peer Review Process .....	4
Technical Charge to External Peer Reviewers .....	5
<b>2. EPA Responses to Peer Reviewer General Impressions .....</b>	<b>7</b>
PFOA-specific Comments .....	7
PFOS-specific Comments .....	9
<b>3. EPA Responses to Peer Reviewer Comments on Charge Questions .....</b>	<b>18</b>
Charge Question 1: Studies Used for Quantification .....	18
Charge Question 2: Additional References .....	23
Charge Question 3: Use of Epidemiology Data .....	30
Charge Question 4: Characterization of Epidemiology Data .....	37
Charge Question 5: Cancer Classifications .....	42
Charge Question 6: Use of Pharmacokinetic Model .....	45
Charge Question 7: Selected Parameters of Pharmacokinetic Model .....	49
Charge Question 8: Volume of Distribution and Half-life Values .....	54
Charge Question 9: Candidate RfDs .....	59
Charge Question 10: Duration.....	63
Charge Question 11: Interspecies Uncertainty Factor .....	68
Charge Question 12: Other Suggestions.....	71
EPA Responses to Specific Editorial and Technical Comments.....	76
<b>4. References.....</b>	<b>93</b>

## 1. Introduction

In 2014, Versar, Inc., under contract to the U.S. Environmental Protection Agency (EPA), Office of Water,<sup>1</sup> conducted an independent, scientific peer review of EPA's draft documents, *Health Effects Document for Perfluorooctanoic Acid* (PFOA) (USEPA 2014a) and *Health Effects Document for Perfluorooctane Sulfonate* (PFOS) (USEPA 2014b). The draft documents and charge questions were prepared by EPA to ultimately develop drinking water health advisories for the chemicals PFOA and PFOS.<sup>2</sup> The goal of the peer review was to ensure that EPA's interpretations of toxicological studies and their conclusions were reasonable, sound, and consistent with the underlying science, and that, as a whole, the documents were clear and scientifically credible. This report describes the external peer review process and provides the peer reviewers' final comments and recommendations (verbatim) and EPA's responses.

### External Peer Review Process

EPA followed the process recommended in its 2013 guidance, Conflict of Interest (COI) Review Process for Contractor-Managed Peer Review<sup>3</sup>, for the draft health effects documents for PFOA and PFOS. On February 28, 2014 EPA published a Federal Register notice<sup>4</sup> calling for public nominations of experts to serve on the panel peer review. The August 2014 draft health effects documents were made public and interested parties were able to submit comments on the draft documents. The contractor (Versar) developed a preliminary list of peer reviewers based on the public nominations and application of traditional peer reviewer identification techniques (e.g., literature searches). On April 30, 2014 EPA published a second notice<sup>5</sup> to announce and request public comment on a preliminary list of peer reviewers. Following closure of the comment period, Versar identified a proposed final peer review panel and consulted with EPA Science Advisor designees on June 20, 2014. On July 10, 2014 EPA published a third notice<sup>6</sup> announcing the final peer reviewers, meeting logistics, and registration instructions. Public comments received during the comment period were provided to the peer reviewers for their consideration during their review of the health effects documents prior to their panel meeting on August 21-22, 2014.

The purpose of the peer review was to provide a documented, independent, and critical review of the draft health effects documents, and identify any necessary improvements to the documents prior to being finalized and published. In assembling these peer reviewers and coordinating the peer review, Versar was charged with evaluating the qualifications of peer review candidates, conducting a thorough COI screening process, independently selecting the peer reviewers, consulting with EPA Science Advisor designees on the proposed final panel, distributing review materials, maintaining

---

<sup>1</sup> Task Order No. 4-10, Contract No. EP-C-07-059, with a period of performance from September 2011 through September 2012.

<sup>2</sup> These chemicals are listed on EPA's third Contaminant Candidate List (CCL) (2009) and on the draft fourth CCL (2015) and are currently being monitored under the third Unregulated Contaminant Monitoring Rule (UCMR3). Results from UCMR3 can be examined as they become available at the following website:

<http://water.epa.gov/lawsregs/rulesregs/sdwa/ucmr/ucmr3/>.

<sup>3</sup> <http://www.epa.gov/osa/conflicts-interest-review-process-contractor-managed-peer-reviews-epa-highly-influential>

<sup>4</sup> <http://www.gpo.gov/fdsys/pkg/FR-2014-02-28/pdf/2014-04455.pdf>

<sup>5</sup> <http://www.gpo.gov/fdsys/pkg/FR-2014-04-30/pdf/2014-09888.pdf>

<sup>6</sup> <http://www.gpo.gov/fdsys/pkg/FR-2014-07-10/pdf/2014-16176.pdf>

contact with the peer reviewers, organizing and hosting the public peer review meeting, and developing a final peer review report.

EPA reviewed the qualifications of the candidates proposed by Versar and verified that the range of the candidates' qualifications met the technical selection criteria. Versar then contracted with the following reviewers to perform the review:

- James V. Bruckner, Ph.D.; University of Georgia, Athens, Georgia
- Deborah A. Cory-Slechta, Ph.D.; University of Rochester School of Medicine and Dentistry, Rochester, New York
- Jamie C. DeWitt, Ph.D.; East Carolina University, Greenville, North Carolina
- Jeffrey W. Fisher, Ph.D.; U.S. Food and Drug Administration, Jefferson, Alaska
- William L. Hayton, Ph.D.; The Ohio State University, Columbus, Ohio
- Matthew P. Longnecker, Sc.D, M.D.; National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina
- Angela L. Slitt, Ph.D.; University of Rhode Island, Kingston, Rhode Island

Versar distributed EPA's draft PFOA and PFOS documents and 12 charge questions (see below) to the peer reviewers, who were asked to evaluate the scientific and technical merit of the draft documents and provide responses to the 12 charge questions. This effort included evaluating the appropriateness of the quality, accuracy, and relevance of the data in the documents. Peer reviewers were not charged with making any regulatory recommendations or reaching consensus in either their written comments or public deliberations. In addition to being provided the draft documents and charge questions, comments submitted to EPA's public docket during the 60-day public comment period and a summary of those comments developed by Versar were provided to the peer reviewers ahead of the meeting for their consideration.

### **Technical Charge to External Peer Reviewers**

The peer reviewers were asked to evaluate the scientific and technical merit of the draft documents and provide their responses to the following charge questions.

1. Please comment on the strengths, weaknesses, and characterization of the studies selected as key for quantification.
2. Please provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA consider adding to the document. Describe where you suggest these references be incorporated.
3. The OW concluded that the human epidemiology data for PFOS/PFOA do not provide adequate quantifiable dose-response information for use as the basis of a candidate RfD because of uncertainty regarding the routes, levels and timing of exposures plus the confounding influences of other PFCs present in serum. Please comment of the OW characterization of the data.
4. Please comment on the transparency and characterization of the epidemiological data.
5. The OW has concluded that the cancer classifications for PFOA and PFOS are most consistent with respective classifications of suggestive evidence for carcinogenicity as described the EPA Guidelines for Carcinogen Risk Assessment (pp. 2-56, 2-57). Please comment on the strengths and weaknesses of this classification.

6. Significant interspecies differences in pharmacokinetics exist for both PFOA and PFOS. Adjusting for interspecies differences was an important step in developing candidate RfDs given the totality of the human and animal data. Please comment on the strengths and weaknesses of the pharmacokinetic model adjustments to accommodate the impact of albumin binding and renal tubule transporters in determining average serum values.
7. Table 5-5 in the PFOA document and Table 5-7 in PFOS document list the parameters used for the ORD pharmacokinetic models that provide the final serum and AUC values for calculating the internal dose point of departure for the RfD calculation. Please comment on the strengths and weaknesses of the selected parameters.
8. The volume of distribution (Vd) and half-life values are critical in the derivation of the interspecies uncertainty factor applied in derivation of candidate RfDs from a NOAEL, LOAEL or a BMDL. The available data for both values are provided in Section 3.5.2 and 3.5.3 of both documents. Please comment the strengths and weaknesses of the values selected.
9. A variety of endpoints and studies were used to compare points of departure and the resultant RfDs for both PFOA and PFOS. In addition, comparisons were provided across RfD outcomes based on the model outputs compared to those for the NOAEL, LOAEL and BMDL points of departure. The range of candidate RfDs derived from the different points of departure is fairly narrow. Please comment on the strengths, weaknesses and transparency of this analysis.
10. The RfDs for PFOS and PFOA are derived from the modeled steady state serum concentrations and their association with effects that include short term and longer term exposures with associated diverse effects. The studies considered included effects due to exposure durations that ranged from 11 to 182 days, and occur at comparable human equivalent dose (HED) levels. The current, draft RfDs do not include an uncertainty factor for study duration because of the apparent concordance HEDs despite duration differences. Given this pattern of response, is it appropriate to conclude that the candidate RfDs are applicable to both short-term and lifetime exposures?
11. In addition to using the average serum values from animal studies to calculate internal doses for humans, the animal to human extrapolation can be accomplished by dividing animal average serum values by the human to animal clearance ratios to project a human average serum point of departure in units of mg/L serum. Please provide recommendations for applying uncertainty factors to the extrapolated average human serum values to determine serum-based thresholds that are protective for humans. A NOAEL expressed in average human serum units would be useful in interpreting NHANES population monitoring data.
12. Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft documents.



## 2. EPA Responses to Peer Reviewer General Impressions

### Bruckner Comments

#### PFOA-specific Comments

**COMMENT 1:** This is one of the most comprehensive Health Effects Documents I have reviewed. The clarity and accuracy of accounts of pertinent research reports/publications are excellent. It is obvious considerable time and efforts were devoted to its composition. If anything, the amount of detail is so great that it is difficult to distill the mass of information on each topic and capture its “essence”. This is likely the result of directions the authors were given for writing the document. Some topics in the Hazard Identification section do have summarizing sentences, in which the key/critical studies and their finding(s) are integrated and conclusions reached. It would be very helpful to devote much more attention to this for more topics, perhaps as an addition to Section 4.4 Hazard Characterization.

**RESPONSE:** In response to this and other similar comments, EPA rewrote major sections of both health effects support documents (HESDs) (in 2014 referred to as the draft health effects documents) to enhance readability, clarity, and transparency (USEPA 2016a, 2016b). As requested by the peer reviewers, a summary section was added to the toxicokinetic section (section 2.6.4 for PFOA and 2.6 for PFOS) and at the end of the epidemiology sections for both the noncancer (sections 3.1.1.12 for PFOA and 3.1.1.8 for PFOS) and cancer endpoints (section 3.1.2.1 for both PFOA and PFOS). Introductions were added at the beginning of the animal toxicity data portion of the report (section 3.2) to inform the reader regarding the material included. An independent summary of the animal toxicology was not prepared to avoid making the subsequent synthesis (section 3.4) of hazard repetitive.

**COMMENT 2:** I do have a real problem with the scientific basis and soundness of certain conclusions in the document. The primary effect of PFOA in different species is increased absolute and/or relative liver weight. These are quite modest, reversible, non-specific effects that usually are not considered toxicologically significant. Livers of mice and rats dosed with PFOA typically exhibited hypertrophy characterized by increased peroxisomes, numerous mitochondria, reduced rough endoplasmic reticulum (RER), proliferation of smooth endoplasmic reticulum (SER), and increased autophagosomes or lipid-like droplets. Such morphological changes, particularly those in RER and SER, are manifestations of microsomal enzyme induction. This is considered adaptive, rather than adverse. Hall et al. (2012) points out that activation of a battery of genes involved in xenobiotic metabolism and transport serve to maintain homeostasis by enhancing the systemic elimination of the foreign chemical. Although PFOA is very poorly metabolized, it does persistently induce microsomal enzymes and the accompanying hepatocellular morphological changes. Upregulation of genes responsible for biliary excretion may be beneficial, since excretion of bilirubin, bile acids and conjugates of toxic chemicals/metabolites would be enhanced.

There are substantial qualitative and quantitative differences in responses of rodents and humans to PPAR $\alpha$  activation. Therefore, many of the PFOA-induced alterations in lipid metabolism/homeostasis and associated biological processes in mice will be absent or an order of magnitude less pronounced at comparable doses in humans. Many of PFOA's effects on the liver of rodents are dependent on PPAR $\alpha$  activation, though some effects appear to be PPAR $\alpha$ -independent. Studies in PPAR $\alpha$ -knockout mice show activation of other nuclear receptors by PFOA, including PXR, CAR, LXRA and FXR. Bjork et al. (2011) observed markedly lower transcriptional responses of PPAR $\alpha$ , PXR, CAR and FXR to PFOA in cultured human than in cultured rat hepatocytes. These more subtle effects lead the investigators to conclude the changes in human cells reflected an adaptive metabolic remodeling rather than overt metabolic dysregulation, or disorder occurring in rat cells. The PFOA document's authors should go into detail discussing and summarizing the relative toxicological significance of non-PPAR $\alpha$  effects in rodents versus humans.

**RESPONSE:** Increased liver weight is acknowledged as a common finding following exposure to PFOA and PFOS in the final HESDs documents (USEPA 2016a, 2016b). Liver weight was not considered as adverse in the absence of other effects as defined by Hall et al. (2012). See also EPA response to Charge Question 1.

The NOAELs and LOAELs that were originally based on increased liver weight were revised so that the LOAELs based on liver effects in the final HESDs reflect a liver endpoint that meets the Hall et al. (2012) criteria for adversity. The revised assessment provides detailed discussions of peroxisome proliferator-activated receptor (PPAR) receptors, the impact of their activation, and associated cellular responses in the final HESDs. Information on other activated receptors such as constitutive androstane receptor (CAR), pregnane X receptor (PXR), and farnesoid receptor (FXR) were also included where appropriate.

**COMMENT 3:** It is important to recognize that clearly adverse effects of PFOA are seen. Loveless et al. (2008), Cui et al. (2009) and others have seen focal necrosis and degenerative changes in the liver of mice and rats given relatively high doses of PFOA, as well as modest elevations in serum (hepatic) enzyme activities. Wolf et al. (2008a) observed a variety of degenerative structural changes in the liver of PPAR $\alpha$ -null mice dosed with PFOA. Sakr et al. (2007a,b) and Olsen and Zobel (2007) reported associations between serum PFOA levels and slightly elevated serum enzyme activities in some occupationally-exposed populations. The increases in enzymes may have been attributable to factors other than PFOA. In light of the foregoing, it would be preferable to utilize hepatic morphological changes in rodents and/or elevated serum enzymes as the critical effect(s), rather than increased liver weight. These are clearly adverse effects seen in both rodents and humans.

An international panel of experts (Hall et al., 2012) opined that an increase in liver weight of  $\leq 150\%$ , at doses of chemical that do not produce structural or biochemical evidence of hepatocellular damage, would not be considered adverse. Absolute and relative liver weights were not increased as much as 50% by most PFOA doses in the majority rodent and monkey studies. Perkins et al. (2004), for example, reported dose-dependent increases in liver/body weight in rats fed 1, 10, 30 and 100 ppm PFOA for 13 weeks of 0, 10, 30, and 41%, respectively. Butenhoff et al. (2002) measured increases of 17, 21 and 37.5% and relative liver weight in monkeys given 3, 10 or 30/20 mg PFOA/kg/day for 26 weeks, respectively. Liver hypertrophy of this magnitude does not warrant such a low RfD. By adhering to EPA policies of calculating a BMDL<sub>10</sub> and using multiple UFs, regardless of the (lack of) severity of the critical effect and relatively low level of concern about other potential health effects, the end result is a vanishingly low RfD (i.e. 0.00002 mg/kg/day). A great deal of time and effort were spent on the PFOA hazard assessment, toxicokinetic modeling and extrapolations, dose metric and POD considerations, etc. Despite all of these scientifically-credible exercises and deliberations, the end result (RfD) seems to this reviewer to have been preordained--to be extremely low.

**RESPONSE:** NOAELs and LOAELs that were originally based on increased liver weight were revised so that the effects noted at the LOAEL are endpoints that met the Hall et al. (2012) criteria for adversity. In the summary of the studies that provide dose response (Tables 4-1 and 4-2 in the final HESDs), liver weight, hypertrophy, and similar effects are acknowledged when part of the spectrum of effects at the LOAEL dose, if they accompany the effect identified as adverse. Because the numbers of animals in some of the studies were low, hepatic necrosis is noted as an effect when it exceeded the incidence in the controls and showed a relationship to dose.

**COMMENT 4:** Logic expressed on page 5-6, in support of use of liver weight gain as a critical effect and biomarker of loss of hepatocellular homeostasis seems flawed. As pointed out in the second paragraph, liver weight changes were not observed in PFOA-treated mice with a humanized PPAR $\alpha$  receptor. It is noted that changes in gene products that modulate lipid metabolism do occur in these mice. EPA argues that this supports adoption of increased liver weight as a biomarker/critical effect. It has not been established that these changes in gene expression are adverse, or whether they are sufficient in magnitude to significantly alter lipid metabolism. It would be expected that repeated dosing with enough of a molecule (i.e., PFOA) that

resembles a fatty acid would affect expression of such genes. Reversible changes in total cholesterol, bile acids, bilirubin, etc. have been observed. It has not been established, however, whether mild fluctuations in these indices are detrimental. No increases in mortality from cerebrovascular disease or ischemic heart disease have been found in PFOA-exposed humans. How then does the concurrence of alteration of expression of such genes and of liver weight gain support the latter as toxicologically-significant effect that should be prevented by setting the RfD low enough?

**RESPONSE:** Based on feedback received from the peer review panel, the critical endpoint selected to serve as the POD for the reference dose (RfD) for PFOA (and PFOS) is no longer increased liver weight. The critical study and endpoint for the derivation of the RfD for PFOA are based on reduced ossification of the proximal phalanges and accelerated puberty in males observed in the Lau et al. (2006) study. For PFOA, the candidate RfDs developed for consideration were based on multiple adverse effects resulting from short-term and long-term exposures and fell within a narrow dose range. Increased liver weight is acknowledged as a common finding following exposure to PFOA (and PFOS) in the revised documents. However, it is not considered as adverse in the absence of other effects as defined by Hall et al. (2012). The NOAELs and LOAELs that were originally based on increased liver weight were revised so that the LOAELs based on liver effects in the final HESDs reflect a liver endpoint that meets the Hall et al. (2012) criteria for adversity.

In a human health context, the associations observed between exposure to PFOA and cholesterol and serum lipids observed in the epidemiology studies are well accepted as risk factors for cardiovascular disease. It is important to note that several of the animal studies published after the completion of the peer review drafts and included in the final HESDs for PFOA and PFOS (USEPA 2016a, 2016b) show that dietary fat is an important variable influencing the presence of fat accumulation in the liver and insulin resistance. Diet is a variable that was not considered in many of the epidemiology studies. The available information from these additional animal studies, taken together with the observed effects on cholesterol in the epidemiology studies, provide support for the identification of hazard for these effects.

## **PFOS-specific Comments**

**COMMENT 5:** This Health Effects Document, like that for PFOA, is quite comprehensive. Its descriptions of the many studies of PFOS are clear, quite complete, and apparently quite accurate. As with the PFOA document, so much detail is given about many studies in the Hazard Identification section, that is difficult to compare study designs/dosage regimens/species/indices/findings/etc. and to draw conclusions. The summary tables for single and multiple studies, however, are quite helpful in this regard. It would also be very useful to have more summary statements or paragraphs at the end of each topic. These should address the scientific importance of findings, their relevance to humans; and their impact on the weight of evidence on an issue.

**RESPONSE:** See the response to Bruckner General Impression Comment 1 above. The correlation between the epidemiology and the animal toxicology results are integrated in the hazard synthesis to reduce redundancy between an independent summary of animal toxicology and the subsequent synthesis of hazard.

**COMMENT 6:** The hazard characterization section (4.4) is, for the most part, inclusive and balanced in its presentation and integration of findings of the more important studies in each subject area. This is true for both non-cancer and cancer effects in humans and animals. It concerns me, however, that the document's authors do not focus in the remainder of the document on science (i.e., the candidate critical effects and their relevance to human health), but merely choose the most sensitive end-points and stress how similar the RfDs are after dosimetry modeling estimates and adjustments. I am not sure how this similarity of derived points of departure and other values, calculated from dissimilar endpoints, supports or validates the final RfD.

**RESPONSE:** The peer reviewed version of the HESD was largely focused on comparing the outcomes from use of NOAEL/LOAEL, lower 95<sup>th</sup> percentile confidence bound benchmark doses (BMDLs), and the HEDs derived from the average serum levels projected by the EPA toxicokinetic model. That exercise demonstrated

that the modeled results were comparable to the outcomes from using the more conventional approaches (i.e., NOAEL/LOAEL and BMD modeling). Based on the feedback received from the peer reviewer panel, the revised HESD presents the results from the toxicokinetic model in developing candidate RfD values. Accordingly, there is now considerably more text that compares the modeled outcomes to the effect doses seen across the spectrum of studies that provide information on dose and response, but lack serum information for modeling. For PFOA, multiple studies were modeled to derive average serum values and from these results candidate RfDs were quantified. The RfD selected is based on developmental effects (reduced ossification and accelerated puberty in males) resulting from gestational and lactational exposures.

The selected RfD for PFOA is supported by the longer-term RfD for effects on the response of the immune system (DeWitt et al. 2008) to external challenges as observed following the short-term exposures to mature rats and the effects on kidney weight observed at the time of sacrifice in the F1 males from the Butenhoff et al. (2004a) study. Support for the selected RfD is also 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.

The RfD for PFOS 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. The RfD is protective of the most sensitive populations (i.e., developing fetus and nursing infant) and the general population. The rationale for selection of the developmental endpoint has been revised and support for each of the modeled endpoints from the studies with NOAELs and/or LOAELs is part of the discussion that accompanies the RfD derivation.

**COMMENT 7:** I recommend that an additional section be written, in which the primary adverse effects of PFOS are discussed-- in terms of their relative toxicological significance, their apparent mechanism(s), their relevance to humans, their likelihood in realistic exposure scenarios, and implications of altered experimental indices to actual organ dysfunction.

**RESPONSE:** In the revised HESDs, an integrated summary of the effects of PFOS on humans and animals is included. Mode of action information presented in the documents include data demonstrating involvement of receptor activation (e.g., PPAR $\alpha$ ) and gap junction communications (both involve proteins) plus oxidative damage. The implications of these mode of actions to human relevance are also discussed. The sources of exposure to PFOS for humans (diet, dusts, indoor air, etc.) are included in the Health Advisory documents (USEPA 2016c, 2016d) that accompanies the HESD.

**COMMENT 8:** I am quite concerned about the increased rat pup mortality in several studies at relatively low maternal doses, but not about reversible liver weight changes or centrilobular hypertrophy. Is the decreased pup survival in several studies at relatively low maternal doses of PFOS relevant to humans?-- Is the dose-response curve steep, as suggested by Luebker et al. (2005a), such that there would be less concern about sub-threshold doses? -- What is the most likely mode of action (pulmonary surfactant or maturation, dietary, hormonal)? -- Is decreased survival PPAR $\alpha$ -related? -- Is the mechanism in rats relevant to other species? -- Does pup mortality occur in other species at comparable doses? -- Might there be a dose-dependent alteration of maternal-fetal partitioning of PFOS?

**RESPONSE:** Yes, decreased pup survival is an endpoint of concern for humans. In the case of PFOS, the selected RfD applies to low birth weight. Effects on increased pup mortality occurred at doses greater than the values for these body weight effects. The toxicokinetic studies show high levels of PFOS in the lung in early life (e.g., Borg et al. 2010). Pup deaths occurred in both rat and mouse studies at comparable doses (Grasty et al. 2003; Lau et al. 2003; Luebker et al. 2005a, 2005b; Yahia et al. 2008; Abbott et al. 2009). Several of these studies suggest involvement of the lung in mortality, but the data of Grasty et al. (2003) do

not fully support lung surfactant as a cause of death, and this potential mode of action is discussed in more detail in the HESD. The observed decreased survival cannot be fully explained by the role of PPAR $\alpha$ . The study by Abbott et al. (2009) evaluated the role of PPAR in mortality, the authors reported early mortality in both wild type and knock out PPAR $\alpha$  mice. The effects on the wild type were impacted to a greater extent than the knock out but survival was decreased for both. The lowest LOAEL for effects on survival was 0.8 mg/kg/day from the Luebker et al. 2005a one-generation study that was quantified and included among the candidate RfDs. The slope associated with the response is curvilinear, in other words the slope is low at the next two highest doses and then increases steeply at the following two doses. Additional data are needed before questions regarding mechanism and dose-response can be resolved with regard to pup/fetal mortality.

### **Cory-Slechta Comments**

**COMMENT 1:** Both documents, although the PFOA document to some degree more than PFOS, overall are more of a tabulation of studies than a critical review of studies from which a rationale is presented for a choice of studies to model and from which to derive associated RfDs. The Executive summaries are too abbreviated and do not include sufficient rationale, description and detail to provide the reader with an understanding of how decisions described in Chapter 5 were made. Since in some cases, this will be the only sections read, they could provide a more informative summary.

**RESPONSE:** The HESDs for both PFOA and PFOS were extensively revised to present a more in-depth analysis of the human epidemiology data, integrated summary of the animal and human evidence, and rationale for selection of the critical studies for quantitative analysis and selection of the RfDs.

**COMMENT 2:** The Executive Summaries of both documents detail the available human and animal data and describe the basis for the RfD and studies supporting that derivation. It would be very helpful to provide a section up front that describes all of the parameters of the literature search, including the years that are included in the document review, as well as descriptions of criteria for studies that were included vs. those that were excluded. In addition, it should be indicated whether there was a criterion that studies be peer-reviewed. This is particularly important given the voluminous size of the data base that has accumulated for these two chemicals. Given that revisions will be done and that such documents do not get updated with any frequency, it would be good to attempt to include as much of the new pertinent literature as possible.

**RESPONSE:** The revised documents include a description of the literature search strategy and search terms used (see Appendix A). The forward of the HESD lists the criteria that were applied in deciding which of the multiple studies reviewed would be included in the final report. Although most of the studies came from peer reviewed journals, some are reports of primary research provided to the EPA Office of Pollution Protection and Toxics. Several of those were published in the peer reviewed literature. The current document includes citations to the unpublished and published reports. It was also updated to include studies recommended by peer reviewers and in public comment.

**COMMENT 3:** The section on Toxicokinetics in the documents present studies in detail, but no real conclusions; this is true of most of the sections in these documents. Chapters 3 and 4 in particular read like tabulations of studies rather than critical reviews and because of that, the documents seem disjointed and Section 5, i.e., derivation of values, tend to be difficult to read through and require constant searching back to the original chapters in which they are described. It is critical to identify the strengths and weaknesses of the various studies, and which were given weight to use in the final determinations. It would be helpful if Sections 3, 4 and 5 included an introductory paragraph describing the goal of the chapter, and that each ends with an overall summary with conclusions. The tables in these chapters also would benefit from the inclusion of additional information that ultimately permits comparisons within the Table and does not require continually returning to the text to recall the species, sample sizes, etc.

**RESPONSE:** EPA rewrote major sections of both HESDs to enhance readability, clarity, and transparency (USEPA 2016a, 2016b). As requested by the peer reviewers, a summary section was added to the toxicokinetic section (section 2.6.4 for PFOA and 2.6 for PFOS) and at the end of the epidemiology sections for both the noncancer (sections 3.1.1.12 for PFOA and 3.1.1.8 for PFOS) and cancer endpoints (section 3.1.2.1 for both PFOA and PFOS). Introductions were added at the beginning of the animal toxicity data portion of the reports (section 3.2) to inform the reader regarding the material included.

A major difference between the peer reviewed and final drafts is the reliance on the modeled, average-serum data for quantification, an approach that was supported by the peer reviewers and an expansion of the discussion of both the strengths and weaknesses, as well as the similarities and differences across the studies that provided dose-response information.

The quantification section is more compressed and more fluid because the now published toxicokinetic model is included in section 2.6.1 for PFOA and 2.5.1 for PFOS with the information on other toxicokinetic models. This facilitates a more streamlined presentation of the average serum and human equivalent doses and a better discussion of the similarities between the effects and critical doses from the modeled studies compared to the studies with dose-response but lacking in serum measurements. Species and effects information are now included in each of the model summary tables so that the reader does not have refer to earlier summary tables to retrieve that information.

**COMMENT 4:** In the sections on Hazard Identification, it is useful that studies are summarized by target organ, but there are almost no conclusions and no discussions of strengths or weaknesses of studies and therefore their use or not in future decisions. In fact, one is left with the impression that all studies are equal, especially in the section describing human studies. Within Chapter 4, the sub-sections entitled “evaluative and integrative” are actually neither. Data are presented simply as positive or negative with no real discussion of the strengths and limitations and what was concluded overall. For this reason, Chapter 5 is also lacking. It provides very little in the way of rationale and conclusions. Thus, the transparency of the process is really insufficient.

**RESPONSE:** The HESDs for both PFOA and PFOS were extensively revised to present a more in-depth analysis of the human epidemiology data, integrated summary of the animal and human evidence, and rationale for selection of the critical studies for quantitative analysis and selection of the RfDs.

## DeWitt Comments

**COMMENT 1:** The information presented throughout the documents appears to be accurate (with one minor exception noted in Table 1 of these comments) and is presented clearly. For PFOA, a reference dose (RfD) of 0.00002 mg/kg/day was determined and evidence of carcinogenicity is considered suggestive with a human equivalent dose (HED) of 0.58 mg/kg/day. The RfD was based on changes in liver weight reported as a common denominator in four rodent (three rat and one mouse) studies and carcinogenicity was based on a limited number of epidemiology studies linking kidney and testicular tumors with exposure and evidence of tumor induction in the liver, testes, and pancreas (the “tumor triad”) in rats. For PFOS, a RfD of 0.00003 mg/kg/day was determined and evidence of carcinogenicity is considered suggestive but with insufficient evidence to determine human carcinogenic potential. The RfD was based on developmental neurotoxicity and changes in liver weight.

