Perfluoro Compounds (PFCs)
Various CASRN Numbers
January 4, 2016

CASRN	PFC [1]	Acronym	Formula	RfD (mg/kg -day)	RfC (mg/m^3)
375-22-4	**Perfluorobutyric acid**	PFBA	$C_4HF_7O_2$	2.9E-03	1.0E-02
375-73-5	**Perfluorobutane sulfonate** (Perfluorobutane sulfonic acid)	PFBuS	$C_4HF_9O_3S$	1.4E-03	4.9E-03
2706-90-3	Perfluoropentanoic acid	PFPeA	$C_5HF_9O_2$	3.8E-06	NA
355-46-4	**Perfluorohexane sulfonate** (Perfluorohexane sulfonic acid)	PFHxS	$C_6HF_{13}O_3S$	3.8E-06	1.3E-05
307-24-4	Perfluorohexanoic acid	PFHxA	$C_6HF_{11}O_2$	3.8E-06	NA
375-85-9	Perfluoroheptanoic acid	PFHpA	$C_7HF_{13}O_2$	2.3E-05	NA
1763-23-1	**Perfluorooctanoic sulfonate** (Perfluorooctane sulfonic acid)	PFOS	$C_8HF_{17}O_3S$	2.3E-05	8.1E-05
335-67-1	**Perfluorooctanoic acid** (Perfluorooctanoate)	PFOA	$C_8HF_{15}O_2$	1.2E-05	4.1E-06
754-91-6	**Perfluorooctane sulfonamide**	PFOSA	$C_8H_2F_{17}NO_2S$	1.2E-05	4.1E-06
375-95-1	**Perfluorononanoic acid**	PFNA	$C_9HF_{17}O_2$	1.2E-05	2.8E-05
335-76-2	**Perfluorodecanoic acid**	PFDeA	$C_{10}HF_{19}O_2$	1.5E-05	5.3E-05
67906-42-7	Perfluorodecane sulfonate	PFDS	$C_{10}F_{21}SO_3$	1.2E-05	NA
2058-94-8	Perfluoroundecanoic acid	PFUA	$C_{11}HF_{21}O_2$	1.2E-05	NA
307-55-1	**Perfluorododecanoic acid**	PFDoA	$C_{12}HF_{23}O_2$	1.2E-05	4.2E-05
72629-94-8	Perfluorotridecanoic acid	PFTrDA	$C_{13}HF_{25}O_2$	1.2E-05	NA
376-06-7	Perfluorotetradecanoic acid	PFTeDA	$C_{14}HF_{27}O_2$	1.2E-05	NA

[1] Bolded PFCs had at least some chemical-specific data (e.g., PFOSA had an LD_{50}).

REVISIONS:

On June 15, 2011, the TCEQ derived oral reference doses (RfDs) for various PFCs using among other uncertainty factors, an animal-to-human UF_A value of 3. However, since that time the TCEQ has finalized the 2012 *TCEQ Guidelines to Develop Toxicity Factors (RG-442)*. Section 5.3.2 of those final guidelines indicates that when deriving chronic noncarcinogenic oral toxicity factors (e.g., RfDs) where the AUC of the parent chemical (or active metabolite) is known or expected to be associated with toxicity, after toxicokinetic adjustments have been made and consistent with carcinogenic risk assessment practice, the TCEQ will generally use a UF_A of 1 (i.e., a toxicodynamic UF > 1 is not needed). Consequently, the RfDs derived in 2011 have simply been revised to reflect final TCEQ guidance concerning use of a UF_A value of 1. Additionally, at this time the TK factor for the PFHxS RfD will be revised (note: the PFHxS RfD is also used as a surrogate for PFPeA and PFHxA) as will be the RfD-based RfC values.

BACKGROUND:

Perfluoroalkyls (a.k.a. perfluoro compounds or PFCs) are stable chemicals made of a carbon chain surrounded by fluorine atoms and an acid or amide group located at the end of the carbon chain. Perfluoroalkyls are not found naturally in the environment, and PFOA and PFOS are the two perfluoroalkyl compounds made in the largest amounts. PFC substances are unique because they repel oil, grease, and water. Consequently, perfluoroalkyls have been widely used in many consumer products, including in surface protection products such as carpet and clothing treatments, coatings for paper and cardboard packaging, and in fire-fighting foams. Food is expected to be an important source of exposure to perfluoroalkyls based on the amounts found in food samples. Most human exposures to perfluoroalkyls are expected to be through contaminated food and drinking water. Thus, they have been widely found in human blood (e.g., PFOA, PFOS, PFHxS, and PFNA are measureable in the serum of most US citizens) (ATSDR 2009).

Once in the human body, perfluoroalkyls tend to remain unchanged for long periods of time. The most commonly used perfluoroalkyls (PFOA and PFOS) stay in the human body for many years, with a half-life of approximately 4 years (laboratory animal half-lives are much shorter). In general, the shorter the carbon chain length, the faster the perfluoroalkyl leaves the body. Studies conducted in rodents and nonhuman primates have not found quantitatively significant metabolism of PFOA, PFOS, or PFDeA, and PFOA was not metabolized when incubated with microsomal fractions of human or rat intestine, kidney, or liver homogenates. Urine appears to be the major route of excretion of perfluoroalkyls (ATSDR 2009, Tardiff et al. 2009).