While the carcinogenicity assessment seems appropriate for the two compounds given the limitations of the data sets, changes in liver weight as a basis of both of the RfDs is questionable in terms of its significance to exposed humans. Exposure to these agents increases liver weight and hepatocellular hypertrophy in rodents (and the definition of these endpoints as “adverse” or “toxic” also is contentious); this has been demonstrated across various rodent strains and under myriad exposure paradigms. However, there is no consensus in the scientific community regarding the mechanism by which exposure to these compounds increases liver weight

and induces hepatocellular hypertrophy in rodents and whether any of the putative mechanisms are sufficient to induce hepatotoxicity in exposed humans. Proposed mechanisms include peroxisome proliferator activated receptor alpha (PPAR $\alpha$ ) activation, activation of other nuclear receptors, peroxisome proliferation (which may or may not be dependent on PPAR $\alpha$  activation), and oxidative stress. Humans can certainly respond to PPAR $\alpha$  agonists (i.e., fibrate drugs are used as hypolipidemic agents) and a handful of epidemiological studies of highly exposed human populations have reported associations between PFOA/PFOS and alterations in liver enzymes, but the clinical relevance of the changes to the liver enzymes reported for these studies is uncertain. These liver-related changes in humans generally occur at higher doses than required to induce changes in the livers of rodents, which occurs at relatively lower doses than other observed effects. Therefore, a critical endpoint that occurs at very low doses in rodents, has no agreed upon mechanism that may or may not be relevant in humans at relatively high doses, may not be the best choice for the basis of a RfD. Liver weight change has been reported to occur in several species, including non-human primates, and at low doses, it may be an adaptive response and not a toxicological response. While this response may be protective of human health because it is common following low dose exposure to PFOA or PFOS, other endpoints may be more relevant to humans, especially endocrine system effects, including changes to thyroid hormones and mammary gland development, and immune system effects. Endocrine and immune system effects have been reported in exposed humans, suggesting that such endpoints may operate via a mechanism that is more relevant to humans than mechanisms related to changes in liver weights.

**RESPONSE:** Based on peer review comments, EPA examined a multitude of effects observed in the available animal studies. For PFOA, EPA modeled data from six studies for effects on development (delayed ossification, accelerated puberty, pup body weight, adult body and kidney weight), liver, and immune system. For PFOS, EPA modeled data from six studies for effects on development (pup body weight, neurodevelopment, pup survival) and liver. For both PFOA and PFOS, the RfDs based on multiple adverse effects resulting from short-term and longer-term exposures fall within a narrow dose range. The HESDs also describe available data on other endpoints (e.g., endocrine system and mammary gland development). EPA selected the most sensitive RfDs based on developmental effects so that they are protective for the general population and sensitive life stages.

**COMMENT 2:** In addition, the one developmental neurotoxicity study used, in part, for the PFOS RfD is only weakly supported by additional studies in rodents or other species and is based on behavioral responses that could be influenced by factors other than direct effects on the nervous system. Additional confirmatory studies are necessary for this observation to be considered a critical effect of PFOS exposure.

**RESPONSE:** The developmental neurotoxicity study by Butenhoff et al. (2009) was retained as one of the studies for dose-response quantification but it was not selected as the critical study for derivation of the RfD for PFOS. The Butenhoff et al. (2009) study and neurotoxicity endpoints are supported by studies by Long et al. (2013) demonstrating effects on spatial learning and memory in mature mice and Wang et al. (2015) showing increased water maze escape latency in prenatally exposed rats.

**COMMENT 3:** Finally, while well-written overall, the documents lacked an overall critical analysis or depth required of a risk assessment. Why specific studies were included or not should be better explicated in the text.

**RESPONSE:** The HESDs for both PFOA and PFOS were extensively revised to present summary sections to the toxicokinetic chapter and the epidemiology sections, a more in-depth analysis of the human epidemiology data for the identification of hazard, more detailed tables summarizing the results of the epidemiology studies, an integrated summary of the animal and human evidence, and a rationale for selecting the critical studies for quantitative analysis and selection of the RfDs.

## Fisher Comments

**COMMENT 1:** The document was well written in terms of balance and presenting information. Summary statements are needed for chapters; a synthesis/analyses of the data are needed in some cases. A more critical evaluation of the human and non-human responses to PFOA/PFOS is required to justify not using human or non-human primate data. A rationale for the modeling approaches is needed given the more recent PBPK models that are available.

**RESPONSE:** The documents have expanded the literature used in the analysis to include papers recommended by the peer reviewers and many identified by the literature searches conducted during the post peer review period.

Summary sections were added to the toxicokinetic chapter and the epidemiology sections to assist the reader. New tables summarizing the results of the epidemiology studies were also developed. The original epidemiology summary tables were expanded significantly as recommended by the peer reviewers and are presented in Appendix B. The synthesis section was revised to better integrate findings between the human epidemiology studies and controlled animal studies. Taken together, the weight of evidence for human studies supports the conclusion that PFOA and 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. That effort may further evaluate and consider these human epidemiology studies.

The current HESDs describe why EPA selected the PK model, in addition to a description of the model and results. EPA notes that the final HESDs utilized a peer-reviewed and updated model (Wambaugh et al. 2013), which was revised as suggested by the peer reviewers.

## Hayton Comments

**COMMENT 1:** The literature that pertains to the health effects of PFOA and PFOS is large and presents a major challenge to accurately summarize and analyze it and develop an RfD for PFOA and PFOS. Reported health effects in animals and humans, sometimes contradictory, include exposure-associated changes in serum cholesterol, lipids, uric acid, and thyroid hormones, obesity-related metabolism, immune system function, and effects on reproduction, development of the mammary gland, the nervous system, and behavior. Target organ effects (e.g., liver, kidney) have been reported, as well as associations of PFOA and PFOS exposure with testicular, prostate and kidney cancer. Studies in several laboratory animal species have added the complications of interspecies comparisons and extrapolation of findings to humans. In humans, there have been a Phase I clinical trial of PFOA, and epidemiological studies of populations exposed to PFOA and PFOS occupationally and in communities with and without water supplies contaminated with PFOA and PFOS. The draft documents have accurately presented in summary form the results of many animal and human studies and used pharmacokinetic methods to link PFOA and PFOS exposure rates to internal dose metrics such as serum concentration. While the overall effort is commendable, there are two issues that the draft documents raise: 1) the literature cited does not include many apparently relevant published works. The cut-off date for cited literature was early 2013 (this should be indicated in the documents), but commenter's noted a number of pertinent publications in 2011 and 2012 that were not cited, and there have appeared several highly pertinent papers since the cut-off date, and 2) while the descriptions of individual studies are generally clear and accurate, there is a lack of independent, critical analysis of the studies and a lack of synthesis of results from multiple studies common to a particular health effect.

**RESPONSE:** Papers recommended by the peer reviewers and from the public comments were retrieved and reviewed for inclusion in the revised documents. As noted in an added literature search strategy appendix,



bimonthly literature searches have been ongoing since 2009. Each identified study and any additional relevant literature published post peer review were reviewed and considered for inclusion. The papers evaluated for inclusion are documented in Appendix B. The evaluation of the epidemiology data was significantly revised and more detailed study summary tables were added. The original summary tables are now included in Appendix B. In addition, the HESDs for both PFOA and PFOS were extensively revised to include tabular presentation of the study details that inform an in-depth analysis of the human epidemiology data, introductory and summary sections for the human and animal health effects information, and an integrated summary of the animal and human evidence.

## Longnecker Comments

**COMMENT 1:** The PFOA and PFOS documents achieve the goal of identifying RfDs that are well founded. My main criticism is that the rationale for not using the human data to provide a POD needs to be strengthened.

For example, in the PFOA document, on page 5-19, first paragraph below the table, it says “human data ... lack the exposure information for dose-response modeling.” This statement is logically inconsistent with techniques that were used to estimate HED on the basis of serum concentration, as given on page 5-17, near the bottom. Or, in some cases, such as in the C8 study, the exposure estimates that were calculated based on water district were sufficiently good that a dose-response analysis would be possible. In other words, because many human studies have serum concentration of PFOA or reasonable estimated exposure values, the corresponding HED could be estimated, and hence the dose-response could be modeled. Granted, some assumptions would be needed, but the methods could be serviceable (see response to item 3 below). (Some of the above also applies to pages 5-1 and 5-2). More compelling arguments for not basing the POD on human data are, e.g., that: 1) the low probability that humans are 1,000 times more sensitive to PFOA than other species (the number is based on the last column in table 5-9 compared with PFOA values in the C8 study and background exposed populations), especially given the relatively tight agreement between LOAEL (average serum concentration basis) among other species, 2) the possibility that the observed associations in humans were due to unmeasured confounding factors or reverse causality, and 3) other weaknesses in the epidemiologic data such as inconsistent results across studies (selected outcomes), unreplicated findings, or associations with clinical chemistry results for which corresponding adverse clinical correlates (i.e., morbidity) are not clearly established.

**RESPONSE:** The HESDs for both PFOA and PFOS have been extensively revised to present a more in-depth analysis of the human epidemiology data, including a more robust discussion of the data that supports the conclusion that there is evidence of an association between exposure to these chemicals and human health hazard. For a few of the outcomes (e.g., serum lipids [PFOS and PFOA], effects on fertility and fecundity [PFOS], and pregnancy-induced hypertension [PFOA]), the associations are particularly strong and fairly consistent. There still remains some uncertainty related to other observed associations, as for various endpoints the data for both PFOA and PFOS are mixed (i.e., some studies show positive associations with the serum PFOA or PFOS value, while others do not).

EPA has limited information to allow estimates of human serum concentrations for a specific, known pathway, such as drinking water. However, EPA does not have sufficient exposure information to attribute the serum concentrations observed in biomonitoring and other studies to specific exposures (time, route, and magnitude) in such a way that would allow dose-response modeling. The serum level at which the effects were first manifested 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 contributed to serum PFOS values come from derivatives or precursors that break down metabolically to PFOA and PFOS. These compounds can originate from the diet and materials used in the home; thus, there is potential for confounding in the C8 studies where the drinking water PFOA was considered to be the primary medium of exposure and for PFOS precursors where degradation produces amines that could contribute to the effects observed. Additionally,

most of the subjects of the epidemiology studies have many PFAS 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. The documents have also been revised to include a discussion of the potential confounding of serum PFOA and PFOS concentrations by low glomerular filtration and the initiation or cessation of menstruation (a route of excretion for females) is included in the discussion of the epidemiology.

Taken together, the weight of evidence for human studies supports the conclusion that PFOA and PFOS exposure is a human health hazard. At this time, for the development of the RfD in support of the development of a drinking water health advisory for PFOA and PFOS, EPA's Office of Water (OW) concludes that the human studies are adequate for qualitative use in hazard identification 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 IRIS assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda. That effort may further evaluate and consider these human epidemiology studies.

### Slitt Comments

**COMMENT 1:** The documents provide a very thorough evaluation of PFOA and PFOS studies. It is logically organized, presenting findings in a way that the reader can understand the findings related to human, monkey, and rodents. The organization of the document makes allows the reader to easily find information about each species within the subchapters and summarizes key points in table form. PFOA is a well-studied compound, with a substantial amount of toxicokinetic and endpoint studies in rodents. Mechanistic data describing the role of membrane transporters to understand gender differences in PFOA elimination in rats is fairly well written. Little data exist regarding contribution of membrane transporters to PFOS disposition and elimination. The documents thoroughly describe species differences in PPAR-alpha signaling that might contribute to observed endpoints in rats, but not humans or monkeys. Overall, both documents are very thorough are provide a reliable basis for PFOS and PFOA evaluation.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

**COMMENT 2:** For PFOA toxicokinetics, mechanisms of PFOA transport are important for understanding species differences in response to PFOA exposure, with focus placed on kidney. Figure 3-2 in the PFOA document does not adequately present the localization of renal transporters with relationship to their contribution to the urine compartment or renal reabsorption. A very nice diagram showing the subcellular localization of renal transporters presented by Klaassen and Aleksunes (*Pharmacol Rev.* 2010 Mar;62(1):1-96) clearly depicts the contribution of various transporters to filtrate or blood. This is an easier diagram to put PFOA elimination into context than the one presented. Contribution of membrane transporters to species differences in PFOA excretion Section 3 (specifically 3.4.1) would be put in better context if a table could be generated to compare Km and Vmax values for PFOA for various transporters, with specific focus on species information for OATps and OATs. Data regarding information on contribution for OATps in liver accumulation of PFOS and PFOA is lacking, with specific regard to species differences. As PFOS is a likely candidate for hepatic uptake transport, understanding a mechanism to explain species differences in hepatic effects possibly due to difference in hepatic exposure is critical. Understanding impact species specific regulation of OATp expression in liver (e.g. whether species difference in PPAR-alpha signaling contributes) is also important in putting rodent distribution data into context.

**RESPONSE:** EPA agrees that additional studies are needed to improve the understanding of uptake and transport of PFOA and PFOS. OW appreciates the recommendation of the Klaassen and Aleksunes publication on transporters (*Pharmacological Reviews.* 2010 Mar;62(1):1-96). The original figure in the document compiled findings from multiple papers. The integrated diagram for the kidney transporter has replaced the original (Figure 2-2).

**COMMENT 3:** Increased liver weight is considered to be a critical effect, but how increased liver weight relates to the observed human and monkey health effects needs to be further explained. In layman terms, if someone is walking around with an increased liver weight, is he or she at risk for disease? Will his/her life span be shortened? To increase transparency of the document, a more comprehensive explanation is needed to justify why increased liver weight should be considered as a critical endpoint for human health.

**RESPONSE:** As a result of multiple comments from peer reviewers on this topic, liver weight is no longer the critical endpoint. In the revised assessment, liver weight was not considered adverse unless accompanied by other hepatic effects, such as necrosis, fibrosis, and/or inflammation as defined by Hall et al. (2012). As a result, the NOAELs and LOAELs in these studies (i.e., previously based liver weight and associated hypertrophy) have also changed. The PODs for both PFOA and PFOS are based on developmental endpoints in the final documents.

**COMMENT 4:** Use of humanized PPAR $\alpha$  mice are a sexy tool to delineate species differences in effects associated with peroxisome proliferation. For transparency, the document should acknowledge the limitations of that model. Specifically, lack of response may not necessarily correlate to a lack of response for human PPAR $\alpha$  because of species differences in binding to DNA elements (e.g. a human receptor may have lower binding capacity to mouse DNA due to structural differences and species differences in co-activator/co-repressor interactions). Wording in the documents using these mice should acknowledge this limitation.

**RESPONSE:** Studies of mice with the humanized PPAR $\alpha$  are included in the HESD to demonstrate that there are liver responses to PFOA that are independent of PPAR $\alpha$  activation. No weight is given to whether or not a response was lacking in either the PPAR $\alpha$ -null or hPPAR $\alpha$  animals because there were effects in each group that could be relevant to humans for these chemicals based on their physical (negative charge nonaromatic) and protein binding properties.

**COMMENT 5:** The documents often have redundancy in information, especially in regard to hormone effects (there are very similar write ups in sections about effects on thyroid hormone) and metabolic/cardiovascular disease risk factors (e.g. lipid endpoints).

**RESPONSE:** For the sake of completeness and transparency in the final HESDs, EPA has described the available epidemiological evidence for each study by health endpoint. Many of the epidemiology studies analyzed potential associations between PFOA and/or PFOS and multiple health endpoints. By organizing the effects assessment by health endpoints (rather than by individual study descriptions), the reader can get a better sense of the weight of evidence supporting the potential associations between PFOA and/or PFOS and each health endpoint.

### **3. EPA Responses to Peer Reviewer Comments on Charge Questions**

#### **Charge Question 1: Studies Used for Quantification**

**Please comment on the strengths, weaknesses, and characterization of the studies selected as key for quantification.**

#### **Bruckner Comments**

##### **PFOA-specific Comments**

**COMMENT 1:** The document's authors have done a good job describing and integrating the findings of the numerous studies in which liver weight gain was observed. Although there is a consensus about the effect and the dosage required to elicit it in different species, this reviewer does not believe it should be utilized, as described above. There are several clearly adverse effects such as elevated serum (hepatic) enzyme activities, focal hepatocellular necrosis, bile duct degeneration and fibrosis, etc. These effects are generally seen in response to relatively high PFOA doses, so the PODs will be higher than with liver weight increase. Alternatively, a human endpoint such as elevated serum cholesterol could be considered. See responses to Charge Question 3.

**RESPONSE:** EPA re-evaluated the outcomes related to PFOA exposure based on peer review comments, and selected an endpoint that reflects adverse effects in the developing fetus and newborn as the most sensitive endpoint to serve as the basis for the derivation of the RfD. The POD for PFOA is based on low birth weight (Lau et al. 2006). Increased liver weight is acknowledged as a common finding, but not considered adverse in the absence of other effects as defined by Hall et al. (2012).

##### **PFOS-specific Comments**

**COMMENT 2:** There have been a substantial number of well-conducted toxicological studies of PFOS. My major concern, as expressed above, is its potential to cause adverse effects in children. Other than that, PFOS doesn't appear to produce effects other than those anticipated from a repetitive, cumulative dose of an 8-carbon fatty acid.

**RESPONSE:** EPA re-evaluated the outcomes related to PFOS exposure based on peer review comments, and selected an endpoint that reflects adverse effects in the developing fetus and newborn as the most sensitive endpoint to serve as the basis for the derivation of the RfD. The POD for PFOS is based on decreased pup body weight in a two-generation rat study (Luebker et al. 2005b). The sensitive endpoint of body weight changes in pups is protective of other offspring effects such as decreased survival or alterations in glucose homeostasis manifested later in life.

#### **Cory-Slechta Comments**

**COMMENT 1:** In general, it appears that, at least with respect to the animal studies, the choices are appropriate both in the case of PFOA and PFOS. The derivation of the RfDs/RfCs are based on studies of sufficient strength, duration and represent the most sensitive endpoints.

**RESPONSE:** EPA re-evaluated the outcomes related to PFOA and PFOS exposures based on peer review comments, and selected endpoints that reflects adverse effects on the developing fetus and newborn as the most sensitive endpoint to serve as the basis for the derivation of the RfDs for both chemicals.

**COMMENT 2:** Having said that, in both documents, the reader is forced to that conclusion with no real assistance from the text itself. There is virtually no discussion of the strengths and weaknesses of the studies overall. Human study outcomes for the most part are simply enumerated, although an occasional statement will be made about a limitation (usually) of one of those studies. There is no discussion in the human studies of the power to detect effects, the sample sizes, etc. Much weight seems to be given to occupational studies in some cases, being used to essentially dismiss effects in a community cohort as the same effect was not seen in occupationally exposed workers, when in fact finding effects in a population with seemingly longer, albeit lower exposure levels actually makes the outcome more robust. Also, population studies with smaller sample sizes that nevertheless find significant effects are in fact more compelling and suggest robust effects which can be detected even with a small sample size. This deficiency is manifest in statements such as those in the PFOS document (p. 5-1) that ‘in most cases the findings are suggestive and not conclusive of an effect’.

**RESPONSE:** The human epidemiology section was substantially rewritten with study type, sample size, and serum levels added for each study where these data were available. Tables were expanded for each major endpoint to summarize the studies described in the text. An overall summary and conclusion was added at the end of the human epidemiology section. In the revised HESD, effects from human studies are used qualitatively as a line of evidence to support the assessment.

**COMMENT 3:** There is a bit more discussion of the animal studies in both documents, at least with respect to methods, but as with the human studies, there is little text addressing which studies represent stronger studies or what the weaknesses are. From these increase liver weight has been chosen as the endpoint from which to derive RfDs. This reviewer does not have an issue with that choice, as while it has been described as adaptive by some, it represents a response to an involuntary exposure with a direction of effect that is potentially associated with adverse consequences. The fact that it is reversible when exposure ends seems irrelevant as reversal of exposure is not happening in the human environment.

**RESPONSE:** Based on peer review comments, liver weight is no longer used as the critical effect. For both chemicals, the RfD is now based on developmental effects, as suggested by others peer reviewers. Additional text was added describing the studies chosen for modeling and selection of the RfD. This discussion includes strengths and weaknesses of the human epidemiology data, the strengths of the animal studies selected for quantitation, and the support for the PODs from studies with dose-response that lacked serum information.

## DeWitt Comments

**COMMENT 1:** *Strengths:* The studies selected as key for quantification were generally well-conducted studies, employing a range of doses and sample sizes large enough for detecting statistical differences. Additionally, the doses associated with LOAELs for the identified critical endpoints were not associated with signs of overt or systemic toxicity in the animal models and nearly all of the studies measured serum and/or tissue concentrations of the parent compounds.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

**COMMENT 2:** *Weaknesses:* No obvious experimental design weaknesses were noted in any of the studies selected as key for quantification.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

**COMMENT 3:** *Characterization:* The studies selected as key for quantification for PFOA are all rodent studies while at least one study selected for PFOS quantification includes a non-human primate study. It is therefore surprising that the PFOA database does not include, as a study key for quantification, the Butenhoff et al. 2002 study of non-human primates. Additionally variability in putative mechanisms among species was

not adequately addressed in the characterization of the selective studies, although all of the selective studies were descriptive and not mechanistic.

**RESPONSE:** The data from the monkey study (Butenhoff et al. 2002, 2004b) were not used because of the small number of animals evaluated and the wide variability in the responses among the individual animals. For example, succinate dehydrogenase activity was highly variable in the six animals given 3 mg/kg/day despite this group having the most consistent liver PFOA concentrations. In addition, although serum steady-state had been attained by 4–6 weeks of dosing, liver PFOA levels ranged from 11.3–18.5, 6.29–21.9, and 16–83.3 µg/g tissue in the 3 (n=4), 10 (n=3) and 20 (n=2) mg/kg/day groups, respectively.

### Fisher Comments

**COMMENT 1:** PFOA and PFOS: Data bases are massive and both need to be updated. Several human studies and a few non-human primate toxicity studies are available. The authors need to explain why these studies are not adequate for causality (dose-response).

**RESPONSE:** A substantial number of human epidemiology studies were added to both documents. The human epidemiology section was substantially rewritten with study type, sample size, and serum levels added for each study where these data were available. Tables were expanded for each major endpoint to summarize the studies described in the text.

EPA is unaware of non-human primate studies other than those included in the HESD. The studies are described in the HESD, but not used in the derivation of candidate RfDs. The effects observed in Seacat et al. (2002) were significant only at the high dose where there was also mortality. Additionally, for both PFOS and PFOA, the liver effects observed in monkeys were inadequate to establish adversity following the Hall et al. (2012) criteria, as recommended by the peer reviewers.

### Hayton Comments

**COMMENT 1:** An advantage to assessment of health effects for both PFOA and PFOS is the large amount of published work that informs the topic. While the draft health-effects documents have summarized the results of many pertinent studies, the literature reviewed was not comprehensive, which projects an appearance of weakness. The documents do not state whether the intention was to include all relevant health-effects literature, or to be selective and summarize those studies judged to be most relevant. Such a statement at the beginning of the documents would be helpful; a cut-off date for the literature review would also frame expectations of readers. If the intention was to be selective, a description of selection criteria would help allay concerns of readers about papers that were not included. If the intention was to comprehensively review all the PFOA and PFOS health-effects literature, then it appears that more work should be done to include omitted works. Public comments list a number of works to consider for inclusion.

**RESPONSE:** One of the challenges inherent in conducting these assessment was the wealth of experimental data published before and during their development. A background section has been added to both PFOA and PFOS HESDs to provide a synopsis of the approach used in identifying and selecting the publications reflected in the final assessment. The criteria used to evaluate each study and to select those for inclusion is provided in the background section of each document. Additionally, a more detailed description of the literature search strategy, including dates of the literature search and search strings used, was added as Appendix A in both documents.

The studies included in the final HESDs are those determined to provide the most current and comprehensive description of the toxicological properties of PFOA and PFOS and the risk they pose to humans exposed to them in their drinking water. EPA has added Appendix B to both PFOA and PFOS HESDs, which

summarizes the studies evaluated for inclusion in the HESD as a result of the peer review and in the time following the peer review and identifies those selected for inclusion in the final assessment.

**COMMENT 2:** A general, albeit minor weakness of the literature is that PFOA and PFOS serum concentrations in control animals were not measured for many studies – they were likely non-zero and, since there is no information on how high they were, it is possible that baseline health-effects metrics were affected and that dose-response relationships were affected, especially in the low dose range. It is perhaps worthwhile to mention this shortcoming somewhere in the health effects documents.

**RESPONSE:** In each case where serum information was available, it was reported in the draft document and used in the development of the Wambaugh et al. (2013) toxicokinetic model applied in the derivation of the RfD. The literature review was updated since the peer review draft was developed and some of the newer studies also include serum data. In such cases, the serum information is included with the study description. For PFOA, only one study in the toxicokinetic section had serum information for the controls. The control levels were identified as below the level of detection. In PFOS, some of the control animal serum levels are given in the toxicokinetic chapter; these are either below the LOQ or are orders of magnitude lower than those of dosed animals.

### Longnecker Comments

**COMMENT 1:** EPA may want to consider the article by AP Hall et al. 2012, about liver hypertrophy. The defense of increased liver weight as the POD (or a POD) could be strengthened by evaluating the evidence in the context of Hall's Figure 9, where evidence regarding hepatotoxicity and toxic mechanisms are also considered. In this case, the possibility of an unknown mechanism exists that could be relevant to humans, and long-term exposure could have effects that have not yet been detected. See Hall page 986, where it defines adverse as: "...affects [response] to an additional environmental challenge". Thus, an adverse effect, via an unknown mechanism, by this definition is possible and has not been studied in animals or humans.

**RESPONSE:** The reference has been added to both HESDs and used in determining whether or not effects on the liver can be considered as adverse. For the studies where liver effects were the only effects observed, the LOAEL was assigned based on effects characterized as adverse by the Hall criteria. Where there was increased liver weight, with or without hypertrophy, those effects are acknowledged in Tables 5-1 and 5-2.

**COMMENT 2:** While AP Hall's article is not all that supportive of using increased liver weight as a point of departure (unless certain criteria are met), they are focused on animal studies, especially those done in rodents. If increased relative liver weight were to occur in a human population, I suspect that it would be considered an adverse outcome, whether or not there was evidence of hepatotoxicity or a specific mechanism. Note also that for PFOA, in monkeys, there was an increase in relative liver weight with chronic exposure (PFOA document, page 4-66), so increase in liver weight in the animal experiments may be relevant to humans.

**RESPONSE:** The POD for both PFOA and PFOS was altered so that liver weight alone is no longer the endpoint of concern. Increased liver weight is acknowledged as a common finding but not considered adverse in the absence of other effects as defined by Hall et al. (2012). EPA reevaluated all studies reporting presence of increased liver weight for other adverse effects using the Hall criteria. The RfD for PFOA is based on reduced ossification in males and females and accelerated puberty in males (Lau et al. 2006). The RfD for PFOS is based on decreased pup body weight (Luebker et al. 2005b) in rats over two generations.

**COMMENT 3:** An additional comment of relevance here pertains to whether the human data support hepatotoxicity. While there are studies that report elevated liver function tests in subjects with higher serum concentrations of perfluoralkyl substances, these elevations do not clearly support the presence of toxicity.

Again, AP Hall's discussion of what constitutes evidence of hepatotoxicity is relevant here, and takes into account the number of LFTs elevated, the specific LFTs involved, and the magnitude of their elevation.

**RESPONSE:** A better summary of the human data is provided in both documents detailing the strengths and weaknesses of the data set and support provided for hazards identified in animal studies. Although serum levels of alanine aminotransferase (ALT) were increased in several of the human studies, the ALT increases were not accompanied by other indices (e.g., increased AST, lactic dehydrogenase [LDH]) that would clearly identify the presence of liver damage.

**COMMENT 4:** Finally, as discussed at the meeting, for the PFOA document on page 5-23 ("RfD Selection"), and the PFOS document on page 5-26 ("RfD selection"), I suggest minor editorial changes to deemphasize the "consistency of response" point and instead focus a little more on how the RfD is robust to choice of POD endpoints. If the selection of RfD does not hinge on increased liver weight as a POD, it will be more defensible.

**RESPONSE:** The POD for both PFOA and PFOS was changed such that liver weight is no longer the endpoint of concern. The critical effect selected as the basis for determining the POD for PFOA is reduced ossification and accelerated puberty in male mice (Lau et al. 2006). The critical effect selected as the basis for determining the POD for PFOS is decreased pup body weight (Luebker et al. 2005b) in rats over two generations. Increased liver weight is acknowledged as a common finding but not considered adverse in the absence of other effects, as defined by Hall et al. (2012).

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 candidate RfD for PFOA and PFOS (e.g., identified low dose, adverse effects). 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, and developmental effects (developmental neurotoxicity, altered puberty, survival), and immune effects. The candidate studies were selected based on their NOAEL and/or LOAEL values and use of a control and two or more doses. From these studies, those that presented serum data amenable for modeling (i.e., determination of human equivalent doses) were selected for dose-response analysis.

For both PFOA and PFOS, the candidate serum-derived RfDs represent multiple adverse effects resulting from short-term and longer-term studies with exposures that fall within a narrow dose range. They are supported by the NOAELs and LOAELs from other studies with dose-response that lacked the serum information needed for modeling. EPA selected the most sensitive RfDs for PFOA and PFOS based on developmental effects that are protective for the general population and sensitive life stages.

**COMMENT 5:** Transparency might be increased by saying why (more clearly, or more clearly by implicit reasoning) the Macon et al. 2011 study, in which the LOAEL was 0.01 mg PFOA/kg from GD10 to GD17, based on delayed mammary gland development, was not considered as a POD, and why the Hines et al. 2009 study, in which the LOAEL was 0.01 mg PFOA/kg from GD1 to GD17, based on various outcomes, was not considered as a POD. The PFOS studies with low LOAELs were considered in the dose-response assessment (no suggestions for improvement there).

**RESPONSE:** The data from the Macon et al. (2011) and Hines et al. (2009) studies are included in the PFOA HESD in sections 3.2.7 and 3.3.3, respectively.

A number of studies have focused on mammary gland development in animals (dams and female offspring) following exposure to PFOA and are described in the HESD for PFOA. Researchers focused on effects resulting from indirect exposure of offspring via treatment of pregnant animals and/or direct exposure of peripubertal animals starting about the time of weaning. These studies show effects on mammary gland



morphology (branching and bud growth) in both dams and pups at low doses. Studies with higher doses demonstrated that exposed neonate pups showed no significant difference in body weight compared to controls despite the fact that there were differences in the gland duct structure. Thus, indicating that the function of maternal milk delivery was not impacted by the structure. In another study, Tucker et al. (2015) demonstrated that a dose-response for developmental mammary gland effects varies by more than an order of magnitude depending on the strain of mouse studied. Increased discussion of mammary gland development and rationale for not selecting this endpoint as the critical effect was added to the document (see section 4.1.1 of PFOA).

## Slitt Comments

**COMMENT 1:** My response is basically the same as my General Impressions above.

**RESPONSE:** See response to General Impressions comments 1-5.

## Charge Question 2: Additional References

**Please provide citations (and, where possible, pdfs or hard copies) for any references you suggest EPA consider adding to the document. Describe where you suggest these references be incorporated.**

References recommended by the peer reviewers and public, along with publications collected from the ongoing literature searches after peer review, were evaluated for inclusion based on selection criteria described in Appendix A. Date of publication and whether or not the publication provided new toxicity information or support for hazard identification or dose response was considered. The appendix documenting literature considered and decisions relative to their inclusion is in the final document. Many of the recommended studies concern liver pathophysiology in general but did not evaluate liver effects as a result of PFOA or PFOS exposure and thus were not included (Ipeki et al. 2003, Morfrad et al. 2003, Oh et al. 2008, Delgado 2008, Wieckowska et al. 2008, Kunde et al. 2005, Lizardi-Cervere et al. 2006, Amarapurka et al. 2006, Chen et al. 2006, Fracanzani et al. 2008, Sorrentino et al. 2004, Uslusoy et al. 2009, Allen et al. 2004).

## Bruckner Comments

**COMMENT 1:** PFOA-specific comments

Fabrega, F. et al. (2014). PBPK modeling for PFOS and PFOA: Validation with human experimental data. Toxicol. Lett. On line. (Hard copy available)

Stahl, T., Mattern D and Brunn, H. (2011). Toxicology of perfluorinated compounds. Environ. Sci. Europe 23: 38-60.

Hall, A. P., et al. 2012. Liver hypertrophy: A review of adaptive (adverse and non-adverse) changes- Conclusions from the 3<sup>rd</sup> International ESTP Expert Workshop. Toxicol. Pathol. 40: 971-994.

Bjork, J. A., Butenhoff, J. L., and Wallace, K. B. 2011. Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rat hepatocytes. Toxicology 228: 8-17.

**RESPONSE:** Hall et al. (2012) and Fàbrega et al. (2014) were added to both final HESDs. The Stahl et al. (2011) paper is a review paper that does not include primary data, therefore it was not included. Bjork et al. (2011) is an in vitro study of nuclear receptors related to PPAR, CAR, FXR, etc. in rats and humans with findings that are mostly duplicative of those from other studies already included in the HESD.

Papers that were not included were those that failed to meet the selection criteria established for the updates to the draft document as follows (described in Appendix B):

- 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.
- There are elements of the study design that merit its inclusion in the draft assessment based on its contribution to the mode of action or the quantification approach.
- The study elucidates the mode of action for any toxicity endpoint or toxicokinetic property associated with PFOS exposure.
- The observed effects differ from those in other studies with comparable protocols.
- The data are relevant to drinking water exposures and to the U.S. population.

**COMMENT 2:** PFOS-specific comments

No additional references were located.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **Cory-Slechta Comments**

**COMMENT 1:** For both PFOA and PFOS, the document should include a description of the process through which studies were identified and how they were processed for inclusion or not. It is not clear what the exact dates of the studies examined included, i.e., what the cut-off date was for these studies. This makes it difficult to evaluate whether there are missing studies. That said, this reviewer is not aware of any specific omissions in the peer-reviewed literature other than those that were discussed at the face-to-face meeting.

**RESPONSE:** One of the challenges inherent in conducting these assessments was the wealth of experimental data published before and during their development. A background section has been added to both PFOA and PFOS HESDs to provide a synopsis of the approach used in identifying and selecting the publications reflected in the final assessment. The criteria used to evaluate each study and to select those for inclusion is provided in the background section of each document. Additionally, EPA added a description of the literature search strategy, including dates of the literature search and search strings used, to Appendix A in both documents.

The studies included in the final HESDs were determined to provide the most current and comprehensive description of the toxicological properties of PFOA and PFOS and the risk they pose to humans exposed in their drinking water. EPA added Appendix B to both PFOA and PFOS HESDs, which summarizes the studies evaluated for inclusion in the HESD as a result of the peer review and in the time following the peer review. It also identifies those selected for inclusion in the final assessment.

### **DeWitt Comments**

**COMMENT 1:** Granum, B., Haug, L.S., Namork, E., et al. 2013. Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. *J Immunotoxicol.* 10:373–379; Looker, C., Luster, M.I., Calafat, A.M., et al. 2014. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *Toxicol. Sci.* 138:76–88.

Any time the Grandjean et al. (2012) findings related to PFAS and vaccine responses are discussed, these references could/should be discussed as well as they report related findings in human populations. Although they also are confounded by multiple PFAS (as was the Grandjean et al. study), they lend additional support to immunotoxicity as an endpoint worthy of consideration. However, it is noted that these references were published after the cutoff date for consideration for inclusion in the document.

**RESPONSE:** Both the Granum et al. 2013 and Looker et al. 2014 studies were added to both HESDs. A summary and conclusions write-up was added to the epidemiology section, which discusses the immune function-related findings together.

**COMMENT 2:** Lopez-Espinosa, M.J., et al. 2012. Thyroid function and perfluoroalkyl acids in children living near a chemical plant. *Environ. Health Perspect.* 120:1036–1041. This study is missing from the discussion of thyroid hormone disruption. It reports a positive correlation between hypothyroidism and PFOA in children from the C8 population aged 1-17.

**RESPONSE:** Lopez-Espinosa et al. 2012 was added to the HESD for PFOA. The PFOA HESD describes results from the C8 study on hypothyroidism.

**COMMENT 3:** Corsini E., et al. 2011. In vitro evaluation of the immunotoxic potential of perfluorinated compounds (PFCs). *Toxicol. Appl. Pharmacol.* 250:108-116. Corsini E. et al. 2012. In vitro characterization of the immunotoxic potential of several perfluorinated compounds (PFCs). *Toxicol. Appl. Pharmacol.* 258:248-255. These studies are in vitro/ex vivo studies of human-derived cells that provide evidence that in vitro measures of immunocompetence in mice may be relevant to the human experience.

**RESPONSE:** EPA reviewed these studies but did not include them in the HESD for PFOA or PFOS because both papers were reviews of the literature, rather than primary reports from the individual studies, and failed the criteria for inclusion on the basis that they would not substantially alter the weight of evidence conclusion for the immunotoxicity findings. The HESDs for both PFOA and PFOS describe available data on the immunotoxicity of these chemicals.

### **Fisher Comments**

**COMMENT 1:** For completeness sake, at least, please update lab animal studies conducted since 2012.

**RESPONSE:** A literature search was conducted on a bimonthly bases between 2009 through 2015. An updated description of the literature search strategy, including dates of searches and search strings used, was added as Appendix A in the documents.

### **Hayton Comments**

**COMMENT 1:** A review of PFOA health-effects literature (GB Post et al. (2012) *Environ. Res.* 116: 93-117) provides an excellent, in-depth discussion of many issues covered in the PFOA health effects document. Consider citing this review in the document.

**RESPONSE:** EPA reviewed the paper, and has included a brief description of the type of review presented by Post et al. 2012 in Appendix B of the HESD for PFOA. Many of the papers referenced in Post et al. 2012 study are included in the HESD.

**COMMENT 2:** The literature on PFOA and PFOS toxicokinetics (Section 3) has been comprehensively covered in the health effects documents, with the notable omission of Wambaugh et al., Dosimetric

Anchoring of In Vivo and In Vitro Studies for Perfluorooctanoate and Perfluorooctanesulfonate. *Toxicol. Sci.* 136:308-327, 2013. This paper informed a significant part of the health effects documents.

**RESPONSE:** This citation (Wambaugh et al. 2013) was added.

**COMMENT 3:** Commenters have suggested a number of references to consider with regard to Section 4 Hazard Identification. Many recent publications report on toxicity associated with PFOA/PFOS exposure. For the Dose-Response Assessment (Section 5) it is desirable to focus on those toxicities that have occurred at the lowest PFOA/PFOS exposures. For PFOA, the literature that is used in Section 5 to determine an RfD was published prior to 2009 (Tables 5-8 – 5-11). The benchmark response chosen based on the Section 4 literature was a 10% increase in liver weight, which was the biological response that occurred at the lowest PFOA exposure; it was acknowledged that this response “... is a biomarker for systemic exposure in rodents, rather than a biomarker of adversity ...” (p. 5-6). More recent studies of hazard have identified potential adverse effects that result from, or are associated with, PFOA exposures that are lower than the LOAEL for a 10% increase in liver weight. For example, adverse effects on fetal, neonatal and early childhood stages of development may occur at lower exposures than does liver weight gain, which suffers in addition from not being a biomarker of adversity, and which therefore raises a question about the validity of any RfD based upon it. Macon et al. 2011 reported an LOAEL for delayed mammary gland development of 0.01 mg/kg administered to pregnant CD-1 mice during GD10 – GD17. As this relatively brief exposure was well below that required for steady state, it is possible that had the dams been at steady state at the time of conception (about 9 weeks of exposure) a much lower LOAEL may have been observed; i.e., a much lower dose rate at steady state would have produced the same exposure to the fetal pups as did the 0.01 mg/kg administered to the dams during GD10 – GD17. The steady state situation is more relevant to adverse effects in humans than is a brief exposure.

**RESPONSE:** The POD for both PFOA and PFOS was changed such that liver weight is no longer the critical endpoint. PFOA is based on 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 gestationally and lactationally (Lau et al. 2006). PFOS is based on decreased pup body weight (Luebker et al. 2005b) in rats over two generations. Increased liver weight is acknowledged as a common finding, but not considered adverse in the absence of other effects as defined by Hall et al. (2012). Reasons for not using delayed mammary gland development are described in the HESDs and include lack of consistent scoring, no effects on body weight of pups nursing from affected dams, and no differences in response to lactational challenge. A discussion of steady state was added to section 4.

One of the challenges inherent in conducting these assessments was the wealth of experimental data published before and during their development. A background section was added to both PFOA and PFOS HESDs to provide a synopsis of the approach used in identifying and selecting the publications reflected in the final assessment. The criteria used to evaluate each study and to select those for inclusion is provided in the background section of each document. Additionally, a detailed description of the literature search strategy, including dates of the literature search and search strings used, was added to Appendix A in both documents.

The studies included in the final HESDs were determined to provide the most current and comprehensive description of the toxicological properties of PFOA and PFOS and the risk they pose to humans exposed in their drinking water. EPA added Appendix B to both PFOA and PFOS HESDs, which summarizes the studies evaluated for inclusion in the HESD as a result of the peer reviewers and public in the time following the peer review. It also identifies those selected for inclusion in the final assessment.

## Longnecker Comments

**COMMENT 1:** I suggest you include the following citation and include a discussion of the evidence presented:

Paula I. Johnson, Patrice Sutton, Dylan S. Atchley, Erica Koustas, Juleen Lam, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth. *Environ Health Perspect*; DOI:10.1289/ehp.1307893 (in press and available through the journal's website).

Based on the meta-analysis in this paper, the evidence that PFOA is associated with lower birthweight is consistent. Thus, the rationale for not basing the POD on the human data needs to be strengthened, as noted above. The Johnson et al. report could be discussed in the section on anthropometric endpoints that begins on p 4-22.

**RESPONSE:** This study (Johnson et al. 2014) and the other reports from the Navigation Guide projects related to PFOA are now included in the HESD for PFOA. In addition, the PODs for both PFOA and PFOS are now based on developmental effects observed in animal studies, with human study results described qualitatively and used to support conclusions.

**COMMENT 2:** The relationship between birthweight and PFOA or PFOS may be confounded because glomerular filtration (and hence excretion of the compounds) is proportional to birthweight, as discussed in:

Morken NH, Travlos GS, Wilson RE, Eggesbø M, Longnecker MP. Maternal glomerular filtration rate in pregnancy and fetal size. *PLoS One*. 2014 Jul 8;9(7):e101897

**RESPONSE:** 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. The Morken et al. (2014) study was added to both of the final HESDs along with the subsequent Verner et al. (2015) paper on the same topic.

**COMMENT 3:** In the PFOA document, on page 4-18, you might want to also cite:

Taylor KW, Hoffman K, Thayer KA, Daniels JL. Polyfluoroalkyl chemicals and menopause among women 20-65 years of age (NHANES). *Environ Health Perspect*. 2014 Feb;122(2): 145-50.

The Taylor et al., like the Knox et al. report (already cited in the PFOA document) is from a large-cross sectional study. Both studies, in their discussion sections, note that the association of PFOA or PFOS concentration in serum with age at menopause could be expected because postmenopausal women have lost a route of excretion for the compound and will have higher serum concentrations on that basis. It would be worth noting this possible explanation in the PFOA document on page 4-18, and in the PFOS document on page 4-8.

**RESPONSE:** This study (Taylor et al. 2014) was added to the HESD for PFOA; menstruation as a route for excretion is covered by additional studies published after work on the 2013 peer review draft was completed.

**COMMENT 4:** Additional data are available on the potential carcinogenicity of PFOA:

Steenland K, Woskie S. Cohort mortality study of workers exposed to perfluorooctanoic acid. *Am J Epidemiol*. 2012;176(10):909-17.

Barry V, Winquist A, Steenland K. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ Health Perspect*. 2013;121(11-12):1313-8

Hall AP et al. *Toxicol Pathol* 2012;40:971-94. (About liver hypertrophy.)

The Steenland and Barry reports could be discussed in Section 4.1.2, on pages 4-28 and 4-29, respectively.

**RESPONSE:** These three studies were added to the HESD for PFOA.

### Slitt Comments

**COMMENT 1:** Evidence is presented for PFOA and PFOS as substrates for the related OATp1d1 in zebra fish. Establishing whether PFOS is an OATp transporter substrate is needed to better understand PFOS accumulation in liver. This study suggests that it might be. The following finding should be included in the PFOS document in Section 3.2.3 and the PFOA document in Section 3.0:

Popovic M, Zaja R, Fent K, Smital T. *Toxicol Appl Pharmacol*. 2014 Interaction of environmental contaminants with zebrafish organic anion transporting polypeptide, OATp1d1 (Slco1d1).

**RESPONSE:** This paper was not included because the literature EPA included for the transporters was limited to mammalian species.

**COMMENT 2:** This publication presents the finding that PFOS inhibits Pgp, Mrp1, and Mrp4 activity. The following finding should be included in the PFOS document in Section 3.2.3 and the PFOA document in Section 3.0:

Dankers AC1, Roelofs MJ, Piersma AH, Sweep FC, Russel FG, van den Berg M, van Duursen MB, Masereeuw R. *Toxicol Sci*. 2013 Dec;136(2):382-91. Endocrine disruptors differentially target ATP-binding cassette transporters in the blood-testis barrier and affect Leydig cell testosterone secretion in vitro.

**RESPONSE:** EPA reviewed this study but did not include it in the HESD for PFOS because it was not a study of PFOS per se, it was a study to determine whether the assay specified would be a reliable tool for identifying endocrine disruption. PFOS was one of a group of chemicals used to evaluate ATP-binding cassette transporters as a tool for identifying endocrine disrupters. See Appendix B in the final report.

**COMMENT 3:** PFOS induced ABC transporters in grey mullets.

de Cerio OD1, Bilbao E, Cajaraville MP, Cancio I. *Gene*. 2012 Apr 25;498(1):50-8. Regulation of xenobiotic transporter genes in liver and brain of juvenile thicklip grey mullets (*Chelon labrosus*) after exposure to Prestige-like fuel oil and to perfluorooctane sulfonate.

**RESPONSE:** EPA did not retrieve this paper because the literature EPA included was limited to mammalian studies.

**COMMENT 4:** These are new publications regarding epidemiology findings for PFOS and PFOA exposure and serum lipids:

Fitz-Simon N, Fletcher T, Luster MI, Steenland K, Calafat AM, Kato K, Armstrong B. *Epidemiology*. 2013 Jul;24(4):569-76. doi: 10.1097/EDE.0b013e31829443ee. Erratum in: *Epidemiology*. 2013 Nov;24(6):941.

Starling AP, Engel SM, Whitworth KW, Richardson DB, Stuebe AM, Daniels JL, Haug LS, Eggesbø M, Becher G, Sabaredzovic A, Thomsen C, Wilson RE, Travlos GS, Hoppin JA, Baird DD, Longnecker MP. Perfluoroalkyl substances and lipid concentrations in plasma during pregnancy among women in the Norwegian Mother and Child Cohort Study. *Environ Int*. 2014 Jan;62:104-12.

Fu Y, Wang T, Fu Q, Wang P, Lu Y. Associations between serum concentrations of perfluoroalkyl acids and serum lipid levels in a Chinese population. *Ecotoxicol Environ Saf*. 2014 Aug;106:246-52.

**RESPONSE:** Fitz-Simon et al. 2013 and Starling et al. 2014 were added to the final PFOS document. Fu et al. 2014 was not added to either HESD because it is a study of serum lipids relative to serum levels of several perfluorocarboxylates among the study population. Other studies demonstrate that the serum PFOA branched chain isomers are higher among Chinese populations compared to U.S. populations because of differences in the process used to manufacture PFOA. The Fu et al. 2014 study did not have a meaningful impact on the conclusions related to serum lipids for PFOS.

**COMMENT 5:** These are publications regarding PFOS exposure and hepatic steatosis:

Lv Z, Li G, Li Y, Ying C, Chen J, Chen T, Wei J, Lin Y, Jiang Y, Wang Y, Shu B, Xu B, Xu S. Glucose and lipid homeostasis in adult rat is impaired by early-life exposure to perfluorooctane sulfonate. *Environ Toxicol*. 2013 Sep;28(9):532-42. doi: 10.1002/tox.20747. Epub 2011 Aug 24. PMID: 23983163 Select item 22484034

Wan HT, Zhao YG, Wei X, Hui KY, Giesy JP, Wong CK. PFOS-induced hepatic steatosis, the mechanistic actions on  $\beta$ -oxidation and lipid transport. *Biochim Biophys Acta*. 2012 Jul;1820(7):1092-101. doi: 10.1016/j.bbagen.2012.03.010. Epub 2012 Mar 28. PMID: 22484034 [PubMed - indexed for MEDLINE] Free Article

Bijland S, Rensen PC, Pieterman EJ, Maas AC, van der Hoorn JW, van Erk MJ, Havekes LM, Willems van Dijk K, Chang SC, Ehresman DJ, Butenhoff JL, Princen HM. Perfluoroalkyl sulfonates cause alkyl chain length-dependent hepatic steatosis and hypolipidemia mainly by impairing lipoprotein production in APOE\*3-Leiden CETP mice. *Toxicol Sci*. 2011 Sep;123(1):290-303. doi: 10.1093/toxsci/kfr142. Epub 2011 Jun 24.

**RESPONSE:** All three references were added to and described in the final HESD for PFOS.

### Charge Question 3: Use of Epidemiology Data

**The OW concluded that the human epidemiology data for PFOS/PFOA do not provide adequate quantifiable dose-response information for use as the basis of a candidate RfD because of uncertainty regarding the routes, levels and timing of exposures plus the confounding influences of other PFCs present in serum. Please comment of the OW characterization of the data.**

### Bruckner Comments

#### PFOA-specific Comments

**COMMENT 1:** The document's authors have done a good job summarizing and accurately characterizing the epidemiology literature for various endpoints in Section 4.4 - Hazard Characterization. It is true there are a number of confounding factors that make estimation of PFOA exposures difficult. The EPA might consider, however, utilization of reverse dosimetry modeling. There is a reasonable body of data on serum PFOA levels, which could be used to estimate a range of PFOA exposures that would result in such internal doses.

**RESPONSE:** EPA did not use a reverse dosimetry modeling approach for this effort but rather relied on animal data and the peer reviewed PK model to develop candidate RfDs for PFOA and PFOS. The available epidemiology studies for PFOA and PFOS provide evidence of hazard from exposure to these chemicals. The HESDs for both PFOA and PFOS have been extensively revised to present a more in-depth analysis of the human epidemiology data, including a more robust discussion of the data that supports the conclusion that there is evidence of an association between exposure to these chemicals and human health hazard. For a few of the outcomes (e.g., serum lipids [PFOS and PFOA], effects on fertility and fecundity [PFOS], and pregnancy-induced hypertension [PFOA]), the associations are particularly strong and fairly consistent. There still remains some uncertainty related to other observed associations, as for various endpoints the data for both PFOA and PFOS are mixed (i.e., some studies show positive associations with the serum PFAS value while others do not).

Although mean serum values are presented in the human studies, actual estimates of PFOA and PFOS exposure (i.e., doses/duration) are not currently available. Thus, the serum level at which the effects were first manifested 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 and PFOS values come from PFOS derivatives or precursors that break down metabolically to PFOA or PFOS. These compounds might originate from PFOA or PFOS in diet and precursor materials used in the home, which creates potential for confounding by the metabolites of the chemicals esterified to the carboxylate or sulfonate functional group. 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. Adjusting for the other PFAS from the acid and sulfonate families is complicated because of the many commonalities in their effects, a factor often acknowledged in the epidemiology 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 IRIS assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda. That effort may further evaluate and consider these human epidemiology studies.



## PFOS-specific Comments

**COMMENT 2:** I agree that human epidemiology data do not provide an adequate basis for calculation of a RfD or RfC. A reverse dosimetry modeling approach, however, could be used to estimate a range of PFOS exposures that could have resulted in measured body burdens. The human data might then be utilized in the risk assessment.

**RESPONSE:** EPA concluded that the human studies are adequate for use qualitatively in the identification hazard, but not quantitatively at this time given the limitations described above (see more detailed response to Dr. Bruckner's comment on PFOA, directly above). EPA plans to begin another effort to determine the range of perfluoroalkyl compounds for which an IRIS assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda. That effort may further evaluate and consider these human epidemiology studies.

## Cory-Slechta Comments

**COMMENT 1:** It is not clear that such an assertion should be used in the construction of this document. It is not clear why the route of exposure should be raised to a concern in the calculations, in fact in the human environment, there are exposures from multiple routes, no doubt and thus this is consistent with human environmental exposures. Further, if there is data on serum levels, it should reflect that cumulative exposure across exposure routes. Indeed, at the end, the goal is to arrive at an RfD based on serum levels. There is, moreover, no guarantee that there is no contamination in studies in animals from food, glassware etc.

Furthermore, in many epidemiological studies in which mixed exposures are the norm, controlling for other exposures is utilized to address this concern and to therefore make conclusions about individual exposures. In point of fact, in every single human study, there will invariably be other exposures and not a single exposure, and thus this strategy essentially says that no human studies can ever be used for any risk assessments. The stated rationales for not using human data based on these statements is not adequate. This is why it is important as well to evaluate the strengths and weaknesses of each of the studies in terms of whether appropriate controlling for other known exposures was carried out and sample sizes sufficient etc. to arrive at some conclusions with respect to their ultimate usability in constructing RfDs.

**RESPONSE:** EPA agrees that the human epidemiology studies provide valuable information on adverse effects resulting from exposure to PFOA and PFOS. The HESDs for both PFOA and PFOS have been extensively revised to present a more in-depth analysis of the human epidemiology data, including a more robust discussion of the data that support the conclusion that there is evidence of an association between exposure to these chemicals and human health hazard. For a few of the outcomes (e.g., serum lipids [PFOS and PFOA], effects on fertility and fecundity [PFOS], and pregnancy-induced hypertension [PFOA]), the associations are particularly strong and fairly consistent. There still remains some uncertainty related to other observed associations, as for various endpoints the data for both PFOA and PFOS are mixed (i.e., some studies show positive associations with the serum PFAS value while others do not).

Although mean serum values are presented in the human studies, actual estimates of PFOA and 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 PFOA and PFOS values come from PFOS derivatives or precursors that break down metabolically to PFOA or PFOS. These compounds might originate from PFOA or PFOS in diet and precursor materials used in the home, which creates potential for confounding by the metabolites of the chemicals esterified to the carboxylate or sulfonate functional group. 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. Adjusting for the other PFAS from the acid and sulfonate families is complicated because of the many commonalities in their effects, a factor often acknowledged in the epidemiology 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 IRIS assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda.

## DeWitt Comments

**COMMENT 1:** While the OW characterization of the epidemiological data for PFOA/PFOS is, technically, true, it also is somewhat misguided. Almost any epidemiological database will contain uncertainty regarding the routes, levels, and timing of exposures and will have confounding influences of other compounds. Very few epidemiological studies are free from these uncertainties, but when similar observations and conclusions are reached from multiple studies with these types of uncertainties, the database becomes useful for determining a candidate RfD or other value relevant to human health. What is particularly valuable about the PFOA/PFOS database is that it is relatively extensive in that it includes data not only from occupationally-exposed humans, but from people highly exposed to environmental concentrations of PFOA/PFOS and from people in the general population who have detectable concentrations of these compounds. Additionally, for establishing an RfD, do all of these uncertainties need to be absent? In other words, do animal studies used to derive RfDs lack these uncertainties?

**RESPONSE:** EPA did not use a reverse dosimetry modeling approach for this effort, but rather relied on animal data and the peer reviewed PK model to develop candidate RfDs for PFOA and PFOS. The available epidemiology studies for PFOA and PFOS provide evidence of hazard from exposure to these chemicals.

The HESDs for both PFOA and PFOS have been extensively revised to present a more in-depth analysis of the human epidemiology data, including a more robust discussion of the data that supports the conclusion that there is evidence of an association between exposure to these chemicals and human health hazard. For a few of the outcomes (e.g., serum lipids [PFOS and PFOA], effects on fertility and fecundity [PFOS], and pregnancy-induced hypertension [PFOA]), the associations are particularly strong and fairly consistent. There still remains some uncertainty related to other observed associations, as for various endpoints the data for both PFOA and PFOS are mixed (i.e., some studies show positive associations with the serum PFAS value while others do not).

Although mean serum values are presented in the human studies, actual estimates of PFOA and 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 PFOA and PFOS values come from PFOS derivatives or precursors that break down metabolically to PFOA or PFOS. These compounds might originate from PFOA or PFOS in diet and precursor materials used in the home, which creates potential for confounding by the metabolites of the chemicals esterified to the carboxylate or sulfonate functional group. 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. Adjusting for the other PFAS from the acid and sulfonate families is complicated because of the many commonalities in their effects, a factor often acknowledged in the epidemiology studies. 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.

While animal studies are designed to address some of these uncertainties, these studies also have related uncertainties. EPA has addressed these uncertainties in the adoption of standard uncertainty factors (USEPA 2002).

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 IRIS assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda.

**COMMENT 2:** What is missing from the OW characterization of the epidemiological data is a thorough evaluation concerning hepatotoxicity and developmental toxicity reported in human populations and how these endpoints are relevant to or related to animal studies.

**RESPONSE:** EPA has added text describing how the epidemiology studies are used qualitatively as additional lines of support to the RfD in both the final HESDs and HAs. Similarities in endpoints observed in the human and animal studies are integrated in the synthesis and evaluation section (section 3.4 in each document).

### **Fisher Comments**

**COMMENT 1:** The use of non-human and human data is very important for interpreting exposure extrapolations from rats. I am not an epidemiologist so I cannot comment with authority on the epidemiology data for dose-response. Justify why human data are not suitable for use in the analysis of the health hazards of PFOA and PFOS.

**RESPONSE:** EPA did not use a reverse dosimetry modeling approach for this effort, but rather relied on animal data and the peer reviewed PK model to develop candidate RfDs for PFOA and PFOS. The available epidemiology studies for PFOA and PFOS provide evidence of hazard from exposure to these chemicals. The HESDs for both PFOA and PFOS have been extensively revised to present a more in-depth analysis of the human epidemiology data, including a more robust discussion of the data that support the conclusion that there is evidence of an association between exposure to these chemicals and human health hazard. For a few of the outcomes (e.g., serum lipids [PFOS and PFOA], effects on fertility and fecundity [PFOS], and pregnancy-induced hypertension [PFOA]), the associations are particularly strong and fairly consistent. There still remains some uncertainty related to other observed associations, as for various endpoints the data for both PFOA and PFOS are mixed (i.e., some studies show positive associations with the serum PFAS value while others do not).

Although mean serum values are presented in the human studies, actual estimates of PFOA and 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 PFOA and PFOS values come from PFOS derivatives or precursors that break down metabolically to PFOA or PFOS. These compounds might originate from PFOA or PFOS in diet and precursor materials used in the home, which creates potential for confounding by the metabolites of the chemicals esterified to the carboxylate or sulfonate functional group. 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. Adjusting for the other PFAS from the acid and sulfonate families is complicated because of the many commonalities in their effects, a factor often acknowledged in the epidemiology 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 IRIS assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda.

## Hayton Comments

**COMMENT 1:** There are a number of epidemiological studies that have been based on large numbers of subjects chronically exposed (over decades in some studies) to the subject compounds over a broad range of intakes. Steady state serum concentrations have also been available for quantification of the systemic exposure. While the route, levels and timing of the exposures may have been uncertain, the long half-lives of PFOA and PFOS in humans and the long periods of exposure to them indicate that 1) subject serum concentrations were generally at steady state, and 2) daily fluctuations in the amount and timing of the exposure would not produce much day-to-day fluctuation in the serum concentration of PFOA/PFOS. These consequences of the long exposure period and long half-life indicate that variability in the route and level of exposure would not have led to a measured serum concentration that was unrepresentative of the subjects' long-term average serum concentration. The serum concentration then should be relatively stable over time and it should reflect an integrated measure of the individual's exposure to PFOA and PFOS.

The serum concentration is a quantitative measure of systemic exposure to the subject chemicals, and is arguably a better metric of exposure than are intake rate. The over-all rate of intake (R) that produces a particular steady state serum concentration (C<sub>ss</sub>) can readily be calculated from the clearance (CL) of the chemicals, which is about 0.08 mL/d/kg body weight:  $R = C_{ss} \times CL$ . The calculated rate of intake would represent all intake routes.

Confounding influences of other PFCs and indeed other chemicals and life-style factors such as smoking, diet, alcohol use, etc. would have to be considered, as is generally the case with epidemiological studies. Methodology exists for dealing with such influences.

Thus it appears that the epidemiological results should be used in the RfD determination. Their strength is that uncertainties associated with extrapolation from laboratory animal studies are avoided. Health effects that are positively associated with serum PFOA/PFOS concentration and that are observed in large populations of subjects should seriously be considered as potentially arising from PFOA/PFOS exposure. If mode of action studies in lab animals or in vitro studies support a cause-effect relationship, then the threshold serum concentration could inform the calculation of the RfD.

**RESPONSE:** Calculations to predict the steady-state concentration (C<sub>ss</sub>) for each of the average serum values used in quantification were included in the final report.

EPA did not use a reverse dosimetry modeling approach for this effort, but rather relied on animal data and the peer reviewed PK model to develop candidate RfDs for PFOA and PFOS. The available epidemiology studies for PFOA and PFOS provide evidence of hazard from exposure to these chemicals. The HESDs for both PFOA and PFOS have been extensively revised to present a more in-depth analysis of the human epidemiology data, including a more robust discussion of the data that support the conclusion that there is evidence of an association between exposure to these chemicals and human health hazard. For a few of the outcomes (e.g., serum lipids [PFOS and PFOA], effects on fertility and fecundity [PFOS], and pregnancy-induced hypertension [PFOA]), the associations are particularly strong and fairly consistent. There still remains some uncertainty related to other observed associations, as for various endpoints the data for both PFOA and PFOS are mixed (i.e., some studies show positive associations with the serum PFAS value while others do not).

Although mean serum values are presented in the human studies, actual estimates of PFOA and 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 PFOA and PFOS values come from PFOS derivatives or precursors that break down metabolically to PFOA or PFOS. These compounds might originate from PFOA or PFOS in diet and precursor materials used in the home, which creates potential for confounding by the metabolites of the chemicals esterified to the carboxylate or sulfonate functional group. Additionally, most of the subjects of the epidemiology studies have many PFAS 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. Adjusting for the other PFAS from the acid and sulfonate families is complicated because of the many commonalities in their effects, a factor often acknowledged in the epidemiology 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 IRIS assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda.