In regard to toxicity, PFOA and PFOS have been the most extensively studied members of this class of chemicals. Although oral administration has been the preferred route of exposure in animal studies, the effects of perfluoroalkyl compounds in laboratory animals do not appear to be route-specific. That is, conclusions can be drawn across exposure routes based on results from studies in animals that indicate that the health effects of these substances are independent of the route of exposure. Short-term inhalation exposure of rats to very high levels of PFOA has caused irritation of the eyes and the nose, with lower levels of PFOA causing damage to the liver and weight loss. Oral exposure to perfluoroalkyls in animals mainly produces alterations in the liver, but also reduces their growth. Acute and intermediate duration oral studies have described primarily effects on the liver, body weight, developmental effects, and effects on the immuno/lymphoreticular system. Alterations in liver and kidneys weight have been reported in some chronic rat studies with PFOA. Whether PFCs would be expected to cause cancer in humans is unclear (ATSDR 2009).

The liver is considered a main target for perfluoroalkyl compounds in animals (Tardiff et al. 2009, ATSDR 2009). Liver toxicity in rodents results in part from the ability of these compounds (with some structural restrictions) to activate the peroxisome proliferator activated receptor-α (PPARα), a member of the nuclear receptor superfamily that mediates a broad range of biological responses, although PPARα-null mice also experience liver toxicity and PPARα-independent mechanisms are also implicated (ATSDR 2009, Tardiff et al. 2009). While studies in mice have identified specific effects that require PPARα activation, for example, postnatal viability and some immunological effects, other effects such as hepatomegaly were reported to be PPARα-independent. Overall, *in vivo* gene profiling experiments confirm that PPARα plays

an important role in the mechanism of action of PFOA and PFOS, indicate that there are similarities and differences in gene modulation between PFOA and PFOS, and provide confirmatory evidence for the existence of PPARα-independent mechanisms. Given the wide range of gene groups affected by PFOA and PFOS, there is the potential for a wide range of biological effects following exposure to these compounds. Further studies in PPARα-null mice will expand knowledge regarding PPARα-independent and exclusively PPARα-dependent effects, to which humans are likely less susceptible, and help inform interspecies extrapolation (ATSDR 2009).

Human data are considered inadequate to derive toxicity factors for perfluoroalkyls as it is difficult to show causality and define a point of departure (Tardiff et al. 2009, ATSDR 2009), and there are challenges in interspecies extrapolation of animal study results to humans. For example, there are large interspecies differences in the toxicokinetics of perfluoroalkyls for which mechanisms are not completely understood. Elimination rates (and very likely elimination mechanisms and hormonal regulation of these mechanisms) vary substantially across chemical species (i.e., carbon chain length is generally inversely related to elimination), animal species (i.e., slower in humans compared to non-human primates and rodents), and show pronounced gender differences within certain species (i.e., faster elimination in female rats). Gender- and dose-dependence of elimination of PFOA, for example, has been attributed in part to capacity-limited tubular secretion of PFOA, which may be hormonally regulated by androgens and estrogens. Additionally, dose-dependence of elimination rates in humans, who are exposed to lower doses than those used in animal studies, have not been studied. Lastly, although work is underway (e.g., Loccisano et al. 2011), no validated and accepted human PBPK models have been developed, and due to much slower elimination in humans, exposure durations required to achieve steady state would be expected to be much longer in humans than in monkeys or rats (ATSDR 2009).

Despite these challenges, it is important to derive toxicity factors for these chemicals (using appropriate adjustments and uncertainty factors reflecting the degree of uncertainty) for use at remediation sites because: (1) PFCs are not known to break down in soil or water and thus contamination and potential exposure will persist; and (2) contamination will likely otherwise go unaddressed (i.e., there will be no cleanup values to trigger remediation and other chemical concentrations of concern may not be present). When combined with reasonable maximum long-term exposure assumptions for standard receptors (e.g., residents, commercial/industrial workers) and multiple simultaneous routes of exposure (e.g., incidental soil ingestion, dermal exposure), TCEQ believes these toxicity factors (e.g., RfDs) will result in sufficiently protective environmental media (e.g., soil) cleanup concentrations based on available data.

INFORMATION SOURCES:

TCEQ found no toxicity factors (e.g., oral reference doses or RfDs) published by EPA's IRIS, PPRTVs, HEAST values, or ATSDR MRLs. EPA's Office of Water and the Minnesota Department of Health, however, have published chronic and/or subchronic RfDs for some PFCs (see below). ATSDR (2009) contains useful information for many of the PFCs listed at the beginning on this document. The Registry of Toxic Effects of Chemical Substances (RTECS) by the Canadian Centre for Occupational Health and Safety also contains useful information for

some PFCs. Various other sources were searched for relevant information, including the Hazardous Substances Data Bank (HSDB) by the US Library of Medicine, EPA's HPV chemical program (see various documents at http://www.epa.gov/chemrtk/pubs/summaries/perfluro/ c13244tc.htm), and international agency documents.

This document only summarizes the critical toxicological information utilized to derive toxicity factors. See the references and scientific literature for a more complete discussion of available studies and greater study detail.

ORAL:

In January 2009, EPA's Office of Water derived Provisional Health Advisories for perfluorooctanoic acid and perfluorooctane sulfonate. The derivation of these Provisional Health Advisories (taken from the EPA document at http://www.epa.gov/region4/water/documents/ d_pha_phoa_pfos_final_010809.pdf) is shown in Appendix A. TCEQ used the same studies as starting points to derive chronic RfDs for these two PFCs as EPA did for their subchronic RfDs (http://epa.gov/ region4/water/documents/ final_pfoa_%20pfos_memo_ oswer.pdf).

(1) For perfluorooctanoic acid (PFOA), several animal toxicological studies have been conducted, including subchronic, developmental/reproductive, and chronic toxicity/carcinogenicity studies in several animal species, in both sexes. Ultimately, EPA used a $BMDL_{10}$ of 0.46 mg/kg-day for increase in maternal liver weight from a mouse developmental study (Lau et al. 2006), a toxicokinetic (TK) interspecies data-derived extrapolation factor of 81 (the half-life in humans is years as opposed to days for laboratory animals), a toxicodynamic (TD) interspecies uncertainty factor (UF) of 3, and an intrahuman UF of 10. TCEQ will use the $BMDL_{10}$ of 0.46 mg/kg-day for liver weight effects as a point of departure to derive a potential RfD. For comparison, TCEQ will also use results from other studies as well.