### Longnecker Comments

**COMMENT 1:** As noted in the General Impressions section above, the human studies with data on plasma or serum concentrations of PFOA and PFOS, especially for several categories of such levels, could be used to estimate dose-response information. However, there are other reasons why the human data may not be useful for setting the RfD (see above). Either PK or PBPK models might be useful for estimating the dose that human are exposed to; an advantage of a PBPK model is that it could incorporate information about routes and timing of exposure. Estimates of the contribution of various routes are available (e.g., Haug et al. 2011; Lorber & Egeghy 2011), and exposure trends could be assumed and evaluated in sensitivity analyses. Some occupational studies had data that allowed an estimate of serum levels, or measured them directly. Several reports show estimated exposure based on serum concentrations of PFOA or PFOS (Locicci et al. 2013; Lorber & Egeghy 2011; Thompson et al. 2010). With respect to confounding, the assessment of how likely this is could be informed by: 1) the correlation of serum concentration of PFOA, PFOS, and other compounds of this type in a particular study population (or in a series of studies), and 2) whether the other compound(s) has been associated with the particular outcome being considered. If the correlation is low or the other compound has not been associated with the outcome, concern about confounding may not be strongly justified. Without additional consideration of data that address these points, it may be premature to assume confounding would be a problem.

**RESPONSE:** A variable portion of the exposures to the general population comes from household and workplace sources (e.g., carpets, furnishings) that contain precursors that degrade metabolically and abiotically to PFOA or PFOS, especially from household dusts and ambient air. These exposures would contribute to the concentrations of serum PFOA and PFOS. Telomere alcohol PFOA derivatives and PFOS/A derivatives that break down metabolically to PFOA and PFOS after consumption are a potential source in addition to direct exposure to PFOA and PFOS. These derivatives can be metabolized and form not only PFOA and PFOS, but other chemically reactive metabolites. Thus, the potential for results to be confounded by the other metabolites adds uncertainty in the observed associations between serum PFOA and health effects. These compounds can originate from the diet and materials used in the home; thus, there is potential for confounding in the C8 studies where the drinking water PFOA was considered to be the primary medium of exposure and for PFOS precursors where degradation produces amines that could contribute to the effects observed. In contrast, in the animal studies, test organisms were dosed with either PFOS or PFOA and potential confounding with other metabolites is reduced.

Taken together, the weight of evidence for human studies supports the conclusion that PFOA and PFOS exposure is a human health hazard. At this time, for the development of the RfD in support of the development of a drinking water health advisory for PFOA and PFOS, OW 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 IRIS assessment is needed, as indicated in the 2015 IRIS Multi Year Agenda. That effort may further evaluate and consider these human epidemiology studies.

## Slitt Comments

**COMMENT 1:** *Strengths of the studies:* Several studies, which all demonstrate a positive association between serum PFOA and/or PFOS and cholesterol or LDL levels are based on drinking water as a route of exposure. These studies are in agreement with Nelson et al., 2010, which was analyzing data from the 2003-4 NHANES study. Steenland et al., 2009 (*Environ Health Perspect.* Jul 2009; 117(7): 1083–1088) as part of the C8 Health Project collected data on 69,030 subjects with findings that serum PFOA was higher for males, those consuming local vegetables, and those using well water rather than public water, and lower for those using bottled water. The estimated response rate for participants >20 years of age was 81% and mean serum PFOA concentration was 83 ng/l. Subjects were eligible to participate in the C8 Health Project if they had consumed drinking water for at least one year before 3 December 2004 supplied by Little Hocking Water Association (Ohio), City of Belpre (Ohio), Tupper Plains Chester Water District (Ohio), Village of Pomeroy (Ohio), Lubeck Public Service District (West Virginia), Mason County Public Service District (West Virginia), or private water sources within these areas that were contaminated with PFOA. Subjects were also eligible if they could document that they had either worked in a contaminated water district or went to school there for at least one year. From this population, which the route of exposure is considered to be primarily via drinking water, serum lipids were analyzed with regard to PFOA levels and a positive correlation was observed for all serum lipids except HDL. Frisbee further characterized this cohort, analyzing 12, 476 children and adolescents included in the C8 Health Project, finding an increase in total cholesterol.

A recent epidemiology study (Fitz-Simon et al., 2013), not included in the current documents, described positive associations between PFOA and PFOS in serum LDL cholesterol. This study examined a study population that consisted of 560 adults living in parts of Ohio and West Virginia where public drinking water had been contaminated with PFOA. They had participated in a cross-sectional study in 2005-2006, and were followed up in 2010, by which time exposure to PFOA had been substantially reduced. Overall, the findings demonstrate a positive association between serum PFOA and PFOS levels and serum and LDL cholesterol.

**RESPONSE:** Fitz-Simon et al. 2013 was added to the document. EPA agrees that the human data for PFOA and PFOS indicate that exposure to these chemicals can impact serum lipids. The human studies are now summarized in the HESD and reported for different endpoints, including reproductive and developmental endpoints. The strongest associations are related to serum lipids with increased total cholesterol and high density lipoproteins (HDLs).

**COMMENT 2:** *Weaknesses:* The studies did not appear to analyze PFOS or PFOA levels in drinking water from the participants analyzed and did not analyze data based on the length of exposure.

**RESPONSE:** The studies of the C8 community included information on the concentrations in drinking water for the impacted public water systems. Concentrations varied temporally within systems and between systems based on the information available.

## **Charge Question 4: Characterization of Epidemiology Data**

**Please comment on the transparency and characterization of the epidemiological data.**

### **Bruckner Comments**

#### **PFOA-specific Comments**

**COMMENT 1:** See comments above.

**RESPONSE:** See corresponding responses above.

#### **PFOS-specific Comments**

**COMMENT 2:** The document's authors have done a good job describing and summarizing the designs and findings of the epidemiology studies.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **Cory-Slechta Comments**

**COMMENT 1:** The PFOA document in particular and to some extent the PFOS document present all of the epidemiological studies but do not actually evaluate them; there is not a consistent indication of individual strengths and limitations of the studies, failures or not to adequately control potential confounding variables. Furthermore, there is no 'power analysis' type of evaluation, i.e., some of these studies included very small sample sizes and thus their power to actually detect effects may be limited, and yet they all appear to be weighted basically the same, i.e., studies with very small sample sizes with obviously extremely limited power to detect any effects appear to be considered the same as those with extremely large sample sizes. Studies with small sample sizes that nevertheless do find an effect of PFOA or PFOS actually suggest a robust type of effect.

**RESPONSE:** The human epidemiology section in both of the final HESDs has been substantially rewritten to include details on study type, sample size, and serum levels where these data were available. Tables were expanded for each major endpoint to summarize the studies described in the text as recommended by the peer reviewers and are now included in Appendix B. Additional, more detailed tables were added to sections 3.1.1 and 3.1.2. They include quantitative information from the studies. An overall summary and conclusion for the cancer and noncancer endpoints was added at the end of the epidemiology section (sections 3.1.2.1 and 3.1.1.12 for PFOA and 3.1.2.1 and 3.1.1.8 for PFOS).

**COMMENT 2:** The discarding of positive associations in human epidemiological studies because they do not produce frank clinical disease seems inappropriate and inconsistent with other EPA documents. For example, p. 4-3 in the PFOS document states that only a small number of ALT values were outside the normal range making the results difficult to interpret in terms of health. Physiological changes that are moving in the wrong direction, even if sub-clinical at the time, are still adverse effects. Are actual clinical diagnoses required for an adverse effect? This is especially the case given that the ranges of normal across populations are extremely broad.

**RESPONSE:** The reviewer is correct in that associations in the absence of clinical disease should not be ignored. In the HESDs, EPA described these studies and used them as another line of evidence to support the finding from animal studies.

**COMMENT 3:** The latter also raises the question of the cumulative toxicity of PFOA and PFOS and whether any consideration is being given to this.

**RESPONSE:** Cumulative exposure and toxicity was taken into consideration when calculating the drinking water health advisory values. Because of the similar toxicological effects at similar concentrations (the RfD for PFOA and PFOS are both 0.00002 mg/kg/day), where PFOA and PFOS co-occur at the same time and location at a drinking water source, EPA recommends that the health advisory guideline be applied as the sum of the concentrations (i.e., additive lifetime health advisory for [PFOA] + [PFOS] = 0.07 µg/L).

**COMMENT 4:** Another such example is in the PFOS document, where it actually refers to a statistically significant, but not toxicologically significant effect (p.4-38); what does that mean? Also, p. 5-4 appears to dismiss any changes in thyroid function since no evidence of clinical hypothyroidism actually occurred. This whole approach with the human studies seems quite inconsistent with the reliance on increased liver weight in the absence of clinical pathology as the endpoint in the human studies.

**RESPONSE:** The sections on thyroid effects in humans were completely revised and new data were added. The statement about a toxicological significance referenced in the comments is no longer in the document. The revisions to the thyroid epidemiology data conclude that “generally null associations were found between PFOA and TSH in people who have not been diagnosed with thyroid disease.” The conclusions of the C8 Panel and other human studies are described in the HESDs and used as a line of evidence supporting the assessment.

### DeWitt Comments

**COMMENT 1:** It is not obviously or abundantly clear how the OW characterized the epidemiological data for either PFOA or PFOS. The studies were well-described, but the contribution of particular studies to the overall assessment was not. The results of studies described in the hazard characterization section (4.4) need to be better characterized. For example, in the PFOA risk assessment:

**COMMENT 1a:** An increase in serum lipids associated with PFOA/PFOS exposure in humans is discussed as a risk factor for cardiovascular disease in humans; however, no evidence of increased cardiovascular disease has been observed in human populations as related to either chemical. Additionally, serum lipids typically are decreased in animal models after PFOA/PFOS exposure, which is thought to be associated with/typical of exposure to agents that activate PPARα. If humans are known to respond to PPARα activators (i.e., fibrate drugs), why would the results between humans and animal models be discordant? This should be discussed.

**RESPONSE:** The most consistent response observed in the epidemiology studies related to serum lipids is a positive association in serum total cholesterol. The epidemiology data for PFOA showed a weak association with increased LDL cholesterol, but no association for HDL cholesterol. For PFOS, when there was an association with LDL and HDL, it was positive for both lipoprotein complexes. The only available studies in animals evaluating serum cholesterol for PFOA and PFOS show a decrease. There are also animal data comparing the effect of PFOA and PFOS to the fibrate Wy 14,643 on cellular histological and biochemical changes and gene activation in the liver. These studies demonstrate that the cellular histological and biochemical changes and patterns of gene activation share some commonalities but also have distinct differences. In humans, treatment with fibrates usually results in a decrease in serum LDL cholesterol and increase in HDL cholesterol (Staels et al. 1998). The animal data do not provide an explanation for the differences in the observations of increased total cholesterol in humans. The mode of action for the observed effects on PFAS impact on serum lipids in humans is not completely understood and rodents may be impacted differently compared to humans by PPARα stimulation when it comes to lipid metabolism. The HESDs describe how PPAR stimulation is involved with lipid metabolism.



**COMMENT 1b:** Several epidemiological studies reporting changes in liver enzymes clearly state that the clinical relevance of the changes in enzymes is unknown. Therefore, stating that the human studies “suggest effects on the liver as indicated by increases in liver enzymes” amounts to a mischaracterization of the data.

**RESPONSE:** There is indirect evidence of an effect on the liver in humans, as indicated by changes in several enzymes that are biomarkers of liver damage. The human epidemiology studies have been revised to further describe these studies. The human epidemiology studies varied in the enzymes biomarkers they evaluated and the results differed across studies; this is described in the HESDs. In the case of PFOA, an association of serum PFOA concentration with elevations in serum levels of ALT and gamma-glutamyl transpeptidase (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 function. For PFOS, there was a slight positive association between serum PFOS levels and increased serum ALT values. The association between PFOS levels and increased serum GGT levels was less defined and overall did not appear to be affected.

Very few of the animal studies examined these liver enzymes other than Seacat et al. 2002, Thomford 2002/Butenhoff et al. 2012<sup>7</sup>, where there was a significant increase in ALT but not AST at some doses. Neither GGT or LDH were evaluated in the animal studies.

**COMMENT 1c:** No direct evidence of hepatotoxicity has been reported in epidemiological studies. This should be discussed.

**RESPONSE:** Considering ALT and GGT results, effects on the liver are suggested; however, hepatotoxicity was not reported in epidemiological studies. In an epidemiology study of highly exposed members of a general population and based on collected serum, information that would inform a diagnosis of hepatotoxicity is unlikely to be available unless medical records were obtained for the individual subjects.

**COMMENT 1d:** More in-depth characterizations are needed for the additional sections of the hazard characterization, with the exception of the thyroid section, which was well-described.

**RESPONSE:** The synthesis and evaluation sections were updated in both documents to better characterize human and animal findings. The revised sections include a comparison between the outcomes from the epidemiology as they compare with the data from the animal studies to emphasize the consistencies and inconsistencies between findings. The characterization of each of the responses observed in the epidemiology studies is covered in the new summary sections for the noncancer and cancer epidemiology findings and integrated with the findings from the animal studies in the synthesis of hazard section 3.4.

**COMMENT 2:** For example, in the PFOS risk assessment: Similarly to the PFOA risk assessment, the hazard characterization section needs to better discussion differences and similarities between effects reported in humans and effects reported in animal models.

**RESPONSE:** The synthesis and evaluation sections were updated in both documents to better characterize human and animal findings for both cancer and noncancer. The revised sections include a comparison between the outcomes from the epidemiology as they compare with the data from the animal studies to emphasize the consistencies and inconsistencies between findings.

---

<sup>7</sup> Thomford (2002) is unpublished, but it contains the raw data. Butenhoff et al. (2012) is the published study.

## Fisher Comments

**COMMENT 1:** I am not an epidemiologist, but it appears to be adequate. Better characterization of the pros and cons of the human analyses and interpretation of the outcomes would be helpful.

**RESPONSE:** The human epidemiology section was substantially rewritten with study type, sample size, and serum levels added for each study where these data were available. Tables for each major endpoint were expanded to summarize the studies described in the text. An overall summary and conclusion was added at the end of the epidemiology section.

## Hayton Comments

**COMMENT 1:** The characterization of the individual epidemiological studies presented seems to be adequate. Public comments have identified the need to distinguish positive and negative associations with statistical significance, which seems to be a fair criticism. As noted in the response to Question 2, there are relevant studies that have not been described in the health-effects documents that ought to be considered and this includes some epidemiological studies. Most of the cited epidemiological studies have focused on healthy adults – workers exposed occupationally, residents of communities with or without contaminated water. These populations might be expected to be less sensitive to adverse effects than would early life stages and particular disease populations. Studies of potentially more sensitive populations would be desirable. The Frisbee et al. (2010) study of children 1-11.9 years and adolescents 12-17.9 years showed significant positive associations with serum lipid levels. Studies such as this one would be informative.

**RESPONSE:** The human epidemiology section was substantially rewritten with study type, sample size, and serum levels added for each study where these data were available. EPA reviewed the Frisbee et al. (2010) study and added it to both the HESD for PFOA and PFOS. See Appendix B for a list of the epidemiology studies that were retrieved, reviewed, and included in the revised HESDs.

## Longnecker Comments

**COMMENT 1:** Please see the long paragraph above, under General Impressions, and some of the comments in response to item #2 above. Another point that the authors may want to consider is that studies that examine external exposure in relation to health outcomes may have special advantages in the case of PFOA and PFOS. While in general it is considered best to have a measure of exposure that is based on a biomarker of internal exposure, this may be problematic for several outcomes for PFOA and PFOS, because of the possibility of confounding or reverse causality that would not be an issue if an external estimate of exposure were used. For example, in Steenland K, Zhao L, Winkquist A., a cohort study of workers exposed to PFOA., (Occup Environ Med. 2014 Jun;71 Suppl 1:A55), when an external estimate of exposure was used for the Washington Works employees, no association with elevated cholesterol was found. The Viera et al. (2013) results are based on external estimates of exposure, whereas the similar study by Barry et al. (2013) are based on serum levels or estimates based on serum levels. The fact that association with kidney cancer is present in the Viera study decreases concern that the association was due to reverse causality. Steenland et al. 2012 used an external estimate of exposure to study cancer mortality and also found an association with kidney cancer. Lundin et al. (external estimate of exposure) had no cases of kidney cancer, though their study was also small.

**RESPONSE:** In the revisions to the HESDs, EPA discussed cases where associations can partially be due to other factors such as BMI, age and diet for elevated cholesterol, and low GFR for low birth weight. The studies specified in the comment (Barry et al. 2013; Lundin et al. 2009; Steenland et al. 2015; Vieira et al. 2013) are all included in the document, as well as a discussion of the links between PFOA and kidney cancer.

## Slitt Comments

**COMMENT 1:** The epidemiology data is well described and a thorough read. The data would be put in better context for the reader if there are average serum concentrations or ranges for the studies summarized in tables in addition to other key pieces of information.

**RESPONSE:** The human epidemiology section in both documents was substantially revised with study type, sample size, and serum levels added for each study where these data were available. Tables were expanded for each major endpoint to summarize the studies described in the text. An overall summary and conclusion section was added at the end of the epidemiology section in each document for both the noncancer and cancer endpoints. There are two sets of epidemiology tables in the final document. Detailed tables presenting quantitative data from the individual studies are in sections 3.1.1 and 3.1.2 and the updated original summary tables are now included with Appendix B.

**COMMENT 2:** A recent publication should be included in the document for consideration. Fitz-Simon N, Fletcher T, Luster MI, Steenland K, Calafat AM, Kato K, Armstrong B. Epidemiology. 2013 Jul;24(4):569-76. doi: 10.1097/EDE.0b013e31829443ee.

**RESPONSE:** This study (Fitz-Simon et al. 2013) was added to both of the final HESDs.

## **Charge Question 5: Cancer Classifications**

**The OW has concluded that the cancer classifications for PFOA and PFOS are most consistent with respective classifications of suggestive evidence for carcinogenicity as described the EPA Guidelines for Carcinogen Risk Assessment (pp. 2-56, 2-57). Please comment on the strengths and weaknesses of this classification.**

### **Bruckner Comments**

#### **PFOA-specific Comments**

**COMMENT 1:** I agree with EPA's choice of "Suggestive Evidence for Carcinogenicity." Epidemiological findings in occupationally-exposed and general populations to date are equivocal. Increases in Leydig cell tumors and liver adenomas have been reported in high-dose male rats. Increased incidences of pancreatic cell hyperplasia/adenomas and ovarian stromal hyperplasia/adenoma have been observed in female rats. More studies are necessary to confirm/expand these findings, and to assess carcinogenic potential in other species. Most mutagenicity and genotoxicity assays have been negative. Thus, there is some, but not undue cause for concern about the human carcinogenic potential of PFOA.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

#### **PFOS-specific Comments**

**COMMENT 2:** The document's authors have adequately and convincingly presented evidence for classifying PFOS as "suggestive of carcinogenicity."

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **Cory-Slechta Comments**

**COMMENT 1:** The classification of both PFOA and PFOS evidence for carcinogenicity as suggestive seems consistent with the clear limitations in the available data bases. In addition, the animal studies are limited to one species and mutagenicity does not occur in response to PFOA.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **DeWitt Comments**

**COMMENT 1:** This classification is appropriate for both PFOA and PFOS given the epidemiological evidence, which is somewhat limited for PFOA and quite limited for PFOS. For PFOA, there is an association between kidney and testicular cancer, but there are limited data in animal models for these cancers and there is uncertainty that the mechanism of PFOA-induced carcinogenicity in animal models is applicable to humans. Studies of PFOS have the same limitations, but epidemiological studies have failed to find an association between PFOS exposure and cancer.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **Fisher Comments**

**COMMENT 1:** I did not review the cancer studies for PFOA and PFOS.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### Hayton Comments

**COMMENT 1:** The classification of “suggestive” is not unreasonable. The epidemiological studies, while showing apparent associations between PFOA exposure and cancer incidence in testicle and kidney as well as other tissues, do not provide a cause-effect relationship. However, they certainly do raise a concern about the carcinogenicity of the subject substances. Studies in animals have demonstrated conclusively that PFOA causes liver cancer in rats but the MOA that involves PPAR activation is absent in humans and it has been concluded that PFOA and PFOS cannot be carcinogenic in humans via this mechanism.

An EPA SAB panel (2006) consideration of this question resulted in a majority of the panel members favoring a classification of “likely to be carcinogenic” for PFOA. Board members acknowledged the PPAR MOA argument against causation of cancer in humans, but also found evidence that liver cancer in rats administered PFOA may also have had a MOA independent of PPAR activation. Recent epidemiological studies have added to the weight of evidence for an association between PFOA/PFOS exposure and cancer. Therefore a classification of “likely” is also not unreasonable to this reviewer. Lacking expertise in the nuances of applying the EPA’s classification scheme, it is difficult for this reviewer to argue in favor of either “suggestive” or “likely”.

**RESPONSE:** 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 C8 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; Lyon, France) to assess the carcinogenicity of PFOA, among other chemicals. Although the assessments have not yet been published (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 available 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.

With regard to mode of action, please see section 3.4.3 in the final HESD for PFOA.

### Longnecker Comments

**COMMENT 1:** The classification as “suggestive evidence for carcinogenicity” for both PFOA and PFOS is consistent with the guidelines put forth in the EPA Guidelines for Carcinogen Risk Assessment (2005). There are few pertinent data, including some suggestive but weak human evidence. There is clearly not enough evidence to classify these agents as likely human carcinogens.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### Slitt Comments

**COMMENT 1:** Overall, the assessments for each PFOS and PFOA appear to be consistent with the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a). Strengths: Both classifications use evidence from human studies as guidance.

**COMMENT 1a:** PFOS: The limited data that exist regarding PFOS and cancer were presented, the classification for PFOS under the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) is currently consistent with the suggestive evidence of carcinogenic potential descriptor. This assessment is reasonable, given that it is based on two studies that show a slight increase in adenomas that occurred in males and females.

**COMMENT 1b:** PFOA: There is conflicting evidence regarding PFOA exposure and cancer risk. However, several human studies have found associations between PFOA exposure and elevation of cancer of the bladder and kidney. This is also supported by a chronic bioassay in rats, which demonstrated that PFOA was tumorigenic.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

## **Charge Question 6: Use of Pharmacokinetic Model**

**Significant interspecies differences in pharmacokinetics exist for both PFOA and PFOS. Adjusting for interspecies differences was an important step in developing candidate RfDs given the totality of the human and animal data. Please comment on the strengths and weaknesses of the pharmacokinetic model adjustments to accommodate the impact of albumin binding and renal tubule transporters in determining average serum values.**

### **Bruckner Comments**

#### **PFOA-specific Comments**

**COMMENT 1:** The adjustments made to accommodate the influence of albumin binding and saturable renal tubular resorption of PFOA seem reasonable. I would defer, however, to someone with more experience in providing for these processes in PBPK models.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

#### **PFOS-specific Comments**

**COMMENT 2:** The PBPK model adjustments to estimate human equivalent doses appear to be appropriate. I defer to someone more qualified on the subject.

**RESPONSE:** Comment is acknowledged; EPA notes that the model used was not physiologically based, but rather an empirical model with physiological (i.e., saturable resorption in the kidney proximal tubules) motivation.

### **Cory-Slechta Comments**

**COMMENT 1:** This falls outside my area of expertise and therefore no significant comments are provided. However, at the face-to-face meeting there was significant discussion regarding the modeling, including clarifications from Dr. Wambaugh that were found by those panel members with expertise to clarify these issues and these particular issues were considered adequately addressed.

**RESPONSE:** The clarifying information provided by Dr. Wambaugh at the meeting was used to update the modeling sections of both HESDs.

### **DeWitt Comments**

**COMMENT 1:** Several PK models have been reported in the literature for these compounds and are relatively well described in the documents. The documents assert that the existing PK models do not consider the impact of renal tubule transporters and albumin binding; while, many of the existing models appropriately predict serum concentrations in humans and other species, but they are mostly based on empirical models. Please explain the weaknesses of such empirical models.

**RESPONSE:** EPA chose to use mathematical models of pharmacokinetics to allow extrapolation within species. Extrapolation assumes that the model accurately captures the relevant phenomena in a way that is applicable to both the calibration data and the new situation for which predictions (extrapolations) are made. In this document, EPA performed within species extrapolation between different dose regimens using a model that was empirically calibrated to PK data for the relevant species. This makes the assumption that the empirical calibration has captured the biological aspects for that species. EPA did not extrapolate across

species because there is currently no model available that explains the cross-species differences in clearance (or half-lives) of the chemicals.

**COMMENT 2:** Additionally, numerous studies for both compounds report serum and tissue concentrations in humans and other species, which can be compared to existing models. Both documents present a revised model that amounts to a reanalysis of data from studies that report serum concentrations. A more thorough discussion of the improvements made by the reanalysis is needed to better understand if the improved model adequately estimates or predicts the clearance rate and other parameters for which confidence is low. Alternatively, the publication (Wambaugh et al., 2013) that thoroughly describes the reanalysis could be referenced.

**RESPONSE:** A description of the publication (Wambaugh et al. 2013) was added to section 2 of both HESDs with the description of the other available models.

### Fisher Comments

**COMMENT 1:** Serum protein binding: Both PFOA and PFOS are highly bound in serum proteins across species, thus model adjustments seem trivial for interspecies extrapolation. Steady-state conditions can be assumed to estimate the free fraction (e.g., 2% based on paper by Han et al., 2005 for humans). I did not find a discussion about the half-life of serum proteins, which may have some influence on the ‘apparent’ serum half-life of PFOA and PFOS. The estimated fraction of free PFOA or PFOS is important for describing urinary and fecal elimination in rats (and other species) and the plasma concentrations of total PFOA and PFOS. Thus, the model predicts total PFOA and PFOS in serum or plasma, but the free fraction estimates drive the gradual clearance of total BPA from plasma or serum by describing clearance of free.

**RESPONSE:** The reviewer is correct that the chemicals are highly bound and EPA’s model incorporates this. The Andersen et al. (2006) model does include binding of PFOA and PFOS when predicting urinary elimination. Fecal elimination is not included in that model. The analysis of the available pharmacokinetic (PK) studies estimated that both chemicals were highly bound across species. The half-life of human serum albumin is long (16–18 days) and levels remain stable except in extreme malnutrition or those with infections, burns or severe injuries. The binding of PFOA to albumin is much greater than that to other serum proteins (see section 2 in the PFOA HESD). No data were identified that examined PFOS binding to other serum proteins.

**COMMENT 2:** Renal reabsorption: The renal reabsorption hypothesis involving species specific and sometimes gender specific transporters to describe the pharmacokinetic data represents sound judgment. This departure from normal allometric scaling is suggestive of active transport processes. Few PBPK models explicitly describe transporters with drugs or chemicals, although the field is moving in this direction. Thus, the approach used for PFOA and PFOS is adequate, that is, a hypothesis was evaluated by employing empirical PK-based kinetic analyses. Because the mechanistic details are missing for each species/gender, scaling of this biological phenomenon is not possible at this time. This is not a weakness, but represents the state of the science.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### Hayton Comments

**COMMENT 1:** A very important strength of the documents is the attempt to deal with the interspecies differences in pharmacokinetics so that adverse effects across species are compared on the basis of internal, systemic exposure to PFOA and PFOS, instead of basing comparisons on the administered mg/kg dosages. PFOA and PFOS have complicated pharmacokinetics that have proven difficult to model. While a relatively



simple one-compartment model appears adequate to analyze single, low doses, this model fails when it is extended to higher doses and repeated doses. Nonlinearities appear associated with saturable plasma protein binding and with saturation of transporters thought to be involved in the reabsorption of the compounds from renal filtrate.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

**COMMENT 2:** A weakness of the pharmacokinetic model adjustments is the lack of robustness of the models. Despite the extensive efforts of talented pharmacokineticists, development of a model that scales across species and handles a range of dosages and a variety of administration routes has proven elusive. The two compartment model of Andersen et al. (2006) has formed the basis of the model used in the draft documents. The model incorporates saturable resorption of PFOA and PFOS from renal tubular filtrate. While protein binding is known to be saturable (fraction free increases with concentration), the model uses a species-specific but constant free fraction. Model parameter values for mouse, rat and monkey were used to predict reasonably well measured serum concentrations after a fixed daily dosing regimen, Tables 5-6 – 5-8 for PFOA and 5-8 and 5-10 for PFOS. This agreement between predicted and measured serum concentrations gives confidence that the model-calculated AUC values and final serum concentrations associated with adverse health effects (or in the case of liver weight, biological marker of exposure) are realistic and a basis for estimation of RfD. While the model used appears adequate for the purpose, the model parameters that were used have some markedly non-physiological values. (Information subsequently provided at the reviewers meeting explained some of the departure from expected physiological values, as discussed in a following section.)

**RESPONSE:** The model used (Andersen et al. 2006) has been demonstrated to be robust across doses, as in Wambaugh et al. (2013) in which good predictive agreement was found across multiple dose regimens in differing studies. This is described in both the PFOA and the PFOS HESDs. When sufficient data exist to allow calibration to specific species, the same model structure, albeit with different parameters, was also shown to be robust in Wambaugh et al. (2013). However, EPA agrees with the reviewer that a unified model would eventually be ideal when the state of the science permits it.

In the PFOA HESD, EPA states that “in this case, an oral dosing version of the original model introduced by Andersen et al. (2006) and summarized early in section 2.6.1 was selected for having the fewest number of parameters that would need to be estimated. A unique feature of the Wambaugh et al. approach was to use a single model for all species in the toxicological studies to examine the consistency in the average serum values associated with effects and with no effects from nine animal studies of PFOA.” A similar discussion appears in the PFOS HESD.

The “non-identifiability” of some parameters is discussed below. For some species the PK data are limited such that parameters may take extreme values and still be consistent with the available data. It is for this reason that protein binding and other potentially non-linear processes have not yet been specifically modeled – there are insufficient data to inform such models. The general, non-linear form of the Andersen et al. (2006) model is assumed to capture all relevant non-linearity for which there is evidence.