To investigate the low-dose effects of PFOA on offspring, Macon et al. (2011) gavage-dosed timed-pregnant CD-1 mice with PFOA for all or half of gestation. In the full gestation study, mice were administered 0, 0.3, 1.0, and 3.0 mg/kg-day from gestation days (GD) 1-17. In the late gestation study, mice were administered 0, 0.01, 0.1, 1.0 mg/kg-day from GD 10-17. Exposure to PFOA significantly ($p<0.05$) increased offspring relative liver weights in all treatment groups (0.3-3.0 mg/kg-day) in the full gestation study, and in the 1.0 mg/kg-day group in the late gestation study. Thus, the LOAEL for increased liver weight in the full gestation study is 0.3 mg/kg-day, which is also the LOAEL for liver effects in other mouse studies (Onishchenko et al. 2011 as cited by Macon et al. 2011, Loveless et al. 2006). This is a more recent and lower point of departure for liver effects than used by EPA, and will be used by TCEQ to derive a potential RfD. More notably, Macon et al. (2011) found that developmental effects on the mammary gland were at least as sensitive as liver effects. Full gestational exposure to the LOAEL of 0.3 mg/kg-day (no NOAEL) significantly reduced mammary gland development that persisted into adulthood, and the NOAEL for these effects could be significantly lower as late gestation exposure to PFOA produced these effects at a LOAEL of 0.01 mg/kg-day, although late gestational exposed mice were evaluated at

postnatal day 21 and not in adulthood. As the mammary gland effects from full gestational exposure are known not to have reversed by the time evaluated in adulthood, the LOAEL of 0.3 mg/kg-day was used to derive a second potential RfD from this study. For comparison, the LOAEL for mammary effects from late gestational exposure (0.01 mg/kg-day) was also used.

The Loveless et al. (2006) subacute study dosed male CD rats and CD-1 mice by oral gavage with 0.3-30 mg/kg-day for 29 days. In rats, 10 and 30 mg/kg-day resulted in systemic toxicity as evidenced by decreases in body weight gain to 74 and 37%, and increases in serum corticosterone levels to 135 and 196% of control, respectively. In mice dosed with 10 and 30 mg/kg-day, marked systemic toxicity and stress were observed as evidenced by a loss in body weight of 3.8 and 6.6 g, respectively (despite a tripling of liver weight), ~230% increase in serum corticosterone, and increases in absolute numbers of peripheral blood neutrophils and monocytes with an accompanying decrease in absolute lymphocyte numbers. Immune-related findings at 10 and 30 mg/kg-day likely represent secondary responses to the systemic toxicity and stress observed at these doses. An increase in organ weight of over 10% is typically considered adverse. Liver weight and liver/body weight were increased over 30% at 0.3 mg/kg-day in Loveless et al. (2006), which will be used as the LOAEL for derivation of a potential RfD and is consistent with the mouse LOAEL of Macon et al. (2011) for liver effects.

In addition to the data-based TK factor (81) and intrahuman UF (10) used by EPA for their subchronic RfD, other study-specific UFs are required for derivation of potential chronic RfDs (see the table next page). Because liver effects in Lau et al. (2006) were in the mothers due to subacute (GD 1-17) exposure in a developmental study and the RfD is for long-term (i.e., chronic) exposure, TCEQ will also use a UF for extrapolation from subacute to chronic exposure. However, the subacute-to-chronic UF will be reduced from 10 to 3 since liver effects have also been found in available chronic studies (see Table 3-3 of ATSDR 2009) and would yield a similar point of departure as that from Lau et al. with a subacute-to-chronic UF of 3 (e.g., 0.46 mg/kg-day / 3 = 0.15 mg/kg-day = chronic LOAEL of 1.5 mg/kg-day divided by a LOAEL-to-NOAEL UF of 10). A subacute-to-chronic UF of 3 will also be used for Loveless et al. (2006), along with a LOAEL-to-NOAEL UF of 3 for that study. For liver effects found in Macon et al. (2011), a LOAEL-to-NOAEL UF of 3 will be used since a NOAEL for liver effects was not identified but study authors believe it may be approximately 0.1 mg/kg-day (i.e., 0.3 mg/kg-day / 3 = 0.1 mg/kg-day). For the mammary gland developmental effects LOAEL from full gestational exposure in Macon et al. (2011), a LOAEL-to-NOAEL UF of at least 10-30 is justified since late gestational exposure produced these effects at a dose 30 times lower (although the persistence of effects into adulthood from late gestational exposure were not evaluated). For the mammary gland effects from late gestational exposure, a LOAEL-to-NOAEL UF of 3 is justified. Lastly, TCEQ will use an animal-to-human UF of 1 (since TK already adjusted for under Section 5.3.2 of the 2012 TCEQ guidelines) and a database UF of 1 as the toxicological database for PFOA is relatively robust, particularly in laboratory animals (see the following figure and Table 3-3 in ATSDR 2009).

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	●	●			●	●	●	●		
Oral	●	●	●	●			●	●	●	●
Dermal	●	●			●	●	●			

Animal

Potential PFOA RfD Values

Study (effect)	POD (mg/kg-day)	TK Factor	TD UF	Subacute-to-Chronic UF	LOAEL-to-NOAEL UF	Intra-human UF	Database UF	Potential RfD (mg/kg-day)
Lau et al. (liver)	0.46	81	1	3	NA	10	1	1.9E-04
Macon et al. (liver)	0.3	81	1	NA	3	10	1	1.2E-04
Macon et al. (mammary glands-full exposure)	0.3	81	1	NA	10-30	10	1	**1.2E-05** to 3.7E-05
Macon et al. (mammary glands-late exposure)	0.01	81	1	NA	3	3-10	1	4.1E-06 to **1.4E-05**
Loveless et al. (liver)	0.3	81	1	3	3	10	1	4.1E-05

The potential chronic RfDs based on liver effects (4.1E-05 to 1.9E-04 mg/kg-day) are very similar and seem reasonable compared to EPA's subchronic RfD (2.0E-04 mg/kg-day) and the Minnesota Department of Health subchronic RfD (7.7E-05 mg/kg-day), which are also based on liver effects. However, examination of the potential RfDs based on mammary gland developmental effects in mice reveals that protection against liver effects may not adequately protect against developmental effects due to *in utero* exposure of the developing fetus to this common PFC. Use of the lower RfD value (1.2E-05 mg/kg-day) based on permanent mammary gland developmental effects in Macon et al. (2011) may be viewed as also offering protection even if the mammary effects due to 0.01 mg/kg-day late gestational exposure did persist into adulthood since use of that lower LOAEL (0.01 mg/kg-day) with a somewhat reduced intrahuman UF of 3 results in the a very similar RfD (see the table above).

An RfD of 1.2E-05 mg/kg-day results in an estimated TRRP residential groundwater ingestion PCL for chronic exposure (≈ 0.29 µg/L) which is reasonable compared to EPA's subchronic provisional health advisory value for PFOA (0.4 µg/L). To confirm its health protectiveness with a margin-of-exposure (MOE) approach, this residential groundwater PCL would be associated with estimated human serum concentrations (0.029-0.0435 µg/mL based on 100:1 to 150:1 median ratios for serum-to-drinking water concentrations; Emmett et al. 2006, Post et al. 2009, ATSDR 2009) which appear amply

below the approximate serum concentration (0.3 µg/mL) associated with mammary gland abnormalities in mice (Macon et al. 2011, supported by White et al. 2011). However, this MOE does not support use of a higher RfD. Thus, the RfD (1.2E-05 mg/kg-day) is based on permanent mammary gland developmental effects in Macon et al. (2011).

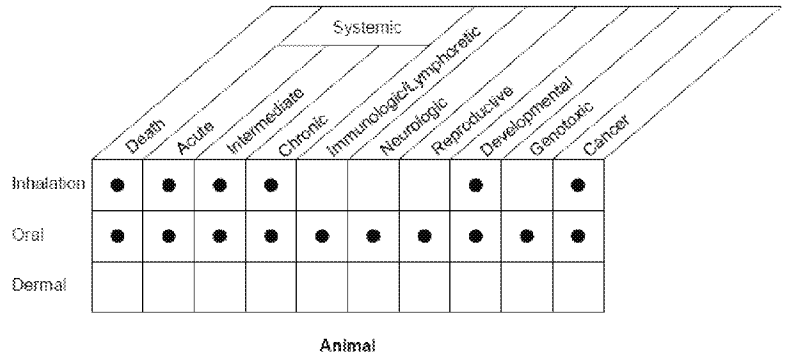
PFOA RfD = 0.3 mg/kg-day / (81 x 1 x 30 x 10 x 1) = 1.2E-05 mg/kg-day

(2) For perfluorooctane sulfonate (PFOS), several animal toxicological studies have been conducted, including subchronic, developmental/reproductive, and chronic toxicity/carcinogenicity studies in several animal species, in both sexes. Ultimately, EPA used a Cynomolgus monkey NOAEL of 0.03 mg/kg-day for increased levels of thyroid-stimulating hormone (TSH) in males, reduced total T3 levels in males and females, and reduced levels of high-density lipoproteins (HDL) in females (Seacat et al. 2002). EPA also used a TK interspecies data-derived extrapolation factor of 13 (the half-life in humans is years as opposed to days for laboratory animals), a TD interspecies UF of 3, and an intrahuman UF of 10. TCEQ will use this study to derive a potential RfD.

While a review of the scientific literature since ATSDR (2009) showed similar or higher initial potential points of departure for different species (e.g., Mollenhauer et al. 2011, Zeng et al. 2011, Onishchenko et al. 2011), interspecies TK differences can potentially result in significantly different points of departure after TK adjustment. In the Zeng et al. (2011) study, pregnant Sprague Dawley (SD) rats were given 0.1, 0.6, and 2.0 mg/kg-day by gavage from GD 0 to GD20. PFOS concentration in the hippocampus of offspring was observed on postnatal day (PND) 0 and PND21. The offspring hippocampus from PFOS-treated maternal groups showed significant adverse changes in the structure of synapses beginning at 0.1 mg/kg-day (active zone length decreased 10%), with all three measures being statistically significantly affected at 0.6 mg/kg-day and above (active zone length, number of vesicles per area, synaptic interface curvature). The structure of synapses affects synaptic connection between neurons, which is critical to normal functioning of the central nervous system. The offspring from PFOS-treated maternal groups also differed significantly from controls with respect to the expression of synaptic vesicle associated proteins, which play an important role in nervous signal transmission. More specifically, the mRNA levels of synapsin1 (Syn1), synapsin2 (Syn2), and synaptophysin (Syp) were decreased in treated groups either on PND0 or on PND21. These study results showed significant adverse synaptic structural changes in the hippocampus (and lower mRNA levels of synaptic vesicle associated proteins) and add to the database of other study results showing developmental neurotoxicity induced by PFOS in laboratory animals (e.g., increased motor activity, reduced habitation, impairment of cognitive function). TCEQ considers the clear LOAEL from this study to be 0.6 mg/kg-day, where all three measures of hippocampus synaptic structure were adversely affected, which will be used to derive a potential RfD.