## Longnecker Comments

**COMMENT 1:** For PFOA and PFOA, the MCMC model results (predicted final serum value) were compared to the measured final serum values, and the agreement was fairly good. For PFOS, the MCMC model results were compared to those from Loccisano et al. (2012b) and were found to be similar, which is also reassuring. Because the PBPK models of PFOA and PFOS are empirical, and have been shown to give results that agree reasonably well with observed data, the adjustments to accommodate the impact of albumin binding and renal tubule transporters are not critical. More data on albumin binding and renal tubule

transporters might allow improved understanding of the pharmacokinetics of these compounds, but may not necessarily cause substantial improvements in the empirical predictions from current models.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **Slitt Comments**

**COMMENT 1:** The current weakness of the models is that data on species differences in PFOA and PFOS for various key transporters is limited and the document is also using mRNA data for various transport proteins to explain gender differences in urinary elimination. First, with regard to PFOS accumulation in the liver compartment, it is necessary to compare affinity of human versus rat for OATP mediated transport. This alone is tricky because of species differences in OATPs. If PFOS-induced liver effects are related to PFOS accumulation in liver, it would be helpful to understand whether a lower affinity of human OATP1b1 and 1b3 compared to rat OATP1a1 predicts lower hepatic PFOS accumulation. More is known about PFOA, but a similar argument can be made for PFOA. In addition, more comprehensive, controlled assessment of renal transporter affinity for PFOA and PFOS is needed to better model the species difference in urinary elimination.

**RESPONSE:** Agreed, but to EPA's knowledge at present this type of information does not exist. EPA agrees that further refinement of the model would eventually be ideal when the state of the science permits it.

**COMMENT 2:** The document often speculates about PFOA or PFOS regulation of transporter expression, but some papers cited (Cheng and Klaasen) do not have enough data at the protein level to support whether these differences in transporter expression are the drivers of toxicokinetic differences between males and females.

**RESPONSE:** There are a number of studies that demonstrate an impact of hormones on renal resorption for PFOA transporters in rats that elucidate their impact on renal excretion and appear to relate to transporter expression. See section 2.5.1 of the HESD.

## **Charge Question 7: Selected Parameters of Pharmacokinetic Model**

**Table 5-5 in the PFOA document and Table 5-7 in PFOS document list the parameters used for the ORD pharmacokinetic models that provide the final serum and AUC values for calculating the internal dose point of departure for the RfD calculation. Please comment on the strengths and weaknesses of the selected parameters.**

### **Bruckner Comments**

#### **PFOA-specific Comments**

**COMMENT 1:** Despite the complexities and unknowns involved in plasma protein binding and renal tubular functions (i.e., glomerular filtration, basolateral tubular excretion and resorption, and apical tubular excretion and resorption), it is necessary to: (a) simply model only for saturable tubular resorption; and (b) use a range, or distribution of parameter values consistent with existing kinetic data. Unfortunately, optimization sometimes results in selection of physiological parameters that are not biologically-realistic, or plausible.

**RESPONSE:** The Andersen et al. (2006) model was selected because it was the simplest model that described the non-linear serum kinetics as a function of dose. Saturable resorption from the kidney is a likely hypothesis for the mechanism, but it is not unique. The difficulty interpreting the values of the model are a limitation of the available PK data, not the model itself. “Optimization” was not performed, rather a formal Bayesian statistical analysis was performed, which generated all possible model parameterizations that were consistent with the available data. Since some (but notably not all) parameter combinations are not consistent with the physiology of saturable renal resorption, this reflects uncertainty with respect to that hypothesis. This uncertainty has been propagated into the predicted serum concentrations for the animal studies.

#### **PFOS-specific Comments**

**COMMENT 2:** The parameters used in the modeling are biologically plausible.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **Cory-Slechta Comments**

**COMMENT 1:** This falls outside my area of expertise and therefore no significant comments are provided. However, at the face-to-face meeting there was significant discussion regarding the modeling, including clarifications from Dr. Wambaugh that were found by those panel members with expertise to clarify these issues and these particular issues were considered adequately addressed.

**RESPONSE:** The model descriptions in the HESD capture the clarifications described to the panel members. In particular, the HESD emphasizes that a single PK model was used to reanalyze all available data. The tables containing the new PK parameter estimates have been retitled “Pharmacokinetic parameters from Wambaugh et al. (2013) meta-analysis of literature data” to further indicate that this reanalysis occurred.

**COMMENT 2:** One unclear component of Table 5-7 in the PFOA document is the column labeled Species/Strain Used for prediction, which in every case is the same as the column labeled Species/Strain and is not otherwise adequately explained.

**RESPONSE:** This information is provided to be consistent with other tables in which the strain used for determining pharmacokinetics could have differed from the strain used in the toxicity study.

## DeWitt Comments

**COMMENT 1:** It is not clear that the parameters in Table 5-5 in the PFOA document and Table 5-7 in the PFOS document are from the Andersen et al. 2006 PK model or if they are parameters used in the reanalysis of the data. This needs to be better explained in both documents. Additionally, all of the units in the tables need to be explained and re-checked for accuracy.

**RESPONSE:** The methods used in model development have been better described to note that this model is a reanalysis of existing data. Units have been checked and corrected where needed.

## Fisher Comments

**COMMENT 1:** The authors should entertain the calculation of data derived AUC (e.g. Table 5-6) to compare to the model derived AUC, just as was done with measurement of total PFOA in serum. This works for the animal studies. The choice of using the empirical model over the more recent physiological models may be a weakness and our understanding of transporters advance. The evolution of chemical-specific PBPK models for use in risk assessment and regulatory applications has repeated itself several times. This is, the first empirical non-physiological model(s) or PBPK models contain hypotheses generating ideas and later models test some of these hypotheses, especially if additional experimental data become available. In the case of PFOA and PFOS, the EPA selected not to use the most recent PBPK models for PFOA and PFOS, but instead use a computational empirical based model (Andersen et al. 2006) that was the first attempt to quantitatively interpret the kinetics of PFOA and PFOS across species of laboratory animals. The authors did publish their model (Wambaugh et al., 2013). The authors chose not to use a human model because a lack of information for Bayesian analyses. The justification for their extrapolation methods should be stated and the published reference for the model should be cited.

**RESPONSE:** A comparison of predicted versus data-derived area under the plasma concentration curve (AUC) is an excellent research idea for further evaluating the modeling described in Wambaugh et al. (2013). At this time the serum time course data for the studies in Table 4-6 have not been collected and organized in a manner that would allow this analysis to be performed. Further, many of the studies only reported a final serum concentration, which would not allow AUC to be calculated in a meaningful way.

A physiologically-based PK (PBPK) model for PFAS would be preferable because it would allow extrapolation between species, provide better estimates of chemical-specific parameters, and allow estimation of chemical concentration in the specific tissues for which toxicity is observed. However, as Dr. Fisher noted earlier (see comment from Fisher above), the state of the science is not yet developed such that extrapolation between species is possible. Calibrating a model developed in animal to humans mitigates the benefits of a PBPK model because there are multiple ways a model might be calibrated and only considering one would understate the uncertainty associated with the use of the model. Further, data for chemical-specific partitioning into tissues are extremely limited. They exist only for PFOA from the single-dose Kemper (2003) rat study and for PFOS for a feed study (i.e., greater dose uncertainty). Wambaugh et al. (2013) found that due to the dose selection of the Kemper (2003) study, the non-linear PK of PFOA was not present. If any portion of the non-linear PK for PFAS is due to tissue distribution (e.g., binding or transport) then these processes would be missed by the Kemper (2003) data set. Given the limitations of the available data for estimating parameters, the simpler Andersen et al. (2006) empirical PK model was preferable.

**COMMENT 2:** Model parameter distributions (Bayesian analyses) appear to be biologically implausible in some cases, covering many orders of magnitude. The authors should discuss this issue and check the units of model parameters in Tables.

**RESPONSE:** EPA believes that the model parameter estimates are correct reflections of the available data. The Bayesian analysis attempted to assess what ranges of parameter values would be consistent with the

available PK data. A wide distribution for a parameter value indicates that there is uncertainty about that value. There are at least two sources of large uncertainty: (1) the data are not informative about the particular parameter, for instance, in the case of species where only single dose PK studies are available, it is hard to characterize the approach to steady-state, and (2) the model is insufficient to describe the data. Because the species for which there are large amounts of PK data lead to parameter estimates with minimal uncertainty, for example PFOA in female CD1 mice, EPA believes that the uncertainties are more associated with the available data. EPA's analysis of the available PK data attributed any indeterminacy of parameter estimates to uncertainty, however, if there were intra-species variability with respect to key parameters, the variability would also be represented by the range of parameter estimates. It is for this reason that the range of values consistent with the data was used to predict PK. Thus, model parameter estimates are correct. Further data collection would be required to determine whether the ranges of parameter values reflected uncertainty or biological variability.

**COMMENT 3:** Both model parameters tables need to include a description of what the parameter represents and cite a figure. The figures showing the Andersen et al. 2006 model do not show all the model parameters and have different nomenclature. The Andersen et al. 2006 paper is a critical paper offering a quantitative explanation for the PFOA and PFOS kinetic data sets.

**RESPONSE:** The first sentence of the captions was changed to: "Means and 95% confidence interval from Bayesian meta-analysis of PK datasets available in peer-reviewed scientific literature are reported (Wambaugh et al. 2013)."

## Hayton Comments

**COMMENT 1:** In the "Pharmacokinetic Model Approach" sections of the documents, it is not made sufficiently clear that the parameter values in Table 5-5 (PFOA) and Table 5-7 (PFOS) were from re-fitting the published data, rather than using parameter values from the original literature reports.

**RESPONSE:** The title of these tables has been changed from "Pharmacokinetic parameters used in the Andersen et al. (2006) model" to "Pharmacokinetic parameters from Wambaugh et al. (2013) meta-analysis of literature data."

**COMMENT 2:** PFOA Table 5-5, p. 5-12

- Body Weight and Cardiac Output values are reasonable and typical.
- $k_a$  values for mouse and monkey seem extremely large; absorption half-lives would be on the order of 10 seconds, which is physiologically unrealistic. All of an oral dose would be absorbed within a minute, mimicking a rapid i.v. bolus dose. Serum concentration-time profiles may not be sensitive to these values, however so they are not disconcerting for the intended use of the models. The rat values appear reasonable.
- $V_{cc}$  values appear reasonable. The total steady-state volume of distribution value [ $V_{ss} = V_{cc} \times (1 + R_{v2:v1})$ ] compares favorably with one-compartment  $V_d$  values for CD1 mouse, but  $V_{ss}$  values for the other columns (species) appear too large, due to the large  $R_{v2:v1}$  values.
- $k_{12}$  values vary a lot across the columns, suggesting that  $k_{12}$  may be highly correlated with another parameter (e.g.,  $R_{v2:v1}$ ).
- $R_{v2:v1}$  values also vary a lot across the columns.
- $T_{maxc}$  values are consistent across the columns; expressed in Gm/hr, they seem very large. For example, 2032 Gm/hr (4.91 moles  $\times$  414 Gm/mole) for the CD1 mouse. Even on a kg body weight basis could mouse renal tubules resorb 2 kg PFOA per hour? This maximum rate of resorption must far exceed the rate of filtration of PFOA at the glomerulus. (Clarification at the reviewers meeting explained this apparent departure from physiological reality. The units had been mis-specified in

Tables 5-5 and 5-7. They were in fact micromole per hour and micromolar for  $T_{maxc}$  and  $k_T$  instead of molar based. Thus  $T_{maxc}$  mouse value was 2 mg/hr, which is physiologically plausible.)

- $k_T$  values are the concentration in glomerular filtrate that half saturates the resorption transporters. Expressed in mg/mL, they seem large, much larger than the urine concentration that would be expected; e.g., for CD1 mouse,  $k_T$  is 15 mg/mL where free serum concentrations ( $Free \times C_{serum}$ ) would be about 0.3  $\mu$ g/mL with 10 mg/kg in the mouse. So the transporter would not become saturated except at extreme doses. The value used by Andersen et al. (2006) for monkey was 0.00001 mg/mL. Unit specified in Tables 5-5 and 5-7 should be  $\mu$ M, not M.
- Free fraction values measured in vitro are 0.01 or less at low PFOA serum concentrations (Table 3-1). The Free values for rat seem much higher than the measured values.
- $Q_{filc}$  is defined as a fraction of blood flow (renal or cardiac output?) to the filtrate (bottom of p. 5-11) but has units of flow in Table 5-5.
- $V_{filc}$  values are much smaller than the 0.01 L value used by Andersen et al. (2006), although Andersen et al. state that the model output is insensitive to this parameter and that their value was assumed.

**RESPONSE:** Comments are acknowledged. The secondary compartment appeared to be statistically-non identifiable for most species, that is, there were insufficient data available to estimate the volume of the second compartment. However, since the compartment was identifiable for the data-rich CD1 mouse, EPA believes that it is relevant to the PK and so that compartment was included when modeling all species. For those species where the second compartment was uncertain, the quantitative uncertainty about that compartment was propagated to the predictions. The reviewer is correct that the units are misreported for  $Q_{filc}$  – that value is a unitless fraction of the cardiac output. This has been corrected in the HESD.  $Q_{fil}$  has units of L/h but is not reported in the table.

**COMMENT 3:** PFOS Table 5-7, p. 5-15

- Body Weight and Cardiac Output values are reasonable and typical.
- $k_a$  values for female mouse and monkey seem extremely large – see comment above for PFOA.
- $V_{cc}$  values appear reasonable. See comment above for PFOA.
- $k_{12}$  values vary a lot across the columns, suggesting that  $k_{12}$  may be highly correlated with another parameter.
- $R_{v2:v1}$  values appear reasonable and consistent with other reports of  $V_{ss}$  values for PFOS.
- $T_{maxc}$  values are highly variable across the columns and seem much higher than physiological reality would allow. See comment above for PFOA.
- $k_T$  values are physiologically unrealistic and highly variable across columns. See comment above for PFOA.
- Free fraction values have been measured in vitro and are 0.01 or less at low PFOS serum concentrations (Table 3-1, p. 3-3). The Free values in Table 5-7 are consistent with the measured values.
- $Q_{filc}$  is defined as a fraction of blood flow (renal or cardiac output?) to the filtrate (bottom of p. 5-14) but has units of flow in Table 5-7.
- $V_{filc}$  values are much smaller than the 0.01 L value used by Andersen et al. (2006), although Andersen et al. state that the model output is insensitive to this parameter and that their value was assumed.

**RESPONSE:** The reviewer is correct that the units are misreported for  $Q_{filc}$  – that value is a unitless fraction of the cardiac output. This has been corrected in the HESD.  $Q_{fil}$  has units of L/h but is not reported in the table.

**COMMENT 4:** While the parameter values for the pharmacokinetic models predict reasonable serum concentrations that generally agree with measured values (Tables 5-6 – 5-8 for PFOA and Tables 5-8 and 5-10 for PFOS), their high interspecies variability suggest that the models may be unreliable for prediction of internal exposures after other intake regimens and during a depuration phase.

**RESPONSE:** EPA believes that an empirical PK model structure including saturable resorption is appropriate for the female, CD1 mouse, which has been extensively studied with respect to saturable resorption (Lou et al. 2009). EPA's modeling assumes that this structure is appropriate for all animal species that EPA analyzed. There is evidence for this in the scientific literature: Andersen et al. (2006) developed the saturable resorption model structure for monkey, Lou et al. (2009) used it for CD1 mouse, and Loccisano et al. (2011, 2012a) applied a physiologically-based model with a similar saturable resorption term to humans and rats. If this model is applicable across species, then, for those species where some parameters have broad uncertainties, uncertainty in the parameter values reflect the inadequacy of the PK data for that species. EPA believes that differing ranges in parameter certainty are an artifact of the available scientific data and do not reflect variation in the overall mechanics of PFOA/PFOS PK between species. For this reason, EPA made serum predictions using the full range of parameter values consistent with the data for each species. If the uncertain parameters had significant impact on the serum concentration, then species where the parameter values were more uncertain had predictions with wider ranges of uncertainty.

### **Longnecker Comments**

**COMMENT 1:** Please see the answer to the previous question.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **Slitt Comments**

**COMMENT 1:** The parameters included appear to be appropriate, but this lies outside of my area of expertise.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

## Charge Question 8: Volume of Distribution and Half-life Values

The volume of distribution (Vd) and half-life values are critical in the derivation of the interspecies uncertainty factor applied in derivation of candidate RfDs from a NOAEL, LOAEL or a BMDL. The available data for both values are provided in Section 3.5.2 and 3.5.3 of both documents. Please comment the strengths and weaknesses of the values selected.

### Bruckner Comments

#### PFOA-specific Comments

**COMMENT 1:** The adult male rat data of Kemper (2003), from which the rat half-life and clearance (CL) were obtained, appear to be solid. It is reasonable to select the human half-life of 2.3 years reported by Bartell et al. (2010), as their study population included equal numbers of males and females. Division of the rat CL by the human CL to yield a value of 219 is fine. I did not examine the publication of Bartell et al. (2010) to evaluate their data or methodology used to derive a human half-life of 2.3 years. Therefore, I am uncertain about its accuracy.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

#### PFOS-specific Comments

**COMMENT 2:** I would again defer to someone with more expertise.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### Cory-Slechta Comments

**COMMENT 1:** This falls outside my area of expertise and therefore no significant comments are provided. However, at the face-to-face meeting there was significant discussion regarding the modeling, including clarifications from Dr. Wambaugh that were found by those panel members with expertise to clarify these issues and these particular issues were considered adequately addressed.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### DeWitt Comments

**COMMENT 1:** While the overview of the individual studies that calculated Vd and half-life for each compound was detailed and complete, the rationale and analysis concerning *why* particular values were selected were insufficient. Additionally, as addressed in Charge Question 6, the rate of clearance/elimination likely contributes to the differences in half-life that are not associated with differences in the Vd. Therefore, a 3-fold uncertainty factor for species differences in pharmacodynamics (UF<sub>A</sub>) was utilized for both compounds. What was the justification for using a UF<sub>A</sub> of 3? The section on UF application needs a more thorough discussion regarding the choice of this value given differences in clearance. If the section on model adjustment (a suggestion in Charge Question 6) is better described, this comment may no longer be applicable.

**RESPONSE:** Sections 2.6.2 and 2.6.3 for PFOA and 2.5.2 and 2.5.3 for PFOS of the HESDs provide the available data on half-life and volume of distribution. In some cases there is only one option for a value such as the human half-life for PFOS. In cases where there was more than one option the reason for the one used is identified. The animal half-lives that were used in the derivation of UF<sub>A</sub> in the peer review draft that



presented a comparison between the derivation of potential RfDs using a clearance ratio between humans and animals to quantify UF<sub>A</sub> were removed based on peer reviewer recommendations that supported the toxicokinetic model average serum approach over the clearance ratio approach.

The interspecies UF represents differences between animals and humans with regard to toxicokinetics and toxicodynamics. In cases where the POD for RfD quantification is the product of toxicokinetic modeling, the toxicokinetic portion of the interspecies UF is not applied. In the absence of data regarding toxicodynamic differences between species the toxicodynamic portion of the UF is retained. The toxicodynamic factor accounts for differences in the way the chemical interacts with tissues in the animals versus humans. The UF applied to account for toxicodynamics in such circumstances is 3 (see section 4.4.5.3 in EPA's document *A Review of the Reference Dose Reference Concentrations Processes*).<sup>8</sup>

## Fisher Comments

**COMMENT 1:** The use of this non-compartmental method should be justified. Why not use a PBPK model? Assuming steady state in the humans does allow for calculation of a human equivalent serum concentration associated with a laboratory animal concentration. In what region of the exposure-dose range would nonlinearity occur in humans? Some type of discussion is needed about the assumptions of this methodology and why it was used. I would like to see statements about if the NOAEL, LOAEL, and a BMDL doses are in the linear range for kinetics.

**RESPONSE:** The non-linear PK of PFOA/PFOS leads to more rapid clearance at high doses in lab animals. More rapid clearance would lead to lower plasma concentrations for the same exposure. The only PK information directly measured for humans is the serum half-life. The only available PBPK models do not have the ability to correctly predict the human serum half-life when extrapolated to humans. Thus, there is no way to confirm that any available PBPK model accurately reflects any non-linearities that might occur in humans. It appears prudent to take a more parsimonious approach, and use a one compartment PK model in which an estimated volume of distribution that is largely consistent with the animal data and a measured elimination rate are the only two parameters.

**COMMENT 2:** The authors should use the Bayesian analysis for animal studies to inform the UF. Use percentiles to explore Vd and half-life to support UF values. I did not see any attempt to use distribution information generated from the model beyond the central tendency or mean values. Please state why this is the case. It seems that the distribution information generated from the Bayesian analysis could be used to support UF development.

**RESPONSE:** The specifics on how to replace uncertainty factors with Bayesian analysis are a matter of ongoing discussion for all chemicals, not just PFOA and PFOS. Since there are no agreed upon guidelines for the new approach recommended by the peer reviewer, EPA used the current Agency approach for determining UF in this assessment.

## Hayton Comments

### PFOA-specific Comments

**COMMENT 1:** For male rat, the Kemper (2003) study appears to be the best source of pharmacokinetic parameter values, which were obtained by a model-independent analysis of serum concentration-time data from rats that were dosed by oral gavage at dosages of 0.1, 1.0, 5.0 and 25 mg/kg. In addition, there was a 1.0 mg/kg dosage administered intravenously, and a 0.1 mg/kg oral gavage dose with an extended sampling

---

<sup>8</sup> <https://www.epa.gov/sites/production/files/2014-12/documents/rfd-final.pdf>

time. Each treatment used four animals. The CL and  $t_{1/2}$  values appeared to be independent of dosage and route of administration. It would therefore be reasonable to average all 6 mean values for each parameter to give an over-all mean of 24 determinations. The average ( $n=24$ ) values for male rat were CL = 0.0209 L/kg/d and  $t_{1/2}$  = 7.83 d. These values can be used to calculate a  $V_d$  value ( $t_{1/2} \times \text{CL} / \ln 2$ ), which is 0.236 L/kg.

**RESPONSE:** The Kemper (2003) data were used in the PFOA model of the Sprague-Dawley rat. Comment is acknowledged; no formal response or action is necessary.

**COMMENT 2:** It is not apparent on p. 5-20 why a  $V_d$  value of 0.17 was used with half-life to calculate  $\text{CL}_{\text{rat}}$  when Kemper (2003) reported CL values and not  $t_{1/2}$  values. (At the peer review meeting, it was clarified that the data of Kemper (2003) were re-analyzed and as a result the parameter values in the health effects documents differ somewhat from those published with the data in the original reports.)

**RESPONSE:** The HESDs were revised to further emphasize that all data were reanalyzed using a single model by Wambaugh et al. (2013), and that these new parameter estimates were used for comparing across toxicological studies.

**COMMENT 3:** The  $\text{CL}_{\text{human}}$  value was taken to be 0.00014 L/kg/d. There are no direct measurements of this parameter. Thompson et al. (2010) assumed that the intake rate of PFOA for subjects using PFOA-contaminated water was 91% of the PFOA in 1.4 L/d of water. This intake rate was used along with a PFOA half-life of 2.3 years to calculate a  $V_d$  value of 0.17 L/kg. This is the same value that was used in the health effects document for the rat (p. 5-20). The  $V_d$  values available in mouse, rat and monkey are about 0.2 L/kg, so the  $V_{d,\text{human}}$  set at 0.17 L/kg is not unreasonable but it lacks the certainty of the rat  $V_d$  value.

**RESPONSE:** Since volume of distribution is best determined experimentally, using known, controlled doses, human data would be required to attain the accuracy of the estimates for animal species. No such published human data are currently available. In silico methods for predicting volume of distribution have not yet been developed for perfluorinated compounds.

**COMMENT 4:** The health effects document used a  $t_{1/2}$  for PFOA in human of 839.5 d (2.3 years), which seems to be toward the low end of the range of values that have been reported. Along with  $V_d = 0.17$  L/kg one arrives at  $\text{CL}_{\text{human}} = \ln 2 \times 0.17 / 839.5 = 0.00014$  L/kg/d.

**RESPONSE:** The Bartell et al. (2010) half-life represents an estimate corresponding to the U.S. general population rather than the occupational populations as reported in studies, such as Olsen et al. (2007). It was derived using the declines in serum values among members of a highly exposed population following a change in residence that lowered the ongoing exposures. The Health Advisory guidelines apply to members of the general population exposed to a chemical through their drinking water. Accordingly, the Bartell et al. (2010) estimate was used rather than one based on occupationally exposed cohorts. The recent NHANES data demonstrate that serum levels are declining among the general population. This strengthens the decision to utilize the Bartell et al. (2010) half-life.

**COMMENT 5:** The ratio  $\text{CL}_{\text{rat}} / \text{CL}_{\text{human}}$  calculated using the mean  $\text{CL}_{\text{rat}}$  from Kemper (2003) would be  $0.0209 / 0.00014 = 149$ , which is about twice the value calculated on p. 5-21. This difference arises from the calculation of  $\text{CL}_{\text{rat}}$  using the  $V_{d,\text{human}}$  and a half life of 11.5 d instead of using the  $\text{CL}_{\text{rat}}$  directly from Kemper (2003). The mean half life from Kemper (2003) was 7.8 d.

**RESPONSE:** The Kemper (2003) study used a non-compartmental analysis of PK. A reanalysis of this data was done by Wambaugh et al. (2013) using a consistent PK model for all species that included a saturable resorption mechanism, which results in CL changing with concentration in blood.

**COMMENT 6:** The  $CL_{\text{mouse}} / CL_{\text{human}}$  ratio is accurate, using Lou et al. (2009) data. A calculation for monkey is not shown.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### PFOS-specific Comments

**COMMENT 7:** Chang et al. (2012) appears to be the best source of pharmacokinetic parameter values for mouse, rat and monkey. Butenhoff and Chang (2007) is given as the reference for a 48-day half-life in rat; this is a final report, internal to 3M. The Chang paper gives half-life values for male and female Sprague-Dawley rat at 2 mg/kg and 15 mg/kg. The average  $V_d$  for the four groups of three/group was 0.71 L/kg. This is higher than the 0.23 L/kg value used in the draft document (p. 5-23). The 0.71 L/kg value is also higher than values for mouse, monkey and human, which are closer to the 0.23 L/kg value used in the draft document. The draft document ought to acknowledge this difference; it may be that the value in the 3M report is lower than the published value; Chang was a co-author for both sources. The Chang et al. (2012) paper gives  $CL_{\text{rat}}$  values that are 0.0051 L/h/kg for female (similar for 2 and 15 mg/kg doses) and for males, 0.022 and 0.011 L/h/kg for the 2 and 15 mg/kg doses. A single average value for  $CL_{\text{rat}}$  would be 0.011 L/h/kg, about 3 times the value used for the  $UF_A$  calculation in the draft document. The male value is about 2-3 times the female value and it may be appropriate to calculate a different  $UF_A$  value for each sex. Using the single  $CL_{\text{rat}}$  averaged across two doses and both sexes (0.011 L/H/kg) would give a  $CL_{\text{rat}} / CL_{\text{human}}$  ratio of  $0.011 / 0.000081 = 135$  and a  $UF_A = 407$ , substantially higher than the value of 123 in Table 5-15.

**RESPONSE:** With respect to volume of distribution, EPA's reanalysis of the Chang et al. (2012) data suggest a range of primary compartment volumes of distribution between 0.264 – 0.637 L/kg across species. For the male Sprague-Dawley rat, EPA estimates a volume of distribution of 0.637 (95% credible interval 0.593–0.68) L/kg, and 0.535 (0.49–0.581) L/kg for female. These values are not that dissimilar from the original Chang analysis that did not account for non-linear PK. Further, EPA notes that in EPA's analysis the volume of distribution for monkeys is 0.303 L/kg, which is closer to the value of 0.23 L/kg that Thompson et al. (2010) inferred for humans and was used for EPA's extrapolation to humans.

With respect to clearance EPA is unsure why the reviewer believes that a "value for  $CL_{\text{rat}}$  would be 0.011 L/h/kg, about 3 times the value used for the  $UF_A$  calculation in the draft document." Because the extrapolation was made on the basis of toxicological study serum concentration to human serum concentration, the animal clearances, including differences between male and female rats, did not factor into the  $UF_A$  calculation. A  $UF_A = 3$  was used to account for pharmacodynamics differences. The only clearance used for determining the RFD was 0.000081 L/kg bw/day, as derived from the Olsen et al. (2007) half-life of 5.4 years and the volume of distribution inferred by Thompson et al. (2010).

**COMMENT 8:** The  $UF_A$  values calculated for mouse and monkey appear to be in line with the literature values for PFOS  $CL$  values in these species.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### Longnecker Comments

**COMMENT 1:** The PBPK model of Loccisano et al. 2013 (for humans) can be used to calculate a volume of distribution for PFOA of 177 ml/kg, which is very close to the value of 170 ml/kg based on Thompson et al.'s 2010 one-compartment model. For PFOS, the corresponding value from the PBPK is 280 ml/kg, compared with the value of 230 ml/kg used in the Health Effects Document. This 22% difference could have an impact on some calculations. (Note: the PBPK model-based volumes of distribution were calculated by Marc-Andre Verner of the University of Montreal. He had calculated these values in the course of a separate project.)

**RESPONSE:** A volume of distribution can be calculated using a PBPK model by summing the tissue volumes weighted by the partition coefficients, as in Verner et al. (2015, EHP) which used the Loccisano et al. (2011, 2012a, 2012b, 2013) PBPK models. For PFOA, the Loccisano et al. (2011, 2012a, 2012b, 2013) model partition coefficients are derived from a single dose rat study (Kemper 2003) for which the tissue data is unpublished. The serum data from Kemper (2003) was shown by Wambaugh et al. (2013) to have been collected at doses too low to explore saturable resorption or other non-linear aspects of the pharmacokinetics. For PFOS partition coefficients, Loccisano et al. (2011, 2012a, 2012b, 2013) used data from male C57Bl/6 mice, which is similarly unpublished and was not available for analysis by Wambaugh et al. (2013). The PFOS data is referenced as DePierre (2009) through personal communication to authors (Loccisano et al. 2012a). Since the Thompson et al. (2010) volume of distribution was estimated for humans, while the Loccisano et al. (2011, 2012a, 2012b, 2013) model value is derived from unpublished data for rats and mice, EPA concluded that the values are consistent but that the choice of the human-derived value is more relevant. EPA further notes that Verner et al. (2015) used “volumes of distribution of 170 mL/kg of body weight for PFOA and 230 mL/kg of body weight for PFOS as estimated by Thompson et al. (2010).”