In addition to other factors and UFs, because the Seacat et al. (2002) monkey study used subchronic (183-day) exposure and the RfD is for long-term (i.e., chronic) exposure, TCEQ will also use a UF of 3 for extrapolation from subchronic to chronic exposure. Additionally, TCEQ will use a database UF of 1 as the toxicological database for PFOS is

relatively robust, particularly in laboratory animals (see the following figure and Table 3-4 in ATSDR 2009).



Potential PFOS RfD = 0.03 mg/kg-day / (13 x 1 x 10 x 3 x 1)
= 7.7E-05 mg/kg-day

The rat study of Zeng et al. (2011) requires a different data-derived TK interspecies adjustment factor. Using the same methodology as EPA did, because data support using the same volumes of distribution for rodents and humans (per EPA), the equations to calculate the TK interspecies factor can be simplified to: human half-life / animal half-life. TCEQ used the same human PFOS half-life as EPA (1,971 days) with a rat PFOS half-life of 7.5 days (ATSDR 2009, Cui et al. 2011), resulting in a TK factor of 263. Zeng et al. (2011) also requires a LOAEL-to-NOAEL UF. Because one adverse effect on hippocampus synapses structure was statistically significant at a dose 6 times lower, TCEQ will use a LOAEL-to-NOAEL UF of 10 along with the TK factor of 263, animal-to-human UF of 1 (since TK already adjusted for under Section 5.3.2 of the 2012 TCEQ guidelines), intrahuman UF of 10, and database UF of 1.

Potential PFOS RfD = 0.6 mg/kg-day / (263 x 1 x 10 x 10 x 1)
= 2.3E-05 mg/kg-day

These potential chronic RfDs are very similar (within a factor of 3.4) and seem reasonable compared to EPA's subchronic RfD (8.0E-05 mg/kg-day) and the Minnesota Department of Health subchronic RfD (8.0E-05 mg/kg-day). However, examination of the potential RfDs shows that protection against thyroid effects may not adequately protect against neurological developmental effects due to *in utero* exposure of the developing fetus to this common PFC. Thus, the RfD will be based on Zeng et al. (2011). Use of the RfD of 2.3E-05 mg/kg-day results in an estimated chronic TRRP residential groundwater ingestion PCL (≈ 0.56 µg/L) which is similar to (within a factor of 3 of) EPA's subchronic provisional health advisory value for PFOS (0.2 µg/L).

PFOS RfD = 0.6 mg/kg-day / (263 x 1 x 10 x 10 x 1) = 2.3E-05 mg/kg-day

(3) For perfluorobutyric acid (PFBA, or heptafluorobutyric acid), relatively few relevant toxicity studies have been conducted (ATSDR 2009). However, the Minnesota Department of Health has published a subchronic RfD based on a subchronic (90-day) rat

study NOAEL of 6.9 mg/kg-day for liver weight changes, morphological changes in the liver and thyroid gland, decreased TT4, and decreased red blood cells, hematocrit, and hemoglobin (van Otterdijk 2007). Review of relevant information in ATSDR (2009) did not identify a lower point of departure. The human equivalent dose of 0.86 mg/kg-day was obtained by the Minnesota Department of Health using a TK interspecies factor of 8 (i.e., 6.9 mg/kg-day / 8 adjusting for half-life duration of 3 days in humans versus 9.22 hours in male rats = 0.86 mg/kg-day). Appropriate UFs are as follows: 1 for interspecies TD differences, 10 for intrahuman variability, 3 for subchronic to chronic, and 10 for significant database insufficiencies (e.g., neither a chronic nor a multi-generation reproductive study has been conducted).

PFBA RfD = 6.9 mg/kg-day / (8 x 1 x 10 x 3 x 10) = 2.9E-03 mg/kg-day

This chronic RfD seems reasonable compared to the Minnesota Department of Health subchronic RfD (2.9E-03 mg/kg-day).

(4) For perfluorobutane sulfonate (PFBuS), the Minnesota Department of Health has published a subchronic RfD based on a rat subchronic (90-day) study NOAEL of 60 mg/kg-day for decreased hemoglobin and hematocrit, and histological changes in the kidney (Leider et al. 2009, York 2003). Review of relevant information in ATSDR (2009) did not identify a lower point of departure. The human equivalent dose of 0.42 mg/kg-day was obtained by the Minnesota Department of Health using a TK interspecies factor of 142. Appropriate UFs are as follows: 1 for interspecies TD differences, 10 for intrahuman variability, 3 for subchronic to chronic, and 10 for significant database insufficiencies (i.e., only one study available).

PFBuS RfD = 60 mg/kg-day / (142 x 1 x 10 x 3 x 10) = 1.4E-03 mg/kg-day

This chronic RfD seems reasonable compared to the Minnesota Department of Health subchronic RfD (4.2E-03 mg/kg-day).

(5) For perfluorooctane sulfonamide (PFOSA), only LD_{50} data were found (RTECS). The rodent oral LD_{50} of > 172 mg/kg for perfluorooctane sulfonamide may be similar to that for PFOA (LD_{50} of 189 mg/kg), another 8-carbon PFC for which the toxicity database is more robust. The RfD for PFOA has a more scientifically-defensible basis than using an uncertain LD_{50} value to derive an RfD for PFOSA. The RfD for PFOA was used as the surrogate for PFOSA.

PFOSA RfD = 1.2E-05 mg/kg-day

(6) For perfluorononanoic acid (PFNA), a few toxicity studies are mentioned in RTECS, but reproductive studies provided much higher points of departure (20-85 mg/kg-day per information from RTECS) than Fang et al. (2010). In Fang et al. (2010), rats receiving 1, 3, or 5 mg/kg-day for 2 weeks showed dose-dependent decreases in the absolute spleen weight (decreased by 22.2%, 28.7% and 57.9%, respectively; $p < 0.01$) compared to the control group. However, the ratio of spleen weight to body weight only significantly

decreased (91.5% of the control, $p < 0.01$) in the group given the highest dose (5 mg/kg-day). Significantly increased levels of pro-inflammatory IL-1, IL-6, and TNF-α (149.4%, 140.5%, 130.1% of the control, respectively), which play important roles in cellular apoptosis, also occurred at 5 mg/kg-day. The number of apoptotic spleen cells significantly increased in animals receiving 3 and 5 mg/kg-day. TCEQ considers 1 mg/kg-day as the NOAEL for spleen cell apoptosis, which also protects against spleen weight decreases (normalized to body weight) and other effects, and will use this NOAEL to derive a potential RfD.

Additionally, ATSDR (2009) cites Kennedy (1987), another subacute study but in mice. In Kennedy (1987), treatment of male and female mice with approximately 5.3 mg/kg-day PFNA for 14 days increased absolute liver weight by 178–190%. ATSDR (2009) indicates 0.5 mg/kg-day is the LOAEL for increases (50-70%) in absolute liver weight (see Table 3-5 of ATSDR 2009). TCEQ will also use this LOAEL to derive a potential RfD.

In the rat, the rate of elimination appears to vary with the perfluoroalkyl carbon chain length, although the gender difference is also a common feature (Tatum-Gibbs et al. 2011, ATSDR 2009). Information for the mouse is less complete, but a similar trend is apparent. Tatum-Gibbs et al. (2011) provides gender-specific rat half-lives for PFNA that average to around 16 days (30 days for males, 1.4–2.4 days for females), which is very similar to the 17 days used by EPA for PFOA in mice. Using the same methodology as EPA did for PFOA and PFOS, because data support using the same volumes of distribution for rodents and humans (per EPA), the equations to calculate the TK interspecies factor can be simplified to: human half-life / animal half-life. Due to the similar carbon chain length of PFOA (8 carbons) and PFNA (9 carbons), similar elimination trends in rats and mice with carbon chain length, and similar PFNA half-lives in rats as PFOA in mice (mentioned above), the PFNA half-life in mice was assumed to be the same as for rats. Furthermore, although PFNA half-life information for humans was not located, the similarity in half-life between PFOA and PFNA in rodents (rats, mice) is assumed to extend to humans. Consequently, the relative half-lives for rats/mice and humans are assumed to be the same for PFNA as for PFOA, maintaining the human-to-rodent half-life ratio of approximately 81. Thus, TCEQ used the TK interspecies factor of 81 calculated by EPA for PFOA for derivation of the PFNA RfD.

To summarize, TCEQ will use the rat NOAEL of 1 mg/kg-day and the mouse LOAEL of 0.5 mg/kg-day with a TK interspecies extrapolation factor of 81, a TD interspecies UF of 1, an intrahuman UF of 10, a UF of 10 for extrapolation from subacute to chronic, and a database UF of 10.

$$\text{Potential PFNA RfD} = 1 \text{ mg/kg-day} / (81 \times 1 \times 10 \times 10 \times 10)$$
$$= 1.2\text{E-05 mg/kg-day}$$

The mouse study (Kennedy 1987) LOAEL requires an additional LOAEL-to-NOAEL UF of 3:

Potential PFNA RfD = 0.5 mg/kg-day / (81 x 1 x 10 x 10 x 10 x 3)
= 2.1E-06 mg/kg-day

These potential RfDs are very similar (within a factor of 6) and both are considered protective based on available data. Thus, TCEQ will use the value based on spleen cell apoptosis in the as the RfD for PFNA:

PFNA RfD = 1 mg/kg-day / (81 x 1 x 10 x 10 x 10) = 1.2E-05 mg/kg-day

(7) For perfluorodecanoic acid (PFDeA), several subacute (e.g., 7-10 day) toxicity studies were available, but other studies provided much higher points of departure (21-120 mg/kg-day per information from RTECS) than Harris and Birnbaum (1989). For Harris and Birnbaum (1989), to determine if PFDeA exhibits teratogenic effects or is a developmental toxin, time-mated C57BL/6*N* mice were administered PFDeA by gavage in corn oil (10 ml/kg) on GD 10–13 or GD 6–15 at levels of 0, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, or 32.0 mg/kg-day or 0, 0.03, 0.3, 1.0, 3.0, 6.4, or 12.8 mg/kg-day, respectively. Dams were killed on GD 18 and maternal and fetal toxicity was assessed. Fetuses were examined for external, visceral, or skeletal malformations. No hydronephrosis, cleft palate, or edema was observed, nor was any other soft tissue or skeletal malformations detected. Maternal body weight gain (corrected for the weight of the gravid uterus) was significantly reduced as a result of PFDeA treatment at 6.4 and 12.8 mg/kg-day (GD 6–15) and 16.0 and 32.0 mg/kg/-day (GD 10–13). Fetal viability was decreased only in those groups showing extensive maternal body weight loss. Fetal weight per litter was decreased 33% at 6.4 mg/kg-day, and fetal body weights were significantly reduced at levels as low as 0.1 mg/kg-day (GD 6–15) and 0.5 mg/kg-day (GD 10–13). As effects on offspring are a particular concern (ATSDR 2009), TCEQ will conservatively use 0.1 mg/kg-day as the LOAEL for decreases in fetal body weight (GD 6-15) to derive a potential RfD.