**COMMENT 2:** For humans, the half-life data all depend on the assumption that ongoing exposure is negligible compared to baseline exposure, a reasonable assumption in most of the populations used to estimate half-life. While the Seals et al. (2011) gave estimates that were slightly different for PFOA in some cases, the methods employed in this study were not as strong as for Bartell et al. (2010) or the Burris et al. studies (2000; 2002). The agreement within species for the half-life estimates for PFOS are reassuring. The animal data on the half-life of PFOA are relatively sparse (2 rat studies that agreed reasonably well, 1 mouse study, 1 monkey study). For PFOA, the UFAs and RfD that were calculated based on the half-lives (expressed as clearance) would not have been substantially altered by alternate choices for specific values. The same is true for PFOS.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### Slitt Comments

**COMMENT 1:** Strengths of the available data is that for the several species thorough evaluated, the half-life values are very consistent. For example, the several human studies cited report a range in calculated PFOS half-life in humans to be 4.1-8.67 years, two studies putting monkeys at 110-132 days, and rat generally has a narrow range with 3 out of 4 values provided ranging from 39.8-48.2 days for PFOS. An inconsistency is the Chang et al., 2012 describing a half-life of females of 66.7 days when in general female rodents may have faster elimination of PFOS.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

## **Charge Question 9: Candidate RfDs**

**A variety of endpoints and studies were used to compare points of departure and the resultant RfDs for both PFOA and PFOS. In addition, comparisons were provided across RfD outcomes based on the model outputs compared to those for the NOAEL, LOAEL and BMDL points of departure. The range of candidate RfDs derived from the different points of departure is fairly narrow. Please comment on the strengths, weaknesses and transparency of this analysis.**

## **Bruckner Comments**

### **PFOA-specific Comments**

**COMMENT 1:** The procedure used to calculate PODs adheres to standard EPA guidelines and policy. The presentation of their derivation is clear, concise and transparent. It is certainly interesting that the range of PODs and resulting candidate RfDs is so narrow. Nevertheless, as discussed previously, I do not agree with their selection.

**RESPONSE:** Dr. Bruckner's objection to the selection of the candidate RfDs applied to the original selection of increased liver weight and hypertrophy as the critical effects for some of the studies quantified in the draft health effects documents. EPA subsequently followed the recommendations of the peer review panel in revising the HESDs and only used liver effects that were characterized by Hall et al. (2012) as adverse when identifying the LOAEL in those studies. In cases where liver effects are nonadverse, but accompanied the adverse effects, they are listed along with the adverse effect in the summary of effects for the LOAEL dose (Tables 4-1 and 4-2).

### **PFOS-specific Comments**

**COMMENT 2:** See my comments under General Impressions.

**RESPONSE:** See previous response to comments.

## **Cory-Slechta Comments**

**COMMENT 1:** While it is the case for both PFOA and PFOS that values from different points of departure are fairly narrow, the transparency of the analyses in neither case is clear. There is no rationale described even as to why these analyses were done on all of the studies, what was the primary study and how others related to that etc., i.e., this presentation does not follow the typical presentation format of IRIS documents in either its presentation of rationales and strategies, nor in the conclusions that it reaches. In both cases, it is only the single sentence indicating that modeling from one particular study will be protective of effects at other studies using higher exposures. This section in both documents needs introductory paragraphs that describe the specific strategy, choices of studies and the rationales for those choices.

**RESPONSE:** For both final HESDs, EPA added text describing the studies chosen for modeling and selection of the RfD. The studies selected as key for quantification were generally well-conducted studies, evaluating a duration of  $\geq 7$  weeks for those other than the developmental studies and the DeWitt et al. (2009) immunological study, use of a control, employing a range of doses and sample sizes large enough for detecting statistical differences, and with serum data amenable for modeling that showed the most sensitive effects following exposure to PFOA and PFOS. Additionally, the doses associated with LOAELs for the identified critical endpoints were not associated with clinical signs of overt toxicity in the animal models and nearly all of the studies measured serum and/or tissue concentrations of the parent compounds.

**COMMENT 2:** As noted in response to Charge Question 3, the rationale for discarding the human epidemiological studies is not sufficient and requires rationale other than that stated and therefore, the question of using the human data remains open. As noted in response to Charge Question 1, in this reviewer's opinion, the increased liver weight can be justified as a departure point for assessment of RfDs, but as discussed at the face-to-face meeting, additional text supporting this choice is needed.

**RESPONSE:** EPA utilized the human epidemiology studies as a line of evidence in this assessment, including a discussion of strengths and weaknesses of the human epidemiology data and strengths of the animal studies relevant to quantitation. Also, EPA followed the recommendations of the peer review panel in revising the HESDs and only used liver effects that were characterized by Hall et al. (2012) as adverse when identifying the LOAEL in those studies. In cases where liver effects are nonadverse, but accompanied the adverse effects, they are listed along with the adverse effect in the summary of effects for the LOAEL dose (Tables 4-1 and 4-2).

### DeWitt Comments

**COMMENT 1:** This particular section contained inadequate detail on why particular studies were or were not chosen. For example, immunotoxicity as an endpoint was not chosen for PFOS, based on "in vitro measures of immunocompetence on mice may not be relevant to the human experience and limited human data from epidemiology studies are inconclusive regarding the immunotoxicity of PFOS in humans"; however, the breadth of data from in vitro/ex vivo immunotoxicity studies for PFOS were not thoroughly discussed (please see Charge Question #2 for two additional in vitro studies).

**RESPONSE:** The synthesis and evaluation section of both documents was revised to better integrate the human and animal findings suggestive of immunotoxicity. Discussion and presentation of the in vitro/ex vivo studies was expanded.

**COMMENT 2:** For both compounds, an increase in absolute liver weight was selected as an endpoint as it was a common effect [sic] in both short and long term studies. However, the toxicological relevance of an increase in absolute liver weight was not discussed other than to indicate that it was a sign of altered homeostasis. Further, the co-occurrence of increases in absolute liver weight with other toxicologically-relevant endpoints (i.e., immunotoxicity and/or reproductive/developmental toxicity) is not a toxicologically valid justification for the use of liver weight as an endpoint for an RfD. Therefore, the analysis was not sufficiently transparent to deduce its relative strengths and weaknesses. Certainly, choosing an endpoint that occurs across species and occurs at relatively low doses will likely be protective of exposed humans; however, will it be a defensible endpoint? As currently written, the choice of this endpoint for an RfD is not adequately defended.

**RESPONSE:** EPA reevaluated the outcomes related to PFOA exposure based on peer review comments, and selected an endpoint that reflects adverse effects in the developing fetus and newborn as the most sensitive endpoint to serve as the basis for the derivation of the RfD. The POD for both PFOA and PFOS was altered so that liver weight alone is no longer the endpoint of concern. Increased liver weight is acknowledged as a common finding but not considered adverse in the absence of other effects as defined by Hall et al. (2012). EPA reevaluated all studies reporting presence of increased liver weight for other adverse effects using the Hall criteria. The RfD for PFOA is based on reduced ossification in males and females and accelerated puberty in males (Lau et al. 2006). The RfD for PFOS is based on decreased pup body weight (Luebker et al. 2005b) in rats over two generations.

## Fisher Comments

**COMMENT 1:** I did not review the toxicity data.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

## Hayton Comments

**COMMENT 1:** For PFOA, a 10% increase in liver weight was selected as the metric for effect, which was "... not made based on toxicity but on the desire to find a common denominator against which to evaluate dose-response across studies and justified by the fact that other adverse effects accompanied the LOAEL for increased liver weight in some cases." The lowest serum concentration associated with an increase in liver weight was calculated for female mouse to be 20.33 mg/L (p. 5-16, PFOA document). These data are referenced to DeWitt (2008); this paper has only summary information on liver weights, all of which exceeded 20% weight gain, going as high as 70%; and it is not apparent in PFOA document how these liver weight gains were used to estimate an LOAEL for 10% liver weight gain.

**RESPONSE:** EPA has re-evaluated the outcomes related to PFOA exposure based on peer review comments, and selected an endpoint that reflects adverse effects in the developing fetus and newborn as the most sensitive endpoint to serve as the basis for the derivation of the RfD. The PODs for both PFOA and PFOS were altered so that liver weight alone is no longer the endpoint of concern. Increased liver weight is acknowledged as a common finding but not considered adverse in the absence of other effects as defined by Hall et al. (2012). EPA reevaluated all studies reporting presence of increased liver weight for other adverse effects using the Hall criteria. The RfD for PFOA is based on reduced ossification in males and females and accelerated puberty in males (Lau et al. 2006). The RfD for PFOS is based on decreased pup body weight (Luebker et al. 2005b) in rats over two generations.

**COMMENT 2:** Many of the animal studies of hazard assessment were conducted under conditions where the duration of the exposure was relatively short compared with the half-life, and steady state had not been achieved. It is not apparent how the NOAEL and LOAEL values from such studies were adjusted to account for the non-steady state situation. For example, the 20.33 mg/L PFOA concentration associated with a 10% increase in liver weight (Table 5-9) emanated from a 15 day drinking water exposure to 0.94 mg/kg/day that resulted in an average serum exposure of 20.33 mg/L (0 – 29.7 mg/L over 15 d, Tables 5-7, 5-9). For a fixed daily dose, the time to 90% steady state for mouse would be about 63 days (3.3 x half life, which was 19 days), and after 15 days the serum concentration would only be about 15% of its steady-state value. This seems to suggest that the RfD would have been over-estimated by a factor of 7, since the 0.94 mg/kg/day at steady state would have produced a serum concentration of about 150 mg/L, not 20.33 mg/L. This analysis is based upon the behavior expected from one-compartment model pharmacokinetics. As discussed on p.5-9 of the PFOA document, the steady-state serum concentration of PFOA is achieved in a much shorter time than one-compartment model kinetics would predict. Whether the target-site steady-state concentration of PFOA also occurs in a much shorter time than one-compartment model kinetics would predict (3.3 x half-life) is apparently unknown.

**RESPONSE:** Lou et al. (2009) demonstrated that the serum concentration of PFOA does reach steady-state faster than 3.3 x half-life. The Andersen et al. (2006) saturable resorption mechanism for PK hypothesizes that the half-life depends upon the concentration of PFOA or PFOS in the kidney filtrate. The clearance is therefore not constant: at low concentrations the chemical is readily resorbed back into the body leading to a long-half-life, while at higher concentrations (more typically generated by animal studies) the half-life is actually shorter. This leads to a rapid approach to steady-state as the result of high dose regimens, followed by a longer half-life for chemical elimination. For this reason the RfD would not be an overestimation because the approach to steady-state for PFOA and PFOS is more rapid than would be calculated using half-lives.

EPA added a table comparing the average serum concentration to an estimate of steady-state for each endpoint used to determine the RfD. In the case of the DeWitt et al. (2008) study referred to by the reviewer, the LOAEL of 3.75 mg/kg/day was estimated to produce a serum concentration that was ~74% of steady-state in 15 days.

### **Longnecker Comments**

**COMMENT 1:** This part of the document seemed especially strong and transparent. The agreement between methods was reassuring. The weaknesses and assumptions were well discussed. Please see the minor editorial comment on this issue given for Charge Question 1, above.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

### **Slitt Comments**

**COMMENT 1:** The RfD Point of Departure was based on animal studies that include monkey and rat.

**RESPONSE:** In the revisions to the document, the data from the monkeys for PFOS and PFOA were modeled and average serum levels were determined. However, in neither case was the study considered as a candidate RfD. In the case of PFOS, the effect level was the highest dose and associated with the deaths of some of the animals. In the case of PFOA the high dose was adjusted part way through the study because of frank toxicity. In both cases the number of monkeys per sex were low ( $\leq 6$ ) and the liver effects that were quantified in the peer review draft did not qualify as adverse under the Hall et al. (2012) criteria.



## **Charge Question 10: Duration**

**The RfDs for PFOS and PFOA are derived from the modeled steady state serum concentrations and their association with effects that include short term and longer term exposures with associated diverse effects. The studies considered included effects due to exposure durations that ranged from 11 to 182 days, and occur at comparable human equivalent dose (HED) levels. The current, draft RfDs do not include an uncertainty factor for study duration because of the apparent concordance HEDs despite duration differences. Given this pattern of response, is it appropriate to conclude that the candidate RfDs are applicable to both short-term and lifetime exposures?**

## **Bruckner Comments**

### **PFOA-specific Comments**

**COMMENT 1:** I do not believe it is appropriate to conclude that the candidate RfDs are applicable to both short-term and lifetime exposures. Steady-state is apparently achieved in monkeys within 4 - 6 weeks (Butenhoff et al., 2002). Steady-state likely takes considerably longer in humans. Thus, RfDs for shorter periods of exposure should be based upon results of studies of similar duration.

**RESPONSE:** The selected RfDs for PFOA and PFOS were revised based on peer review comments and now are based on developmental effects on the developing fetus and offspring resulting from exposures that occur during gestation and lactation (see section 4.1.2 in the PFOA HESD and 4.1.1 in the PFOS HESD). 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 a number of various stages in development, a single exposure at a critical time in development can produce an adverse effect (USEPA 1991). Additionally, PFOA and PFOS are 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 effects identified for both PFOA and PFOS are developmental endpoints and can potentially result from a short term exposure during a critical period of development, the lifetime drinking water health advisories are applicable to both chronic and short-term risk assessment scenarios; e.g., weeks to months, including during pregnancy and lactation.

### **PFOS-specific Comments**

**COMMENT 2:** I do not believe the candidate RfDs, as calculated, are applicable to different durations of exposure.

**RESPONSE:** Peer reviewers were in agreement that the serum values in some of the studies were not at steady state. As a result, the percent of steady state was determined for each of the modeled serum values using the Wambaugh et al. 2013 model, and considered during the application of uncertainty factors for a duration adjustment. For PFOA, EPA added a duration adjustment of 10 to DeWitt et al. (2008) because the study was a 15 day study for an immunological effects that could occur across more than once across a lifetime exposure. In the case of PFOS an uncertainty factor to address duration was not applied to Seacat et al. (2003) because there were chronic exposure data for the same endpoint (Thomford 2002/Butenhoff et al. 2012) that demonstrated that the serum levels had decreased to 50%. Thus, protecting for the exposure that was associated with the subchronic exposure that lead to a higher serum level would protect the lower serum levels observed later in life. The dietary dose associated with the LOAEL was the same for both studies. An

uncertainty factor of 1 was used for the Luebker (2005a, 2005b) because EPA did not use one for an exposure associated with a sensitive life stage.

### **Cory-Slechta Comments**

**COMMENT 1:** While initially believing that it was appropriate conclusion for PFOA and PFOS, based on the correspondences in RfDs across short and longer term exposure, discussion at the face-to-face meeting made clear that this approach is not reasonable and requires additional consideration.

**RESPONSE:** The final RfDs for PFOA and PFOS were revised based on peer review comments and now are based on developmental effects on the developing fetus resulting from exposures that occur during gestation and lactation (see section 4.1.2 in the PFOA HESD and 4.1.1 in the PFOS HESD). 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. Consistent with EPA policy, 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 (USEPA 1991). Because the developing organism is changing rapidly and is vulnerable at a number of various stages in development, a single exposure at a critical time in development can produce an adverse effect (USEPA 1991). Additionally, PFOA and PFOS are 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 effects identified for both PFOA and PFOS are developmental endpoints and can potentially result from a short term exposure during a critical period of development, the lifetime drinking water health advisories are applicable to both chronic and short-term risk assessment scenarios; e.g., weeks to months, including during pregnancy and lactation.

### **DeWitt Comments**

**COMMENT 1:** This approach may be appropriate given the relative similarity of serum concentrations attained regardless of study duration, i.e., steady state in serum is attained after a relatively short period of exposure. This appears to be consistent across studies with various species of animal models. However, the document authors might need to reconsider given what we may or may not know about liver hypertrophy. In the Hall et al. (2012) paper on liver hypertrophy (discussed during the public meeting), increase in liver weight is an adaptive response that may not be adverse UNLESS weight increases >150% over a three month or longer period may. Following this large and prolonged increase in weight, the end result may be a hepatocarcinogenic response. However, none of the studies contained in the documents indicate that longer term exposures increase liver weight to this degree.

**RESPONSE:** EPA adjusted the NOAELs and LOAELs for all the studies in the peer review draft that had used liver weight and hypertrophy as critical effects to correspond to the Hall et al. (2012) criteria for adverse liver effects.

The final RfDs for PFOA and PFOS were revised based on peer review comments and now are based on developmental effects on the developing fetus and offspring resulting from exposures that occur during gestation and lactation (see section 4.1.2 in the PFOA HESD and 4.1.1 in PFOS HESD). 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. Because the developing organism is changing rapidly and is vulnerable at a number of various stages in development, a single exposure at a critical time in development can produce an adverse effect (USEPA 1991). Because the critical effects identified for both PFOA and PFOS are developmental endpoints and can potentially result from a short term exposure during a

critical period of development, the lifetime drinking water health advisories are applicable to both chronic and short-term risk assessment scenarios; e.g., weeks to months, including during pregnancy and lactation.

### Fisher Comments

**COMMENT 1:** The departure from  $K=CXT$  (Haber's law) should be based on the toxicity endpoints of concern and what is known about dose-exposure kinetics/responses for these chemicals and other chemicals that target the same endpoint, not that the HED values are comparable. The NAS AEGL committee only considered primary irritation for inhaled chemicals as an endpoint that was independent of duration of exposure. There is an SOP if needed for reference.

**RESPONSE:** EPA's statement that the HEDs were consistent across studies is equivalent to saying that the average serum concentrations were equivalent across studies. Haber's law relates effect to the product of concentration and duration. For the HEDs, EPA considered state conditions, determining the human dose that would produce a steady-state serum concentration equivalent to the average serum concentration in each study. In other words, EPA calculated an HED that is expected to produce human serum concentrations equal to the concentrations that the modeling has predicted to consistently produce adverse effects in toxicological studies.

**COMMENT 2:** The time to steady state should be included in a table for the lab animals. Toxicity studies conducted for less than 30 days (perhaps?) are not at steady state for the pharmacokinetics of PFOA. Thus the measured serum levels would be different than at steady state. The shorter the duration of the toxicity test, the more impact this could have on extrapolation to chronic exposures in humans. My personal preference would be to use PBPK models for all species and consider only long term exposures for extrapolation to humans.

**RESPONSE:** In response to peer review comments, EPA calculated the fraction of steady-state achieved for all the studies used for extrapolation to human chronic exposures and included this as an additional table. Because the PK of PFOS is believed to be non-linear, there is no unique value for the time to steady-state for a species. The time to steady-state depends on the dose regimen (e.g., magnitude and spacing of doses). Under the assumption of constant infusion dosing, an analytic solution exists for the Andersen et al. (2006) model that allows the steady-state concentration to be predicted for a given dose rate. The average serum concentration during a given study were compared to steady-state, indicating that for most studies the average serum concentration was between 36–96% (mean 75%) for PFOA and 9–69% (mean 31%) for PFOS of the ideal steady-state. Thus, for PFOA, the toxicity studies appear to be appropriate for informing steady-state human conditions. The studies that have  $C_{ss}$  values less than 80% are mostly developmental studies that represent a sensitive life stage where effects occur at serum concentrations well below the predicted steady state concentration yet have lifetime consequences. That is the situation for most of the studies that were quantified for PFOS.

### Hayton Comments

**COMMENT 1:** This depends in part on how quickly the PFOA/PFOS concentrations at sites of toxicity come to steady state. Since the  $V_d$  for these chemicals is small ( $\sim 0.3$  L/kg) it seems likely that the concentrations in tissues rise in pseudo equilibrium with the rise in serum concentration. That said, the half-lives are relatively long due to the very small clearance ( $t_{1/2} = \ln 2 \times V_d / CL$ ). If one-compartment kinetics apply, then a guideline for time to 90% steady state is  $3.3 t_{1/2}$ . For studies that expose animals for a period of time shorter than  $3.3 t_{1/2}$ , the serum concentration would not be at steady state and the internal systemic exposure (serum concentration) would be less than what it would be if the exposure were longer than  $3.3 t_{1/2}$ . This effect would seem to lead to overestimation of the intake rate that was associated with a particular internal exposure and associated biological endpoint. For example, the  $t_{1/2}$  of PFOS in mouse is about 36

days and  $3.3 t_{1/2}$  is 120 days. Consider a 28-day exposure using a fixed daily dose that produced an LOAEL of “X” mg/kg/day. On Day 28, the body level would only be 42% of the steady state level, and the average body level over the 28-day period would be about 21% (approximating the increase as linear and not exponential). The true LOAEL would be 0.21 “X” mg/kg/day; i.e., intake of 0.21 “X” mg/kg/day would produce a body level at steady state that was the same as the average body level produced by X mg/kg/day administered over 28 days. The time to 90% steady state for a fixed intake rate is quite long; from the literature in the health effects documents, the times in the following table were calculated. From this line of reasoning, exposure times less than two half-lives begin to significantly overestimate intake rates associated with particular endpoints. This analysis is based upon the behavior expected from one-compartment model pharmacokinetics. As discussed on p.5-9 of the PFOA document, the steady-state serum concentration of PFOA is achieved in a much shorter time than one-compartment model kinetics would predict. Whether the target-site steady-state concentration of PFOA also occurs in a much shorter time than one-compartment model kinetics would predict ( $3.3 \times$  half life) is apparently unknown.

Species	CL		Vd		$t_{1/2}$		Time to 90% steady state	
	[mL/d/kg]		[mL/kg]		[d]		[d]	
	PFOA	PFOS	PFOA	PFOS	PFOA	PFOS	PFOA	PFOS
Mouse	6.6	5	180	265	19	36	63	120
Rat - Male	23	16	273	947	8.4	40	28	92
Rat - Female	776	5.2	150	476	0.13	66	0.43	218
Monkey	6.3	1.4	190	238	27	121	89	400
Human	0.085	0.08	170	230	1378	2000	12.5 yr	18 yr

**RESPONSE:** EPA calculated the fraction of steady-state achieved for all the studies used for extrapolation to human chronic exposures and included this as an additional table. The average serum concentrations during a given study were compared to steady-state, indicating that for most studies the average serum concentration was between 36–96% (mean 75%) for PFOA and 9–69% (mean 31%) for PFOS of the ideal steady-state. See the response to the above question for a full discussion.

However, the final RfDs for PFOA and PFOS are based on developmental effects 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. Because the critical effects identified for both PFOA and PFOS are developmental endpoints and can potentially result from a short term exposure during a critical period of development, the lifetime drinking water health advisories are applicable to both chronic and short-term risk assessment scenarios; e.g., weeks to months, including during pregnancy and lactation.

**COMMENT 2:** In addition, this line of reasoning may be incorrect if the assumption of one-compartment kinetics is incorrect. For multi-compartment models the serum concentration and target organ/tissue could come to their pseudo steady state levels relatively quickly while slowly equilibrating (deep) sites slowly approached steady state. Simulation with PBPK models for PFOS and PFOA may help answer this question.

Associated with the uncertainty introduced by exposures that were shorter than the time to achieve steady-state concentration at the target site is the exposure time required for the adverse effect to be expressed. While some adverse effects may occur immediately and directly in proportion to the concentration of PFOA or PFOS at the target site, other adverse effects may be slow to become manifest. These “indirect adverse response” behaviors are well known in the drug action arena; e.g., certain antidepressant drugs require several weeks of exposure to the target site before the effect of the drug appears. This lag time is not associated with pharmacokinetics (time to steady state) but with indirect-response pharmacodynamics. It

could be argued that uncertainty factors are needed for both pharmacokinetics (pre-steady state condition) and pharmacodynamics (or toxicodynamics) to account for possible indirect response behavior.

**RESPONSE:** Because the PK of PFOS is believed to be non-linear, there is no unique value for the time to steady-state for a species. The time to steady-state depends on the dose regimen (e.g., magnitude and spacing of doses). The average serum concentrations during a given study were compared to steady-state, indicating that for most studies the average serum concentration was between 36–96% (mean 75%) for PFOA and 9–69% (mean 31%) for PFOS of the ideal steady-state. EPA calculated the fraction of steady-state achieved for all the studies used for extrapolation to human chronic exposures and included this as an additional table. See the response to the Fisher’s comment above for a full discussion.

### Longnecker Comments

**COMMENT 1:** EPA might want to consider using an uncertainty factor for duration, for two reasons. First, the monkey data for PFOS used for the point of departure were from a study where the duration of exposure was relatively short-term relative to the half-life, and it appeared that duration of dose affected liver and other adverse outcomes detected at higher doses, and no monkey data were used in the POD for PFOA. Second, questions raised by Drs. Hayton and Fisher at the peer-review meeting made me less comfortable with the calculations that used average serum concentration derived from the AUC and duration of dosing to compare with humans, who are more likely to be near steady-state.

**RESPONSE:** The monkey studies are no longer used for the quantification of the RfD. In the case of PFOS, the effect level was the highest dose and associated with the deaths of some of the animals. In the case of PFOA the high dose was adjusted part way through the study because of frank toxicity. In both cases the number of monkeys per sex were low ( $\leq 6$ ) and the liver effects that were quantified in the peer review draft did not qualify as adverse under the Hall et al. (2012) criteria. EPA no longer considers use of points of departure associated with death of the animals as appropriate for RfD derivation, especially when there are data that identify points of exposure that associated with effects earlier in the spectrum of adversity than death.

### Slitt Comments

**COMMENT 1:** Yes, but this lies outside of my area of expertise.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.

## **Charge Question 11: Interspecies Uncertainty Factor**

**In addition to using the average serum values from animal studies to calculate internal doses for humans, the animal to human extrapolation can be accomplished by dividing animal average serum values by the human to animal clearance ratios to project a human average serum point of departure in units of mg/L serum. Please provide recommendations for applying uncertainty factors to the extrapolated average human serum values to determine serum-based thresholds that are protective for humans. A NOAEL expressed in average human serum units would be useful in interpreting NHANES population monitoring data.**

### **Bruckner Comments**

#### **PFOA-specific Comments**

**COMMENT 1:** No comment.

**RESPONSE:** No response necessary.

#### **PFOS-specific Comments**

**COMMENT 2:** No comment.

**RESPONSE:** No response necessary.

### **Cory-Slechta Comments**

**COMMENT 1:** In initial response to charge questions, I found it difficult to understand specifically what this charge question was asking for a response to: Does this refer to the data in Table 5-10 for PFOA? Wouldn't you include animal to human UF values at the least. Since the data for the studies listed in the Table is not clear as to their duration (columns are needed for this information, or add to the Study box), it is not clear whether a UF for study duration is warranted. It is not clear how sex differences are being accommodated in any of these.

At the face-to-face meeting, however, with some additional input from EPA, it was clear to all that there was no need to do such derivations from animal to human, which could instead be derived directly from the human data and thus presumably this is no longer an issue.

**RESPONSE:** The starting point for derivation of the RfD is an HED derived from the modeled average serum value for the NOAEL and/or LOAEL. The use of a pharmacokinetically-derived HED based from the animal studies reduces the interspecies UF from a 10 to a 3 according to EPA policies. Per the USEPA (2002) report *Review of the Reference Dose and Reference Concentration Processes* the 10-fold intraspecies factor accounts for both toxicokinetics and toxicodynamics (section 4.4.5.3). In the absence of data, each component receives an uncertainty value of  $10^{1/2}$ . The 3-fold UF that was applied for interspecies differences accounts for pharmacodynamics differences between animals and humans.

### **DeWitt Comments**

**COMMENT 1:** Would this approach take into account differences between animal studies that have a defined exposure duration and data from NHANES, where exposure duration is assumed to be continuous (although it may not be), if exposure duration does not appear significantly impact serum concentrations?

Additionally, how would the half-life estimations from the Seals et al. (2011) study, which contained two half-life estimations based on concentration and time, impact this approach?

**RESPONSE:** EPA calculated the fraction of steady-state achieved by the average serum concentration for the animal toxicity studies used to inform the HEDs. For PFOA, the studies are generally close to achieving steady-state, making the comparison to steady-state conditions easily reconcilable. Seals et al. (2011) found that individuals with higher estimated exposures had lower estimated half-lives (high clearance). The difference between the half-lives for higher exposed (2.9 years) and lower exposed (8.5 years) groups was roughly 3-fold. If the longer half-life was used, a lower HED would be estimated because the clearance would have been slower.

Seals et al. (2011) suggested that, if their assumptions were correct, a simple first order elimination model might not be appropriate for PFOA given that the rate of elimination appeared to be influenced by both concentration and time. There was a difference in the clearance for the two locations even though the range of years elapsed since relocation was the same for both communities. The authors identified three potential limitations of their analysis: the cross-sectional design, the assumption that exposure was uniform within a water district, and a potential bias introduced by exclusion of individuals with serum values <15 ng/mL. EPA chose to use the Bartell et al. (2010) half-life derived from the decline in serum values for individuals who had moved away from the C8 high exposure area because they have the closest correlation with the general population members whose exposures are declining due to the phase out of production of PFOA and PFOS.

EPA used the half-life for Bartell et al. (2010) as the one that is most relevant to the general populations because it was derived using the declines in serum values among members of a highly exposed population following a change in residence that lowered the ongoing exposures. The NHANES data demonstrate that serum levels in the U.S. population are also declining.

### Fisher Comments

**COMMENT 1:** Again, is the system linear in the exposure/dose ranges of interest? I would try to determine an UF by exploring a range of predicted human serum levels. Attempt to use 5,50, and 95% for animal serum concentrations with a 5,50, and 95% CL values in the animals and for the human perhaps use two CL values representing a high and low. The idea is to use as much information as you can to determine the possible range of values. This will help guide the selection of uncertainty values.

**RESPONSE:** Unfortunately, the data necessary to inform the linearity of pharmacokinetics in humans are lacking. The affinity for PFOS and PFOA for the relevant transporters and the expression levels of those transporters would need to be included in a model that also included any endogenous substrates for those transporters that have sufficiently high concentration to produce competitive inhibition. These data and models are not yet available. The Seals et al. (2011) study did find preliminary evidence for differing half-lives in humans. There are some data for organic anion transporter (OAT) and organic anion transporting polypeptide (OATp) kinetics from ex vivo studies but a lack of information that applies to other transporters known to function in the kidney.

### Hayton Comments

**COMMENT 1:** This calculation is equivalent to dividing the animal dosage by the CL<sub>human</sub>, assuming that the animal serum concentration is at steady state (C<sub>ss,animal</sub>) maintained by a constant dose rate (DR).

$$C_{ss,animal} / CL_{human} \div CL_{animal} = CL_{animal} * C_{ss,animal} / CL_{human} = DR / CL_{human}$$

This calculation would give the steady-state serum concentration in human that would be produced by the animal dose rate. (I will have to study this to understand the question; the calculation does not make sense to me.)

At the peer review meeting, the aim of this calculation was clarified. Authors desired a way to calculate a steady-state serum concentration ( $C_{ss, human}$ ) that would result from the human equivalent dose rate (HED) administered until steady state. The appropriate calculation would be:

$$C_{ss, human} = HED / CL_{human}$$

**RESPONSE:** In response to Dr. Haydon's suggestions, the percent of steady state ( $\%C_{ss}$ ) was determined for each of the average serum values. The need for the  $UF_s$  was determined based on the percent steady state result. If the  $\%C_{ss}$  was 80% or greater no duration was applied. If the effect was one that could only occur during a sensitive life stage (e.g., pregnancy/lactation) and the serum represented that life stage in the animals, no UF was applied. If the endpoint was one that could occur across the lifetime, a full 10-fold factor for UF was applied unless serum data supported a lower data derived UF.