Additionally, ATSDR (2009) cites 1.2 mg/kg-day as the NOAEL for increased liver weight (≈ 30%) in a subacute (1-week) rat study (Kawashima et al. 1995). More specifically, Kawashima et al. (1995) compared the effects of lower dietary doses of PFDeA (1.2-9.5 mg/kg-day) and PFOA (2.4-38 mg/kg-day) on hepatic effects in male rats in a 7-day dietary study. PFDeA was considerably more potent than PFOA in reducing body weight gain and food consumption, and causing hepatomegaly. Both chemicals had comparable potencies in elevating hepatic cholesterol and triacylglycerol, but only PFOA elevated hepatic phospholipids. PFDeA lowered the activity of GSH-related enzymes in the same manner as PFOA. The LOAEL for increased liver weight (≈ 30%) was 2.4 mg/kg-day, with an associated NOAEL of 1.2 mg/kg-day which will be used by TCEQ to derive a potential RfD.

TCEQ recognizes there is significant uncertainty in interspecies extrapolation for PFDeA given: (1) the absence of chemical-specific half-life data for derivation of a rat-to-human TK factor; (2) rat data indicate a decreasing elimination rate trend with increasing perfluoroalkyl chain length; and (3) the elimination of PFDeA in male-female rats is estimated to be about 7-140 times slower than PFOA (ATSDR 2009). In recognition of

this uncertainty, TCEQ will use the most conservative data-based TK interspecies extrapolation factor available from other RfD derivations for longer carbon chain PFCs as a surrogate for PFDeA (i.e., the TK interspecies extrapolation factor of 81 for PFOA (8-carbon) is the most conservative surrogate value for PFDeA (10-carbon)). That is, in order to derive an RfD for a chemical which may otherwise go unaddressed at a site, TCEQ will assume the ratio of human-to-rodent half-lives for PFDeA is the same as that for PFOA (i.e., the PFDeA half-lives for both humans and rats/mice are assumed to be increased by the same factor over those for PFOA, maintaining the human-to-rat half-life ratio of approximately 81). The following UFs will also be used for both the rat NOAEL and mouse LOAEL: a TD interspecies UF of 1, an intrahuman UF of 10, and a database UF of 10 for significant insufficiencies (e.g., no chronic or subchronic studies).

The subacute rat study (Kawashima et al. 1995) requires an additional subacute-to-chronic UF of 10:

Potential PFDeA RfD = 1.2 mg/kg-day / (81 x 1 x 10 x 10 x 10)
= 1.5E-05 mg/kg-day

The developmental mouse study (Harris and Birnbaum 1989) LOAEL requires an additional LOAEL-to-NOAEL UF of 3:

Potential PFDeA RfD = 0.1 mg/kg-day / (81 x 1 x 3 x 10 x 10)
= 4.1E-06 mg/kg-day

These potential RfDs are very similar (within a factor of 4) and both are considered protective based on available data. Thus, TCEQ will use the value based on reduced rat body weight as the RfD for PFDeA:

PFDeA RfD = 1.2 mg/kg-day / (81 x 1 x 10 x 10 x 10) = 1.5E-05 mg/kg-day

(8) For perfluorohexane sulfonate (PFHxS), ATSDR (2009) indicates that a single study was available. The subchronic (42-56 day) study evaluated the reproductive and developmental effects of this perfluoroalkyl compound in male and female rats exposed from premating until PND 21 (females) (Hoberman and York 2003). Doses of 0, 0.3, 1, 3, or 10 mg/kg-day were administered by oral gavage. PFHxS did not significantly affect any reproductive or developmental parameter nor did it induce maternal toxicity assessed by clinical chemistry and hematology tests and organ histopathology. PFHxS did induce hematological alterations in male rats at ≥ 0.3 mg/kg-day and liver and thyroid effects at ≥ 3 mg/kg-day. More specifically, treatment of male rats with doses ≥ 0.3 mg/kg-day for at least 42 days significantly increased prothrombin time, doses ≥ 1 mg/kg-day significantly decreased hemoglobin concentration, and doses ≥ 3 mg/kg-day decreased erythrocyte count and hematocrit. Treatment of female rats with up to 10 mg/kg-day PFHxS did not significantly alter hematological parameters. The thyroid effects in male rats were thought to be a compensatory response to liver hypertrophy. The dose of 0.3 mg/kg-day is the LOAEL for hematological alterations in male rats (ATSDR 2009). TCEQ recognizes there is significant uncertainty in interspecies extrapolation for PFHxS

given the absence of chemical-specific half-life data for derivation of a rat-to-human TK factor. In recognition of this uncertainty and that half-life generally increases (i.e., elimination rate decreases) with increasing carbon chain length (ATSDR 2009), TCEQ will use a data-based TK interspecies extrapolation factor available for an 8-carbon PFC (PFOS) as a surrogate for the 6-carbon PFHxS. This appears reasonable based on available half-life data since the human half-life for PFOS (1,053-2,701 days) is most similar to that for PFHxS (2,662 days) among PFCs with reported human half-lives (Table 3-8 of ATSDR 2009). That is, in order to derive an RfD for a chemical which may otherwise go unaddressed at a site, TCEQ will assume the ratio of human-to-rat half-lives for PFHxS is the same as that for PFOS, maintaining the human-to-rat half-life ratio of approximately 263. The following UFs will also be used: a TD interspecies UF of 1, a LOAEL-to-NOAEL UF of 3, an intrahuman UF of 10, and a database UF of 10 for significant insufficiencies (e.g., only one study).

PFHxS RfD = 0.3 mg/kg-day / (263 x 1 x 3 x 10 x 10) = 3.8E-06 mg/kg-day

(9) For perfluorododecanoic acid (PFDoA), ATSDR (2009) indicates that dosing of Sprague-Dawley rats with 5 mg/kg-day PFDoA by gavage for 14 days resulted in a 25% reduction in final body weight relative to a control group, as well as decreased serum testosterone and estradiol (Shi et al. 2007). This subacute study had a NOAEL of 1 mg/kg-day for reduced body weight.