### Longnecker Comments

**COMMENT 1:** The proposed division by animal clearance ratios does not make sense to me. The average serum values from animal studies is already taking pharmacokinetic variability in blood levels during the observation period into account, and human blood levels will be relatively constant. Thus, it would make sense to directly compare the POD estimated average serum concentrations from animal models to the blood levels in NHANES. With respect to uncertainty factors that would be need consideration for this approach, it seems that  $UF_H$ ,  $UF_L$  (For LOAEL and  $HED_{LOAEL}$ ),  $UF_D$ , and the component of  $UF_A$  that takes pharmacodynamics into account would all still be applicable.

**RESPONSE:** An estimate of human clearance (based upon serum half-life and estimated volume of distribution from epidemiological studies) was used to determine the human dose that would produce a given serum concentration. The extrapolation is necessary to relate serum concentrations to potential exposures (e.g., drinking water concentration). This extrapolation did not involve a ratio between the human and the animal clearance as had been done for the  $UF_A$  in the NOAEL/LOAEL and BMDL derivations in the peer reviewed documents. Derivations derived from those endpoints are not included in the final documents.

The final documents retain the  $UF_A$  for toxicodynamics and apply  $UF_D$  and  $UF_L$  using agency guidelines that recommend a 10-fold factor as a default. There are two places where other than a 10-fold factor was used. In the first situation (Luebker et al. 2005a) a 3-fold factor was applied for the  $UF_L$  because the Luebker et al. (2005b) two-generation study showed that the difference between the NOAEL and LOAEL supported a value of 3. The one-generation Luebker et al. (2005a) study lacked a NOAEL. The model only applied to the toxicokinetic portion of  $UF_A$ . In the second case (Seacat et al. 2002), a  $UF_D$  of one was applied because the serum values measured in the rats that were maintained until the end of their life were half of those values seen at the end of the subchronic duration. As a result, a potential RfD that protected at that early stage would also protect over a lifetime. The chosen RfD is the value from the two-generation Luebker et al. (2005b) study not the one-generation (2005a) study.

### Slitt Comments

**COMMENT 1:** This is outside of my area of expertise.

**RESPONSE:** Comment is acknowledged; no formal response or action is necessary.



## **Charge Question 12: Other Suggestions**

**Please describe any suggestions you have for improving the clarity, organization, and/or transparency of the draft documents.**

### **Bruckner Comments**

#### **PFOA and PFOS-specific Comments**

**COMMENT 1:** See specific observations.

**RESPONSE:** Specific observations are addressed as noted in the following section.

### **Cory-Slechta Comments**

**COMMENT 1:** While the EPA authors are aware of updates in the IRIS process, it might be very helpful to look at some of the new documents coming through that process for guidance as to the levels of critique and evaluation that are now included in these documents. They also include an introductory chapter focused specifically on the literature searches and literature that is included vs. excluded.

**RESPONSE:** A description of the literature search was added as an appendix to the document and the criteria used for selecting papers during development of the documents is included in background section. A second appendix provides a list of the papers recommended by the peer reviewers and those from literature search conducted between August 2014 and December 2015 that were retrieved and evaluated for inclusion in the revised HESDs.

**COMMENT 2:** The Executive summary does not provide sufficient rationale and descriptions to lead a reader through the steps to what is concluded and reads more like an abstract than an Executive Summary. Since this may be the only section read by many reviewers, it is important that it provide a succinct journey through the process. Here again, the new IRIS documents could provide a useful template.

**RESPONSE:** The executive summary in each of the HESDs was revised to reflect changes made to the documents.

**COMMENT 3:** Chapters 3, 4 and 5 could each benefit from an opening paragraph describing what the section's goals are, and integration and conclusion sections at the end that establish the basis for the presentation in Chapter 5. Currently the Hazard Identification studies generally treat all studies as of equal strength/power, which is certainly not the case. These chapters should present that kind of critical and transparent assessment as it ultimately serves as the basis for decisions that are made.

**RESPONSE:** In section 3, an overall summary and conclusions section was added after the human epidemiology section for noncancer and cancer endpoints. Introductory statements were added at the beginning of each major section in the animal study portion of section 3, and the synthesis and evaluation of the combined human and animal studies were revised in response to the comments received. A summary was also added to the section on toxicokinetics.

**COMMENT 4:** The inclusion of sections on in vitro data did not ultimately seem particularly relevant in the outcome for these compounds and could be significantly shortened to add more to Chapter 4 on study strengths and weaknesses. However, where pertinent, it would probably be more useful to break that section up and insert test where it follows an in vivo discussion.

**RESPONSE:** For PFOA and PFOS, there are a large number of published papers on mechanism, some linked to topics with in vivo data and others not linked. There are cases where some of the data are included with the in vivo topic (e.g., neurotoxicity) or when there are both in vivo and in-vitro components of the same study.

**COMMENT 5:** Tables could be considerably improved and made far more useful to the reader for comparative assessments. As of now, they require going back and forth to the text to capture additional details of the studies, e.g., sample sizes, species etc. and could benefit the reader significantly with those additions. For the human assessments, it is equally important to include these details in the chapter as well as a column of study strengths and limitations.

**RESPONSE:** The tables in section 3.1 were completely revised to include more of the data from the published papers. The original tables in the human epidemiology section were expanded to include study type, sample size, and serum levels as recommended by the peer reviewers. They are now in Appendix B.

In the section on quantification, tables that identify each of the studies modeled also identify the species and critical effects for the study, reducing the need to consult earlier portions of the document to find that information.

**COMMENT 6:** While charge questions ask whether the appropriate studies were chosen as key studies, this reviewer does not remember that that term was even used in the documents, certainly no explicit mention was made as to which studies were considered key studies. This would seem to be a section that should be included in Chapter 4 more explicitly. Chapter 5 of both documents, more so PFOA, are confusing as almost all studies are subjected to modeling, for reasons that are never presented in sufficient detail and simply followed by statements that a selected study (not really well presented in Chapter 4 as a selected study) will protect against other adverse effects.

**RESPONSE:** The synthesis section in section 3 is revised. The studies that identified a NOAEL or LOAEL in section 4 are the initial group of key studies. Only a subset of those studies had the serum information needed to pharmacokinetically model dose response. They are the ones that provided the average serum results used in the determination of potential RfDs. The use of serum, rather than dose, permits consideration of the nonlinear toxicokinetics exhibited by both PFOA and PFOS. The study, species, and effects are now given in each of the tables that present the average serum results for the NOAELs and LOAELs, the Human Equivalent Doses, and the PODs for the RfD.

## DeWitt Comments

**COMMENT 1:** The documents lack a critical analysis of differences between findings of epidemiological studies and findings of animal models. As stated in the comments to Charge Question #3, what is particularly valuable about the PFOA/PFOS database is that it is relatively extensive in that it includes data not only from occupationally-exposed humans, but from people highly exposed to environmental concentrations of PFOA/PFOS, and from people in the general population who have detectable concentrations of these compounds.

Critical to this analysis is a discussion of concordance and lack of concordance between human data and animal model data. For example, immunotoxicological findings appear to be consistent between humans and rodent models whereas serum lipids are not. How do these differences impact the overall confidence in the database and derivation of the RfD?

**RESPONSE:** The human epidemiology tables were expanded for each major endpoint to summarize the data for the studies described in the text. An overall summary and conclusion was added at the end of the epidemiology section for the cancer and noncancer endpoints. The epidemiology tables from the peer review

draft were revised to include details on study type, sample size, and serum levels where those data were available. Those tables are now in Appendix B of the final report. Section 3.4 in each of the final HESDs provides a synthesis of the human and animal data (i.e., discussion of concordance and lack of concordance between human data and animal model data) for each of the key effects.

**COMMENT 2:** All of the sections related to the PK models developed by ORD need additional information for clarity and transparency. As written, it is not clear that the PK values presented throughout the document actually represent a reanalysis of existing data from studies that reported serum concentrations. The Wambaugh et al. (2013) study could be referenced to shorten this exercise as this publication provides details on the reanalysis of existing data.

**RESPONSE:** The serum data presented with the description of the studies are the data reported by the authors of the referenced papers for both the epidemiology and animal toxicity studies. They are not a reanalysis of the original data. The revised HESDs provide the details of the data used to develop the toxicokinetic model that identified average serum from the animal data from which to derive the HED published in Wambaugh et al. (2013). Information from other published pharmacokinetic or toxicokinetic models is also provided. As a result, the quantification of dose response in section 4 to arrive at the RfD is much more focused on the application of the model results in obtaining average serum values, the human equivalent dose, and the RfD.

**COMMENT 3:** Justifications for choosing or not choosing particular values or endpoints needs to be more thoroughly detailed throughout both documents, especially for endpoints that appear to occur in both experimental animal models and exposed humans (i.e., thyroid hormone disruption and immunotoxicity).

**RESPONSE:** The dose-response assessment (section 4) of each of the HESDs was substantially revised to improve clarity and justification of EPA's endpoint selection. The studies were selected because of the data they provided, including having dose-response information that identified a NOAEL and LOAEL, or a LOAEL without a NOAEL and for the final document, serum information that could be used to determine the average serum associated with the NOAEL or LOAEL plus consideration of study quality.

Despite the breadth of the available data, the critical effects from studies with dose response fell into five broad categories for both chemicals: those linked to liver, kidney, reproductive/developmental, immunological, and/or neurological effects for both chemicals. Support for the liver, kidney, developmental and immunological effects from the epidemiology data are moderate to strong.

The candidate RfDs that cover the spectrum of critical effects differ by less than an order of magnitude for each chemical. EPA made the choice among the candidate RfDs for each chemical based on the endpoint and the exposure conditions associated with the effect (e.g., a sensitive life stage) as described in both the HESD and the companion Health Advisory documents.

## **Fisher Comments**

**COMMENT 1:** These documents represent an enormous undertaking to describe studies with PFOA and PFOS. Keep the same writing style for reporting studies. This was very good. A synthesis of the most important studies is needed and some statements about why other studies are not used by EPA. It is easy to get lost in the document because of its size, but if there was an analysis or synthesis section for the key toxicity studies and another for PK modeling rationale, it would help readers.

**RESPONSE:** The synthesis part in section 3 and the discussion of relevant studies in section 4 was revised extensively to focus on key studies and better describe why certain ones were chosen for modeling. The effects observed at the LOAEL in the animal studies are included in Tables 4-1 and 4-2 and are carried over to the tables that include the modeling and quantification results so that the reader does not have to refer back

to the earlier summary tables for the species and effects associated with the each average serum, HED, and/or potential RfD entries.

## Hayton Comments

**COMMENT 1:** It would be helpful to use one set of units for test article amount and concentration. The draft documents use ng/mL, µg/mL, µg/L, ppb, ppm, and µM for PFOA/PFOS concentration in water, diet, and serum. It would be more straightforward to use one concentration term, preferably ng/mL, and perhaps µg/mL in addition as necessary. But making comparisons among ng/mL, ppm, and µM is a distraction.

**RESPONSE:** The units reported for the animals studies are those used by the authors. The important variable is the dose which is usually given in units of mg/kg/day. In some cases a paper does not present dose. In those situations, EPA (1988) conventions for converting concentration in drinking water or diet to dose were applied.

**COMMENT 2:** In Section 3 of both documents, it would be helpful to include a summary table of primary pharmacokinetic parameter values for the species included in this section. Tables 3-17 – 3-20 in the PFOS draft document are a good start. In the PFOA document, Table 3-23 lacks CL values, and Tables 3-24 and 3-25 lack  $V_d$  values. For the pharmacokinetic model analyses presented, primary parameters values could be limited to CL,  $V_{dss}$ , and half life (see table in response to question 10). The CL and  $V_{dss}$  values should be normalized to body weight. Where there are multiple models for a species, there should be separate entries for each study. Where there are multiple dosages for a species, there should be separate entries for each dosage. For the PBPK models,  $V_{dss}$  values are not available and therefore should not be included. Such a table would be helpful to show consistency or lack thereof among studies and would facilitate selection of the best available values for CL and  $V_{dss}$  for use in a human PK model that would predict steady-state serum concentration from intake (dosing) rate and, conversely, predict intake rate from steady-state serum concentration. These predictions are probably the primary reason to include a pharmacokinetics section in the documents.

**RESPONSE:** EPA provided this information in tables, where data were available. For Table 2-24, clearance was not given in the paper with the other parameters; it was stated that clearance was optimized. Also EPA does not have  $V_d$  values from Kemper (2003) to add to Tables 2-26 and 2-27. Extensive details of the Wambaugh et al. (2013) model were added in tables and include model parameters for mice, rats, and monkeys and output by dose for predicted average serum and AUC.

**COMMENT 3:** The pharmacokinetic sections of both documents lack example graphs of serum concentration-time data on semilog coordinates for PFOA and PFOS. Inclusion of a few representative graphs would help the reader evaluate the consistency of the data used to generate the pharmacokinetic parameter values, and where model-based equations have been fitted to the data, the scatter of the measured concentrations around the model-predicted line would be informative as to the goodness of fit and the validity of the model and its parameters.

**RESPONSE:** While EPA agrees that graphical representation is often useful with data evaluation, EPA elected not to generate graphs from the published tabular data for distribution and excretion results. The data were utilized in the development of the PK models used to estimate average serum.

## Longnecker Comments

**COMMENT 1:** I can see advantages to treating this more like a systematic review of the literature, where the specific search algorithm for included articles is laid out, as are the range of dates of publication to be considered, and any other selection criteria applied for articles considered. In these documents, while the review of earlier literature appears to be comprehensive, after some point there must have been some decision making about which of the more recent articles to include.

The EPA has many guidelines about how data like these are to be evaluated, yet in the document few, if any, references to these guidelines were cited. Because so many guidelines exist, it could help readers if the authors cited specific places in critical documents that provide guidance for specific decisions.

**RESPONSE:** A description of the criteria used to evaluate each study is included in the background in each document. The literature search strategy is now included as Appendix A.

## Slitt Comments

**COMMENT 1:** The document reads very well. Although not included in the RfD determination, including a table of the observed human effects along with serum concentrations in Section 5.0 would put Tables 5-2 and 5-3 into context. Some sort of layman explanation to help understand why only non-human exposures are being included would be helpful to the general public.

**RESPONSE:** Human serum levels are included in the summary of epidemiology in section 3 of the HESDs for comparison to the tables of animal data and the animal serum information used in quantification. The description of the use of human data qualitatively, as an additional line of evidence in the derivation of the RfD, has been added.

## EPA Responses to Specific Editorial and Technical Comments

### Bruckner Comments

#### PFOA-specific Comments

Page	Paragraph	Comment or Question	Response
3-11	5, lines 7-11	It is stated that the PFOA concentration in bile increased by a factor of 12.5 with the increase in PFOA dose from 12.5 to 25 umol/kg in wild-type mice and 19.5 in PPAR $\alpha$ -null mice. These factors should be 2.8 for wild-type and 6.1 for PPAR $\alpha$ -null mice. The document's authors may want to rethink their interpretation of the data. The results for the wild-type mice do suggest saturation of transport from liver to bile ducts, but the PPAR $\alpha$ -null results do not, indicating a role for PPAR $\alpha$ in this process. In contrast to the foregoing, the findings of Lou et al. (2009) (p. 3-11, pgr. 2) indicate their highest dose of PFOA is cleared from the blood of mice more rapidly than lower doses, suggesting saturation of hepatic and/or renal reuptake transporters. What is the relative importance of biliary and renal elimination of PFOA?	Bile numbers have been corrected. EPA agrees with the reviewer's interpretation. Text has been changed to reflect non-saturation in PPAR $\alpha$ -null mice and suggestion of PPAR $\alpha$ -mediated clearance.
3-12	3, lines 2-4	It should also be stated that upregulation of MRP3&4 and the OATs may be <u>beneficial</u> , due to increased biliary excretion of bile acids, bilirubin, conjugated metabolites of toxic chemicals, etc.	Sentence inserted.
3-14	1 & 2	It might be stated that the findings of Hinderliter (2004) support those of Han (2003), in regards to development of female rats.	That these studies support each other has been added.
3-14&3-15		It is problematic to try to compare values in Table 3-14 with values referred to at the end of the second paragraph on p. 3-17. Whole pup and pup serum PFOA levels decrease between PND 1&18 for each dosage in the table. It would be preferable to include another table showing the PFOA levels with body weight taken into account.  Table 3 – 14 and other tables should include the species in the title. It would also be helpful to include some details of the experimental protocol in the footnotes.	Species name was added to the table titles for Tables 2-11 to 2-15. An additional table was not added as data are presented as published. Details of the experimental protocol in the footnotes of tables were not added because this information is clearly laid out in nearby paragraphs. Also, this has not been done for any of the other tables in the document.

Page	Paragraph	Comment or Question	Response
3-20		It would be useful at the end of this section (Distribution During Pregnancy and Lactation) to summarize the primary findings, or conclusions that can be drawn from the data that were presented.	An overall summary has been added at the end of the Toxicokinetic section, which includes distribution during pregnancy and lactation.
3-23	4, line 2	It should be emphasized that urinary excretion of PFOA was substantially higher in female than male rats.	Changed.
3-28	2, line 4	Replace “receptors” with “transporters”.	Done.
3-28	6	Did 10 uM PFOA inhibit PAH and estrone uptake to a greater extent than 100 uM PFOA?	The % uptake at each concentration has been added.
3-29	3 & 4	It is not clear what Yang et al. (2009) concluded about the role of OATp1a1 in the uptake of PFOA from glomerular filtrate.	As stated in the paragraph, levels are much higher in male rats than females, which would favor resorption.
3-32	3 & 4	These two summary paragraphs are very helpful.	Comment noted.
3-37	1, line 1	Should “adsorption” be “absorption”?	Changed.
4-7 & 4-9	Tables 4-1 & 4-2	Tables 4-1 and 4-2 are quite helpful in integrating the results of studies of occupationally-exposed populations.	Comment noted; these tables have been extensively revised.
4-13		A concluding sentence should be added to summarize the findings of a lack of association of PFOA with diabetes, metabolic syndrome, etc.	Sentence added.
4-32		The NOAEL and/or LOAEL for this study should be stated at the end of the paragraph.	These have been added before reference to the immunological endpoints.
4-34	2	Is the LOAEL for liver effects 1 ppm in the study of Loveless et al. (2008)?	The LOAEL is 10 mg/kg/day based on increased liver weight, hypertrophy, and necrosis. This has been added.
4-38	1	Include the meaning of the abbreviation “mPPAR $\alpha$ ”.	Added.
4-39		Inclusion of the table for Minata et al. (2010) would be useful to help readers better comprehend the study findings.	EPA agrees that tables are often useful in presenting data, however, an additional table was not added as the results are described with a clear NOAEL/LOAEL statement.
4-40		A table of short-term LOAELs and NOAELs should be added here or in Section 5.	This is included in section 4.
4-47	2	It is hard to believe, judging from the slight difference in mean values and their standard deviations, that absolute and relative liver weights are significantly higher than controls in the 1 mg/kg/day group.	Data are presented as published.
4-67	2, line 5	Insert “absolute” before “liver weight”.	Done.

Page	Paragraph	Comment or Question	Response
4-69	1, lines 1 & 2	It might be worthwhile to point out that the actual study by Butenhoff et al. was conducted prior to 2004.	Done.
4-73		A summary sentence (or two) should be added at the end of the Mutagenicity and Genotoxicity section.	Done.
4-83		A summary paragraph should be included at the end of the Immunotoxicity section.	An introductory paragraph has been added at the beginning of the section.
4-101	1, line 14	Insert the word “some” before “occupational studies”. In order to present a more balanced perspective of findings in occupational studies, the following sentences could be added at the end of the paragraph: “Olson and Zobel (2007) examined groups of male workers at 3 fluorochemical production facilities. Serum PFOA concentrations were not associated with total cholesterol, LDL or HDL in workers at these facilities.”	This paragraph has been re-written along with the revised epidemiological data such that this revision is no longer relevant.
4-102	4	It should be stated that the increases in serum enzyme activity in workers were quite modest/small. The following sentence should be added at the end of the paragraph: “Emmett et al. (2006), however, found no association between serum PFOA and liver or renal enzymes”.	See above comment.
4-103	2, line 2	Change “apoptotic or necrotic damage of” to “apoptosis or necrosis of”. Apoptosis and necrosis are types of cell death, not damage/injury.	Done.
4-103	3, line 1	It is true that PFOA may interfere with the biliary excretion of other compounds that are transported by the same transporters. Upregulation of the genes for these transporters, however, may be beneficial in that the excretion of bile acids, bilirubin and conjugates of toxic chemicals/metabolites may be hastened.	This has been revised.
4-103	4, line 2	I would avoid the word “critical” until the section on Dose-Response Assessment.	Done.
4-103	4	Increases in absolute and relative liver weights were dose-dependent (Cui et al., 2009; Elcombe et al., 2010; Wolf et al., 2008a)	Done.



Page	Paragraph	Comment or Question	Response
4-103	5	It is important to distinguish between effects of PFOA on rough and smooth endoplasmic reticulum (RER and SER). RER content was diminished, but there was a proliferation of SER.	Distinction added.
4-104	2, line 5	This last line should be amended to read “that PFOA has some effects of unknown toxicological significance that appear to be independent of PPAR $\alpha$ activation.	Done.
4-104	4, line 3-5	The meaning of the sentence is not clear. Has something been omitted?	This paragraph has been revised.
4-105	3, line 3	Add “of offspring” between “abilities” and “at 6 and 18”.  Include Fei and Olsen’s (2011) finding of no association between prenatal PFOA exposure and behavioral or coordination problems in children at age 7.	Changes made.  Sentence added.
4-109	3	The species (i.e., mice) studied by White et al. (2009) and by Wolf et al. (2007) should be stated.	Paragraph no longer present in revised document.
4-111	4, line 2	Replace “examine” with “determine whether there was”.	Paragraph no longer present in revised document.
4-112	2, lines 1 & 2	The first sentence is misleading and should be rewritten. Butenhoff et al. (2012) did not see a significant increase in liver adenomas or carcinomas. Biegel et al. (2001) reported an increased incidence of hepatic adenoma but not carcinoma.	This section has been extensively revised.
4-112	2, line 13	What is hepatic cystoid degeneration?	Definition added.
4-114	2, line 3	Insert “decreased” before “apoptosis”.	Paragraph revised such that comment no longer relevant.
4-115	5, line 2	What is meant by “PRAR exposures”?	This has been changed to PPAR activation.
4-116		There is no mention of PFOA-induced changes in expression of genes (e.g., cell cycle control, peroxisomes biogenesis, inflammation, etc.) that are PRAR $\alpha$ -dependent. There is no mention of the role of PRAR $\alpha$ or peroxisomes in oxidative injury and carcinogenesis.	These are discussed in the MOA for liver tumors on the previous pages. The mechanism for PFOA-induced Leydig cell tumors has not been fully elucidated.
4-120	1, lines 11 & 12	Insert “these” between “that” and “hormones”.	Done.

Page	Paragraph	Comment or Question	Response
4-121	3	It would be helpful to give the PFOA dosages of White et al. (2007) and one or two other studies, so the reader will have some idea of the magnitude of PFOA exposure required to alter mammary gland development.	Doses added.
5-1		RfD: Omit the word “wealth” from the bullet pertaining to epidemiology studies. There have been relatively few epidemiology studies of PFOA-exposed populations.	This section extensively revised; comment no longer relevant.
5-2	1, lines 2-6	Another obvious point should be made here, mainly that occupational exposures result in much higher plasma PFOA levels and body burdens than do environmental exposures. Thus, it would be anticipated that adverse effects would be more apparent in PFOA facility workers.	Serum levels have been added.
5-2	1, line 5	Include the words “in some instances” between the words “shown” and “between”. Otherwise, it appears from this paragraph the serum PFOA concentrations are consistently/usually associated with the various maladies.	This section extensively revised; comment no longer relevant.
5-2	3, line 8	Insert “failure to attain” between the words “with” and “developmental”.	Done.
5-7	2, line 4	Insert the word “rodent” between “between” and “species”	This section extensively revised; comment no longer relevant.
5-19	1, line 1	Insert “from some studies” between “data” and “have”.	Done.

#### PFOS-specific Comments

Page	Paragraph	Comment or Question	Response
3-2	5, lines 2 & 3	It is stated here that “the ratio of PFOS identified in serum and liver tissue are similar”. Do the authors mean that PFOS concentrations in the serum and liver are similar?	The reviewer is correct: “ratio” has been changed to “concentration”.
3-2	6	How does PFOS distribute between plasma lipoproteins and proteins/albumin?	Sentence changed to state that incubation was with separate protein fractions.
3-5	1, lines 9& 10	How much lower were milk PFOS levels than serum levels?	Deleted reference to serum levels since these were not measured in the study. Added mean milk and hepatic levels.
3-7	1, line 2	Oral and gavage are redundant.	Deleted oral.
3-16	Figure 3-1	This figure nicely illustrates relative PFOS levels in dams and fetuses/pups over time.	Comment is acknowledged; no formal response or action is necessary.

Page	Paragraph	Comment or Question	Response
3-19	1, line 3	Insert “groups” between “day” and “on”.	Done.
3-21	1, line 10	Substitute “longer” for “slower”.	Done.
3-23	2	It is not clear who conducted the human PBPK modeling nor which model they used.	Reference added to line 3: Loccisano et al. 2011.
4-21	2, lines 1-3	What did the 2nd monkey die from?	It is stated in the following sentence that the cause of death was unknown.
4-26	3, line 3	The word “concentrations” should be replaced by “doses”.	Done.
4-39	1	Does an increase in motor activity on PND 17, but no such effect on PND 13, 21 or 61, constitute a toxicologically-significant effect?	In the analysis by EPA, this is considered a toxicologically significant effect.
4-56	2, lines 1 & 2	It is stated that “taken together, these studies suggest a PPAR $\alpha$ -independent mechanism...” Of the studies reviewed to this point in the document, only that of Abbott et al. (2009) supports this premise. Qazi et al. (2009), Rosen et al. (2010) and other groups of investigators have reported other PPAR $\alpha$ -independent effects of PFOS.	“Taken together, these studies...” has been replaced with “The studies by Abbott et al. (2009) and Rosen et al. (2010)...”
4-60	2, lines 15-17	Is oxidative damage likely to be operative to a significant extent at lower PFOS doses?	No data were available.
4-61	2, line 4	What is meant by “The concentration...”?	The concentration used in the culture; this has been added.
4-61	4, line 2	Change “dose of exposure is” to “levels of exposure are”.	Done.
4-62	1, lines 2 & 3	What did Olsen et al. (2003) find correlation between?	This has been revised to note correlation between serum and hepatic levels.
4-62	3, lines 4 & 5	Identify the species (i.e., rat) studied by Chang et al. (2009) and Stein et al. (2012).	Done: added rat and human, respectively.
4-62	5	The liver of rats and monkeys was examined for histopathological changes, but the histological changes should not be considered lesions nor pathological.	Changed to microscopic lesions.
4-68	4, lines 5 & 6	The elevated incidence of hepatocellular adenomas/ carcinomas was almost entirely due to adenomas. Only 1 of 60 high-dose female rats exhibited carcinoma.	No changes made. Increased adenomas in females is already stated in the sentence.

<b>Page</b>	<b>Paragraph</b>	<b>Comment or Question</b>	<b>Response</b>
4-69	5, lines 3 & 4	<p>It is stated here that there was no increase in hepatocellular proliferation detected in the subchronic study of Seacat et al. (2003).</p> <p>It is stated previously on page 4-69 that “the data for PFOS are adequate to support some but not all key events...” I assume that cell proliferation is thought to be a missing event. Seacat et al. (2003) reported that the average hepatocyte proliferation index was not increased, but that some animals exhibited mild increases. It is clear in the current document that PFOS is not as potent a PPAR<math>\alpha</math> inducer as PFOA.</p>	Comment is acknowledged; no formal response or action is necessary.
5-4	2 & 5, line 7	Again the terms “histopathological” and “lesions” are misnomers.	Changed to microscopic lesions.
5-4	3, line 9	What is meant by a “biologically significant decrease in survival” at 0.8 mg/kg?	This section was revised with better wording.

## Cory-Slechta Comments

### PFOA-specific Comments

Page	Paragraph	Comment or Question	Response
Chapter 5		The text of Chapter 5 in the PFOA document (and other places) continues to state that a 10% increase in liver weight would not be an adverse effect, but merely a denominator for loss of homeostasis. On what basis was this conclusion derived? What is the support for this statement? It appears that benchmark dosing was applied to studies that had liver weight as the common denominator, but does this accommodate the lowest NOAELS and LOAELS observed for any endpoint in the long duration studies? Use of just studies with the common denominator because they provide replication ignores the fact that some other effect may occur at lower levels but simply hasn't been evaluated in as many studies as focused on PPARα-based targets. If this isn't the case, then the text should clearly address this.	The POD for PFOA has been changed to be based on low birth weight, developmental delays, reduced body weight, and increased kidney weight in mice and rats (Lau et al. 2006, Butenhoff et al. 2004a). Increased liver weight is acknowledged as a common finding but not considered adverse in the absence of other effects as defined by Hall et al. (2012).
5-7	2	States that the BMDL <sub>10</sub> values all fall below the experimental LOAELs. So, what does that mean, is there some conclusion that is supposed to be reached from this? IF so, please state it.	This is no longer relevant since the BMD analysis is not used in the RfD determination.
5-13	1	States "Generally these values were similar." What does similar mean? What is acceptable in this context?	The sentence has been deleted.

Page	Paragraph	Comment or Question	Response
5-16	3	<p>States that the half-life value Bartell et al. (2010) was used for half-life because it seemed more relevant to scenarios where exposure result from ingestion of contaminated drinking water by members of the general population.</p> <p>This rationale does not appear to consider the potential different strengths and weaknesses of the other potential studies. Is it necessarily the case that general population is more important than occupational studies? The rationale needs to be described in greater detail. Virtually no rationale is provided for the choice of the Thompson et al. (2010) study for a volume of distribution value.</p>	<p>The Bartell et al. (2010) half-life represents an estimate corresponding to the U.S. general population rather than the occupational populations as reported in studies, such as Olsen et al. (2007). It was derived using the declines in serum values among members of a highly exposed population following a change in residence that lowered the ongoing exposures. The Health Advisory guidelines apply to members of the general population exposed to a chemical through their drinking water. Accordingly, the Bartell et al. (2010) estimate was used rather than one based on occupationally exposed cohorts. The recent NHANES data demonstrate that serum levels are declining among the general population. This strengthens the decision to utilize the Bartell et al. (2010) half-life.</p> <p>With regard to the volume of distribution for PFOA, none of the available studies provide data for calibration of volume of distribution of PFOA in humans. However, several researchers have attempted to characterize PFOA exposure and intake in humans (Thompson et al. 2010; Lorber and Egeghy 2011) through pharmacokinetic modeling. In the models, volume of distribution was defined as the total amount of PFOA in the body divided by the blood or serum concentration.</p> <p>Both research groups defined a volume of distribution for humans using a simple, single compartment, first-order pharmacokinetic model (Thompson et al. 2010; Lorber and Egeghy 2011). The models developed were designed to estimate intakes of PFOA by young children and adults and the general population. In both models, the volume of distribution was calibrated using human serum concentration and exposure data from NHANES, and it was assumed that most PFOA intake was from contaminated drinking water. Thus, the value for volume of distribution was calibrated so that model prediction of elevated blood levels of PFOA matched those seen in the study population.</p>

Page	Paragraph	Comment or Question	Response
5-16	3		Thompson et al. (2010) used a single compartment, first-order pharmacokinetic model to predict PFOS concentration in blood serum as a function of dose, elimination rate, and volume of distribution. The volume of distribution was first obtained for PFOA by calibrating human serum and exposure data. The volume of distribution for PFOS (230 mL/kg) was adjusted from the calibrated PFOA data by 35% in accordance with the differences in PFOA and PFOS volumes of distribution calculated by Andersen et al. (2006), the study used by Wambaugh et al. (2013) in the development of the model utilized in the determination of the RfD for PFOA.

#### PFOS-specific Comments

Page	Paragraph	Comment or Question	Response
1-1	4	There are similar concerns for the PFOS document. Loose terminology should be eliminated, e.g., what is a ‘finding of note’ as used in the executive summary for PFOS.	The Executive Summary has been revised; comment no longer relevant.
Executive summary		The PFOS executive summary is of limited utility; for many readers this may be as much of the document as they read; as currently written it is not clear or transparent nor does it sufficiently explain how it arrived at an RfD.	The Executive Summary has been revised; comment no longer relevant.
3-3	Table 3-1	Couldn’t a sentence essentially substitute for Table 3-1; it really isn’t useful.	Possibly, but table has been retained in the document.
3-25	1	Loose terminology should be eliminated, e.g., what is “generally good”	The word “generally” has been deleted.
3-26	Figure 3-7	Figure 3-7 has no explanation of what is the black vs. gray line.	This is indicated in the figure caption.
All tables		There is a need to improve all of the tables; they should always include study name/year, sample size and exposure duration information on them; this would make all of the comparisons easier to evaluate and not require the reader to continue to go back and forth to the text.	All tables have references footnoted at bottom of table. All of the epidemiology tables have been changed to include study name, sample size, and exposure duration, if provided.

Page	Paragraph	Comment or Question	Response
4-4	Table 4-1	For example, table 4-1 has only study name and year, but what really matters is also exposure duration and sample sizes, because the comparisons of outcomes in the Table depend upon the power of the study to detect effects at the very least.	All tables of human epidemiology data have been revised to include type of study, sample size, serum levels, and outcomes.
4-9	Table 4-2	The same comment applies to Table 4-2 and any others with this intended purpose.	All tables of human epidemiology data have been revised to include type of study, sample size, serum levels, and outcomes.
4-11	Table 4-3	Table 4-3 needs sample sizes, exposure duration etc.	All tables of human epidemiology data have been revised to include type of study, sample size, serum levels, and outcomes.
4-24	Table 4-7	Tables that summarize a significant amount of data from a single study (e.g., 4-7) should include the study authors and year in the Table title so it doesn't have to be searched for.	This information is given directly below each table.
		In several instances in the PFOS document, adverse effects early that appear to be reversed at a later age are discounted with the suggestion that they therefore do not matter; given our increasing understanding of the importance of early changes in terms of epigenetic changes, this is no longer appropriate and in fact, misleading.	EPA has attempted to revise all incidences of this language to note reversibility, but not discount the effect.
5-16	Table 5-8	What do the parentheses signify?	Numbers in parentheses indicate standard deviation as noted below the table.
5-17	Table 5-9	What do the parentheses signify?	Numbers in parentheses indicate standard deviation as noted below the table.

## DeWitt Comments

### PFOA-specific Comments

Page	Paragraph	Comment or Question	Response
4-102	2 & 3	DeWitt et al. 2009 also included data on triglyceride levels in C57BL/6 mice exposed to PFOA for 15 days; triglyceride levels were dose-responsively decreased.	A sentence containing these data has been added.

### PFOS-specific Comments

No specific observations.



## Fisher Comments

No specific observations.

## Hayton Comments

### PFOA-specific Comments

Page	Paragraph	Comment or Question	Response
1-2	Last, line 5	Delete “in”; should read “... in rats was analyzed ...”	Paragraph has been revised such that this comment is no longer relevant.
3-2	1, lines 6-8	Assumption that fecal excretion represented unabsorbed PFOA is problematic; suggest rephrasing this sentence.	The phrase “and did not include biliary loss” has been added to this sentence.
3-3	Table 3-1	Protein binding is important for PK modeling, where the fraction unbound (fup) is the important parameter, not the fraction bound. Suggest listing fup values rather than percent bound.	Data are as presented in the reference. The study author did not include fup values.
3-6	Last, line 3	“concentration” should be “dose rate”	Changed.
3-8	2, line 4	In addition to liver, kidney, and blood, other tissues are prominent. E.G., Table 42 of Kemper shows that in male at 1 mg/kg, t=Tmax, GI tract, GI contents, muscle, bone and skin contained a greater percentage of dose than did the kidney.	Sentence changed to note other tissues.
3-8	2, line 8	“Blood to kidney” should be “kidney to blood”	Sentence was revised.
3-8	2, line 10-11	In Kemper, Tables 44-45, blood to kidney ratios are not 10 or higher in males.	Sentence changed to state blood levels were 10-fold or higher than kidney levels.
3-8	2	This paragraph reports both percent of dose found in tissues, and concentrations found in tissues. But Tables 3-4 and 3-5 present only the former. When presenting tissue concentrations, please make it clear that those data are not shown.	Changed to note distribution in tissues.
3-18	Last, line 3	“were” is repeated.	Deleted.
3-19	1, line 1	Technically incorrect to say that the level peaked at PND7; that was the earliest sample time. The peak may have occurred before PND7.	Changed to “at or before”.
3-19	Table 3-15	The last dose was on GD17; strange that at 1 and 3 mg/kg the serum concentration increases from PND7 to PND14.	Comment noted.
3-22	4	Last sentence is garbled.	The paragraph has been revised.

Page	Paragraph	Comment or Question	Response
3-22	4, 5	Agree that biliary elimination is possible, but it could be that chloestyramine binds PFOA and PFOS in the GI tract lumen after they passively diffuse from the blood to the gut. There seems to be no direct evidence of biliary elimination, e.g., bile collected from treated animals.	These two paragraphs have been revised with reference to elimination in bile noted as possible.
3-23	Last, line 4	Should be Table 3-18.	Table numbers corrected.
3-34	Last, line 9	Should be “nonlinear least squares”	Corrected.
3-35	Table 3-23	Column 2, “Adsorption” should be “Absorption”	Corrected.
3-38 3-38	2 Figure 3-7	The arrow from Gut to Liver appears to point in the wrong direction; it should represent biliary excretion of PFOA from Liver to Gut.	The figure is as presented in the reference, Loccisano et al. 2011. Absorption from the gut was included in the model, but possible biliary elimination to the gut was not included.
3-43	Last line	“... indicating the absence of active excretion in human kidneys.” This does not follow from the observation of renal clearance being about 0.001% of GFR. A plasma free fraction of 0.001 would account for the CL <sub>r</sub> being 0.1% of GFR, and passive tubular reabsorption would make it 0.001% of GFR since urine flow is about 1% of GFR. Other scenarios are possible that do not invoke the absence or presence of active excretion.	Phrase has been deleted.
3-44	Table 3-24	Should report all data values with three significant figures. For example, Lambda z values have only one sig. fig., while T <sub>1/2</sub> values have 5-6.	All values are as presented by the study author.
3-46	2	This reviewer does not follow the derivation and use of a value for volume of distribution with regard to intake rate and serum concentration of PFOA. If the subjects were at steady state, the body burden would have to be known. At steady state, the serum concentration would be independent of the volume of distribution, so any V value ought to match the intake rate to the steady state serum concentration.	The description of the calibration of volume of distribution is as given by the study authors.
4-9	1	Log transformed concentration was 1.51 and 1.48 ng/mL – are these the logarithms? IE, are the actual concentrations $10^{1.51} = 32$ and $10^{1.48} = 30$ ng/mL?	Reported as log PFOA concentration in the paper. It was not clear if actual concentrations are 32 and 30 ng/mL, so left this as stated in the reference.
4-20	2, line 8	Anderson here is spelled Andersen in the reference list.	Corrected.
4-30	1, line 9	prostrate should be prostate.	Corrected.

Page	Paragraph	Comment or Question	Response
4-31	4, line 10	decreased should be decrease.	Corrected.
4-112	1	It would be helpful to restate the serum concentrations for the Eriksen and Vieira studies, or refer reader to p. 4-29 where they are provided.	Serum levels have been added to this section.
4-112	1, line 9	Delete “for”.	Paragraph was revised; no longer relevant.
4-112	2, line 12	Delete “were”.	Paragraph was revised; no longer relevant.
4-118	4	Delete “of actions” after MOAs	Done.
4-120	3	The broad range of half lives could also be due to person-to-person variability in the free fraction of PFOA in serum (fup). This is the case for highly bound drugs; e.g., warfarin.	“...and binding..” has been added to the sentence.
5-1	3	Pharmacokinetic is misspelled.	This section has been completely revised; comment no longer relevant.
5-1	5	Disagree – exposure assessment based on the human data is feasible. In fact, the serum concentrations are a better measure of exposure than are intake measures as they reflect all intake pathways and eliminate bioavailability and pharmacokinetic influences on internal exposure.	This section has been completely revised; comment no longer relevant.
5-12	Last	Table numbers should be 5-6, 5-7, and 5-8.	Corrected.

#### PFOS-specific Comments

Page	Paragraph	Comment or Question	Response
3-5	3	The low CSF : serum concentration ratio could also be due to an export transporter that pumps PFOS out of the CSF and/or to extensive serum protein binding, where only the free serum concentration of PFOS is in equilibrium with the free PFOS concentration in the CSF.	Comment is acknowledged; no formal response or action is necessary.
3-22	2	The free fraction used for the model is much larger than that determined experimentally, Table 3-1; this should be pointed out in the text.	The text accurately states what is used in the model; Table 2-1 represents in vitro data so is not directly applicable.
3-22 3-23	2 Figure 3-5	The arrow from Gut to Liver appears to point in the wrong direction; it should represent biliary excretion of PFOS from Liver to Gut.	Figure is copied from Loccisano et al. 2011.
3-24	4	Anderson should be Andersen.	A search and replace was done for the entire document.
4-26	4	“concentrations” should be “dosages”.	Changed.

Page	Paragraph	Comment or Question	Response
5.2	3	Should note for many of these studies, that steady state may not have been achieved due to the long half-life of PFOS. Half-life values from Section 3 are: mouse, 37 days; rat male, 40 days and female 64 days; monkey, 120 days. Using a one-compartment PK model, the time to 90% steady state is 3.3 half lives.	Sentence added: It is noted, however, that in some of these studies, steady states of PFOS may not have been achieved due to the long half-life of PFOS in animal models (see discussion of steady state in section 4.1.1.1).
5-5	3	The NOAEL for liver effects in rats of 0.072 mg/kg/day is not consistent with p. 5.4, para. 2, which states that lesions of the liver <u>were</u> observed in male rats after 104 weeks at this dosage.	This sentence has been removed in the revision.
5-7	2	For female rat, the PFOS half life is about 60 d and the period of gestation is about 20 d or one-third of a half life. If PFOS is administered to the dam only during gestation at a fixed daily dose, the serum concentration of PFOS would rise from 0 to 21% of the steady-state serum concentration that the fixed dose rate would produce at steady state. The exposure of the fetus during gestation would average only about 10% of the exposure that would have occurred if the dam had received PFOS for 4 half-lives (240 days) prior to mating. BMDs based on such a fixed dose could be elevated by as much as a factor of 10 compared with the steady state situation. Steady state would be the relevant situation for humans. For the Luebker study (Table 5-3) the serum concentration during gestation would have increased from about 38% to 50% of the eventual steady state concentration.	A discussion of steady state has been added to section 4.1.1.1. It is noted that “the average serum values from the studies that do not approach steady state have lower average serum LOAELs for endpoints of toxicological concern. Thus, the data do not appear to indicate increasing sensitivity as steady-state is approached. If anything, the average serum values appear to be more protective than serum concentrations at steady state.”

## Longnecker Comments

### PFOA-specific Comments

Page	Paragraph	Comment or Question	Response
3-28	1 <sup>st</sup> complete	Should the end of the sentence be “increase the transporters” rather than “increase the receptors”?	Done.
3-30	2 <sup>nd</sup> complete	L 3, would insert “transfected” between “OAT3” and “cells”	Done.
3-39	1 <sup>st</sup> complete	Next to last sentence: I doubt that Olsen assumed the major source of exposure was drinking water in the occupational study	Agreed, the sentence has been deleted.
3-41	4 <sup>th</sup> complete	In the first formula listed, the plus sign should be an equal sign	Corrected.

Page	Paragraph	Comment or Question	Response
4-9	1 <sup>st</sup> complete	L 3 from bottom: the values of 1.51 and 1.48 given are probably better described as geometric means.	This section has been completely revised; comment no longer relevant.
4-16	2 <sup>nd</sup> complete	L 3 from bottom: would insert “draw” after “blood”	Done.
4-21	2 <sup>nd</sup> complete	L 5: the value of 6.78 ug/L is a water level, not a serum level; this issue recurs on P 4-23, paragraph at bottom	This section has been completely revised; comment no longer relevant.
4-30	1 <sup>st</sup> complete	L 8: should read “exposure categories” rather than “cancer categories”?	Done.
4-37	Table	Would note dose of PFOA somewhere in table or footnote	10 mg/kg has been added.
4-55	Last para	L 3: should the “>” be a “<”?	Done.
4-79	Last para	Last sentence: should “50 and 25” be “50 and 250”?	Done.
4-80	1 <sup>st</sup> complete	The last sentence does not accurately describe the table. E.G., the CD4+CD8+ cells decreased at the 47.21 mg/kg/d dose	Decrease for CD4+CD8+ cells has been added.
4-82	Next to last para	Last sentence: the 37.5 mg/kg/dose is not mentioned earlier, so this is a little confusing.	Deleted; changed to note three highest dose groups.
4-85	Last para	L 2: should “0.5” be “0.05”?; Same issue for L 5.	Yes, corrected.
4-89	4 <sup>th</sup> para	How long were the animals dosed?	Added “for 7 days”.
4-110	3 <sup>rd</sup> complete para	L 5: should “serum” be “blood”?	Yes, changed.
4-113	3 <sup>rd</sup> complete para	L 1: insert “in” before “liver cells”	Done.
5-4	Last para	Were the criteria for inclusion in Table 5.2 the same as for Table 5.1?	This section has been revised and reason for including studies on the tables is given.
5-12	Para below table	8-6, 8-7, and 8-8 should be 5-6, 5-7, and 5-8	Corrected.
5-16	Last line	I do not see in the Thompson et al. (2010) study any mention of using exposure data from NHANES to calibrate the volume of distribution. Other sources of data were used, where the water had been contaminated.	This was described in section 2.5.3.
5-17	1 <sup>st</sup> formula	“/day” should be deleted from “0.17 L/kg <sub>bw</sub> /day”	Done.
5-20	Table 5-12	The first three values in the UF <sub>total</sub> column need to be corrected; they should be 21900, 219000, and 21900	The UF <sub>a</sub> derived from clearance ratios has been deleted; comment no longer relevant.
5-21	Paragraph above table	Last sentence: UF <sub>L</sub> should be UF <sub>H</sub>	This section has been deleted; comment no longer relevant.
5-21	Last sentence	UD <sub>s</sub> should be UF <sub>s</sub>	This has been deleted; comment no longer relevant

Page	Paragraph	Comment or Question	Response
5-27	Calculations	The text says the body weight conversions should be based on the $\frac{3}{4}$ power. If so, the HED formulas are incorrect, and the HED should be $1.99 \times 0.0254 = 0.0506$ , the dosimetric adjustment factor should be 0.0254, and the CSF should be 1.57. All the figures here should be checked as should the paragraph on P 5-28. The HED is 2,530-fold greater than the RfD, not 29,000.	Correct as written since the calculation is for a DAF which uses inverse of BW $^{3/4}$ resulting in BW $^{1/4}$ .  The sentence comparing HED to RfD has been deleted; comment no longer relevant.

### PFOS-specific Comments

Page	Paragraph	Comment or Question	Response
1-1	2 <sup>nd</sup>	1 <sup>st</sup> sentence: would revise for clarity. Do you mean uncertainties exist about whether PFOS-induced peroxisome proliferation is involved in causing PFOS-induced hepatic lesions?	Sentence has been revised for clarity by adding “hepatic lesions induced by PFOS”.
1-1	3 <sup>rd</sup>	1 <sup>st</sup> sentence: would revise for clarity; the occupational studies were done at PFOS production plants, but to my knowledge there are no residential populations that have been studied for health effects who lived near PFOS production plants. (Mid-Ohio valley factory was a source of PFOA.) In the 2 <sup>nd</sup> sentence, I do not believe that exposure was mainly through contaminated drinking water in any of these studies.	First sentence has been revised to note that the population lived near a PFOA plant. Second sentence has been deleted.
4-66	2 <sup>nd</sup>	The earlier summary of the Bloom et al. study (P 4-10) said the results were not statistically significant, whereas here the interpretation appears to be that the study found an association. The interpretation does not seem consistent across the two sections.	This paragraph has been revised to more accurately describe the data presented in the epidemiology section.
5-17	Below table	L 3: the word “terminal” should be deleted from this sentence	Done.
5-20	1 <sup>st</sup> formula	The “/day” should come out of “0.23 L/kg bw/day”	Done.
5-26	L 2 from bottom	This should be 35 ug/L not 35 mg/L	Done.

### Slitt Comments

No specific observations.

#### 4. 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 on expression of peroxisome proliferator activated receptor-alpha (PPAR $\alpha$ ) in the mouse. *Reproductive Toxicology* 27:258–265.
- Allen, D.G., G. Pearce, J.K. Haseman, and R.R. Maronpot. 2004. Prediction of rodent carcinogenesis: An evaluation of prechronic liver lesions as forecasters of liver tumors in NTP carcinogenicity studies. *Toxicologic Pathology* 32(4):393–401.
- Amarapurka, D.N., A.D. Amarapurkar, N.D. Patel, S. Agal, R. Baigal, P. Gupte, and S. Pramanik. 2006. Nonalcoholic steatohepatitis (NASH) with diabetes: predictors of liver fibrosis. *Annals of Hepatology* 5(1):30–33.
- Andersen, M.E., H.J. Clewell 3<sup>rd</sup>, 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.
- Barry, V., A. Winquist, 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.
- 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.
- Bjork, J.A., J.L. Butenhoff, and K.B. Wallace. 2011. Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rat hepatocytes. *Toxicology* 228:8–17.
- 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.
- Butenhoff, J., G. Costa, C. Elcombe, D. Farrar, K. Hansen, H. Iwai, R. Jung, G. Kennedy, P. Lieder, G. Olsen, and P. Thomford. 2002. Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicological Sciences* 69:244–257.
- Butenhoff, J.L., G.L. Kennedy, S.R. Frame, J.C. O’Conner, 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 Jr, P.M. Hinderliter, P.H. Lieder, R. Jung, J.K. Hansen, G.S. Gorman, P.E. Noker, and P.J. Thomford. 2004b. Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys. *Toxicological Sciences* 82(2):394–406.
- 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<sup>+</sup>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 perfluorooctane sulfonate in Sprague Dawley rats. *Toxicology* 293:1–15.
- 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.
- Chen, C.-H., M.-H. Huang, J.-C. Yang, C.-K. Nien, C.-C. Yang, Y.-H. Yeh, and S.-K. Yueh. 2006. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of Taiwan: Metabolic significance of nonalcoholic fatty liver disease in nonobese adults. *Journal of Clinical Gastroenterology* 40(8):745–752.
- Delgado, J.S. 2008. Evolving trends in nonalcoholic fatty liver disease. *European Journal of Internal Medicine* 19(2):75–82.
- 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., C.B. Copeland, and R.W. Luebke. 2009. Suppression of humoral immunity by perfluorooctanoic acid is independent of elevated serum corticosterone concentration in mice. *Toxicological Sciences* 109:106–112.
- Fàbrega, F., V. Kumar, M. Schuhmacher, J.L. Domingo, and M. Nadal. 2014. PBPK modeling for PFOS and PFOA: validation with human experimental data. *Toxicology Letters* 230:244–251.
- 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* 24:569–576.
- Fracanzani, A.L., L. Burdick, S. Raselli, P. Pedotti, L. Grigore, G. Santorelli, L. Valenti, A. Maraschi, A. Catapano, and S. Fargion. 2008. Carotid artery intima-media thickness in nonalcoholic fatty liver disease. *The American Journal of Medicine* 121(1):72–78.
- Frisbee, S., A. Shankar, S.S. Knox, K. Steenland, D.A. Savitz, T. Fletcher, and A.M. Ducatman. 2010. Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents. *Archives of Pediatrics and Adolescent Medicine* 164:860–869.
- Fu, Y., T. Wang, Q. Fu, P. Wang, and Y. Lu. 2014. Associations between serum concentrations of perfluoroalkyl acids and serum lipid levels in a Chinese population. *Ecotoxicology and Environmental Safety* 106:246–52.



- 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* 10:373–379.
- 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: Developmental and Reproductive Toxicology* 68:465–471.
- 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 3<sup>rd</sup> International ESTP Expert Workshop. *Toxicologic Pathology* 40:971–994.
- 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.
- Ipekci, S.H., M. Basaranoglu, and A. Sonsuz. 2003. The fluctuation of serum levels of aminotransferase in patients with nonalcoholic steatohepatitis. *Journal of Clinical Gastroenterology* 36(4):371.
- 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.
- 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.
- Klaassen, C.D., and L.M. Aleksunes. 2010. Xenobiotic, bile acid, and cholesterol transporters: Function and regulation. *Pharmacological Reviews* 62:1–96.
- Kunde, S.S., A.J. Lazenby, R.H. Clements, and G.A. Abrams. 2005. Spectrum of NAFLD and diagnostic implications of the proposed new normal range for serum ALT in obese women. *Hepatology* 42(3):650–656.
- 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.
- 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 Sciences* 90:510–518.
- Lizardi-Cervera, J., L. Cuéllar-Gamboa, and D. Motola-Kuba. 2006. Focal nodular hyperplasia and hepatic adenoma: A review. *Annals of Hepatology* 5(3):206–211.

- Loccisano, A.E., J.L. Campbell, M.E. Andersen, and H.J. Clewell. 2011. Evaluation and prediction of pharmacokinetics of PFOA and PFOS in the monkey and human using a PBPK model. *Regulatory Toxicology and Pharmacology* 59:157–175.
- Loccisano, A.E., J.L. Campbell, J.L. Butenhoff, M.E. Andersen, and H.J. Clewell. 2012a. Comparison and evaluation of pharmacokinetics of PFOA and PFOS in the adult rat using a physiologically based pharmacokinetic model. *Reproductive Toxicology* 33:452–467.
- Loccisano, A.E., J.L. Campbell, J.L. Butenhoff, M.E. Andersen, and H.J. Clewell. 2012b. Evaluation of placental and lactational pharmacokinetics of PFOA and PFOS in the pregnant, lactating, fetal and neonatal rat using a physiologically based pharmacokinetic model. *Reproductive Toxicology* 33:468–490.
- Loccisano, A.E., M.P. Longnecker, J.L. Campbell, Jr., M.E. Andersen, and H.J. Clewell. 2013. Development of PBPK models for PFOA and PFOS for human pregnancy and lactation life stages. *Journal of Toxicology and Environmental Health, Part A* 76:25–57.
- 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(1):e54176.
- Looker, C., M.I. Luster, A.M. Calafat, V.J. Johnson, G.R. Burleson, F.G. Burleson, and T. Fletcher. 2014. Influenza vaccine response in adults exposed to perfluorooctanoate and perfluorooctanesulfonate. *Toxicological Sciences* 138:76–88.
- 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.
- Lou, I., J.F. Wambaugh, C. Lau, R.G. Hanson, A.B. Lindstrom, M.J. Strynar, R.D. Zehr, R.W. Setzer, and H.A. Barton. 2009. Modeling single and repeated dose pharmacokinetics of PFOA in mice. *Toxicological Sciences* 107:331–341.
- 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.
- Lundin, J.I., B.H. Alexander, G.W. Olsen, and T.R. Church. 2009. Ammonium perfluorooctanoate production and occupational mortality. *Epidemiology* 20:921–928.


- 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 Sciences* 121(1):134–145.
- Mofrad, P., M.J. Contos, M. Haque, C. Sargeant, R.A. Fisher, V.A. Luketic, R.K. Sterling, M.L. Shiffman, R.T. Stravitz, and A.J. Sanyal. 2003. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 37(6):1286–1292.
- 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.
- Oh, M.K., J. Winn, and F. Poordad. 2008. Review article: Diagnosis and treatment of non-alcoholic fatty liver disease. *Alimentary Pharmacology & Therapeutics* 28(5):503–522.
- 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.
- Perkins, R., J. Butenhoff, G. Kennedy, and M. Palazzolo. 2004. 13-Week dietary toxicity study of ammonium perfluorooctanoate (APFO) in male rats. *Drug & Chemical Toxicology* 27:361–378.
- Post, G.B., P.D. Cohn, and K.R. Cooper. 2012. Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: a critical review of recent literature. *Environmental research* 116:93–117.
- 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* Volume 2010, Article ID 794739, 23 pp.
- Seacat, A.M., P.J. Thomford, K.J. Hansen, G.W. Olsen, M.T. Case, and J.L. Butenhoff. 2002. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. *Toxicological Sciences* 68:249–264.
- Seacat, A.M., P.J. Thomford, K.J. Hansen, L.A. Clemen, S.R. Eldridge, C.R. Elcombe, and J.L. Butenhoff. 2003. Sub-chronic dietary toxicity of potassium perfluorooctanesulfonate in rats. *Toxicology* 183:117–131.
- Seals, R., S.M. Bartell, and K. Steenland. 2011. Accumulation and clearance of perfluorooctanoic acid (PFOA) in current and former residents of an exposed community. *Environmental Health Perspectives* 119:119–124.
- Sorrentino, P., G. Tarantino, P. Conca, A. Perrella, M.L. Terracciano, R. Vecchione, G. Gargiulo, N. Gennarelli, and R. Lobello. 2004. Silent non-alcoholic fatty liver disease—a clinical-histological study. *Journal of Hepatology* 41(5):751–757.

- Staels, B., J. Dallongeville, J. Auwerx, K. Schoonjans, E. Leitersdorf, and J.C. Fruchart. 1998. Mechanism of action of fibrates on lipid and lipoprotein metabolism. *Circulation* 98(19):2088–2093.
- Stahl, T., D. Mattern, and H. Brunn. 2011. Toxicology of perfluorinated compounds. *Environmental Sciences Europe* 23:38–60
- 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., L. Zhao, and A. Winquist. 2015. A cohort incidence study of workers exposed to perfluorooctanoic acid (PFOA). *Occupational & Environmental Medicine* 0:1–8.
- Taylor, K.W., K. Hoffman, K.A. Thayer, and J.L. Daniels. 2014. Polyfluoroalkyl chemicals and menopause among women 20-65 years of age (NHANES). *Environmental Health Perspectives* 122:145–150.
- 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. Volumes I-IX. Covance Study No. 6329-183. 3M Company, St. Paul, MN.
- 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.
- 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.
- 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). 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/osa/review-reference-dose-and-reference-concentration-processes>.
- USEPA (U.S. Environmental Protection Agency). 2005. *Guidelines for Carcinogen Risk Assessment*. EPA/630/P-03/001B. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. <https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment>.
- USEPA (U.S. Environmental Protection Agency). 2014a. *Health Effects Document for Perfluorooctanoic Acid (PFOA)*. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. <https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OW-2014-0138-0002>.

- USEPA (U.S. Environmental Protection Agency). 2014b. *Health Effects Document for Perfluorooctane Sulfonate (PFOS)*. U.S. Environmental Protection Agency, Washington, DC. Accessed May 2016. <https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OW-2014-0138-0003>.
- 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>.
- Uslusoy, H.S., S.G. Nak, M. Gülden, and Z. Biyikli. 2009. Non-alcoholic steatohepatitis with normal aminotransferase values. *World Journal of Gastroenterol* 15(15):1863–1868.
- 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, and M.P. Longnecker. 2015. Associations of perfluoroalkyl substances (PFASs) 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.
- 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): 318–323.
- 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.
- Wang, F., W. Liu, Y. Jin, F. Wang, and J. Ma. 2015. Prenatal and neonatal exposure to perfluorooctane sulfonic acid results in aberrant changes in miRNA expression profile and levels in developing rat livers. *Environmental Toxicology* 30(6):712–723.
- Wieckowska, A., B.G. Papouchado, Z. Li, R. Lopez, N.N. Zein, and A.E. Feldstein. 2008. Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. *The American Journal of Gastroenterology* 103(6):1372–1379.
- Yahia, D., C. Tsukuba, M. Yoshida, I. Sato, and S. Tsuda. 2008. Neonatal death of mice treated with perfluorooctane sulfonate. *The Journal of Toxicological Sciences* 33:219–226.

## Appendix B:

January 3, 2017 Teleconference Note: Conversation with Jim Hurlburt,  
Hoosick Falls Water Department, Subject: Village Well 6. (1 page)

**TELECON NOTE****DATE: January 3, 2017****Project Name:** Saint-Gobain Performance Plastics**TDD No.** 0004/1601-01**Between:** Jim Hurlburt, Superintendent, Hoosick Falls Water Department**Phone No.:** (518) 857-8007**And:** Scott Snyder, Weston Solutions, Inc. **Time:** 1315 Hours**Subject:** Village Well 6

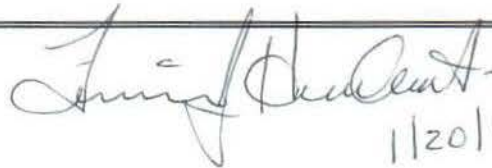
Spoke to Jim Hurlburt of Hoosick Falls Water Department. He confirmed that Village Well 6 is used as an emergency backup well. For maintenance purposes Well 6 is used approximately once per month for approximately thirty to forty minutes at a time. The water pumped from Well 6 is pumped to the pre-treatment tank, processed through the water plant, pumped to the clearwell, and then pumped out to the distribution system. Wells 3 and 7 are disconnected while Well 6 is pumping.

Jim stated that currently, the actual pumping rates of the three village wells are as follows:

Well 7 – 700 gallons per minute (gpm); pumps 365 days/year

Well 3 – 700 gpm; pumps 365 days/year

**Well 6 – 300 gpm; pumps 12 days/year**

  
1/20/17