TCEQ recognizes there is significant uncertainty in interspecies extrapolation for PFDoA given: (1) the absence of chemical-specific half-life data for derivation of a rat-to-human TK factor; and (2) rat data indicate a decreasing elimination rate trend with increasing perfluoroalkyl chain length. In recognition of this uncertainty, TCEQ will use the most conservative data-based TK interspecies extrapolation factor available from other RfD derivations for longer carbon chain PFCs as a surrogate for PFDoA (i.e., the TK interspecies extrapolation factor of 81 for PFOA (8-carbon) is the most conservative surrogate value for PFDoA (12-carbon)). That is, in order to derive an RfD for a chemical which may otherwise go unaddressed at a site, TCEQ will assume the ratio of human-to-rat half-lives for PFDoA is the same as that for PFOA (i.e., the PFDoA half-lives for both humans and rats are assumed to be increased by the same factor over those for PFOA, maintaining the human-to-rat half-life ratio of approximately 81). The following UFs will also be used: a TD interspecies UF of 1, a subacute-to-chronic UF of 10, an intrahuman UF of 10, and a database UF of 10 for significant insufficiencies (e.g., no chronic or subchronic studies).

PFDoA RfD = 1 mg/kg-day / (81 x 1 x 10 x 10 x 10) = 1.2E-05 mg/kg-day

(10) No toxicity data were found for perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorodecane sulfonate (PFDS), perfluoroundecanoic acid (PFUA), perfluorotridecanoic acid (PFTrDA), and perfluorotetradecanoic acid (PFTeDA). Recognizing that elimination rate generally decreases as carbon chain length increases and there is uncertainty associated with assigning surrogate values, an RfD from a PFC with the same or longer carbon chain

length was conservatively assigned as the surrogate RfD value for these PFCs, except for PFTrDA and PFTeDA. For PFTrDA (13 carbon) and PFTeDA (14 carbon), there is no PFC of the same or longer carbon chain length with an RfD, so the RfD for PFDoA (12 carbon) was used.

PFPeA RfD = RfD for PFHxS = 3.8E-06 mg/kg-day
PFHxA RfD = RfD for PFHxS = 3.8E-06 mg/kg-day
PFHpA RfD = RfD for PFOS = 2.3E-05 mg/kg-day
PFDS RfD = RfD for PFDoA = 1.2E-05 mg/kg-day
PFUA RfD = RfD for PFDoA = 1.2E-05 mg/kg-day
PFTrDA RfD = RfD for PFDoA = 1.2E-05 mg/kg-day
PFTeDA RfD = RfD for PFDoA = 1.2E-05 mg/kg-day

INHALATION:

(1) For PFOA, only two relatively low-exposure inhalation studies were available (ATSDR 2009). In one study, male CD rats were exposed head-only 6 hours/day, 5 days/week for 2 weeks to ammonium perfluorooctanoate (APFO) dusts (Kennedy et al. 1986), whereas in the other study, a developmental study, pregnant Sprague-Dawley rats were exposed whole-body to APFO dusts 6 hours/day on GD 6-15 (Staples et al. 1984). The lowest LOAEL was 7.6 mg/m^3 for exposure concentration-related increases in absolute and relative liver weight and histological alterations in the liver; no significant effects were reported at 1 mg/m^3 (Kennedy et al. 1986). Serum PFOA levels were not monitored in this study, but a TK study in male rats exposed nose-only 6 hours/day, 5 days/week for 3 weeks reported that PFOA serum levels in a group exposed to 10 mg/m^3 had achieved a steady-state concentration of approximately 20,000 ng/mL by day 14 of the study (Hinderliter et al. 2006). Kennedy et al. (1986) also examined several organs and tissues microscopically and reported that no significant alterations were observed. In the developmental study, an exposure concentration of 25 mg/m^3 induced a 10% decrease in newborn body weight on PND 1; this exposure concentration decreased weight gain in the dams by 37% on GD 6-15 (Staples et al. 1984). Serum PFOA levels were not monitored in this study. TCEQ will use a NOAEL of 1 mg/m^3 for increases in absolute and relative liver weight and histological alterations in the liver in rats (Kennedy et al. 1986) to derive a reference concentration (RfC) for PFOA.

The TK interspecies data-derived extrapolation factor of 81 for PFOA used by EPA for their subchronic RfD will also be used to account for interspecies TK differences following inhalation, along with: a TD interspecies UF of 3, a UF of 10 for extrapolation from subacute to chronic, an intrahuman UF of 10, and a database UF of 10 for significant insufficiency in the inhalation database (e.g., no subchronic or chronic studies).

PFOA RfC = 1 mg/m^3 / (81 x 3 x 10 x 10 x 10) = 4.1E-06 mg/m^3

Given the limited inhalation data available, this RfC shows reasonable agreement with the derived oral RfD extrapolated to the inhalation pathway (i.e., 1.9E-05 mg/kg-day x 70

kg / 20 m^3-day = 6.6E-05 mg/m^3, within a factor of 16) and the TCEQ long-term effects screening level (ESL) used for air permitting (1.0E-05 mg/m^3, within a factor of 2.5).

As with the RfD for PFOA, the RfC will serve as a surrogate for PFOSA:

PFOSA RfC = 4.1E-06 mg/m^3

(2) For PFNA, male CD rats exposed nose-only to ≥ 590 mg/m^3 ammonium perfluorononanoate dusts for 4 hours (Kinney et al. 1989) exhibited lung noise and labored breathing during exposure and throughout a 12-day recovery period, and final body weight was reduced 18% five days post-exposure (ATSDR 2009). For this acute study, the NOAEL for these effects in males was 67 mg/m^3, which will be used to derive an RfC.

As with oral exposure for PFNA, TCEQ will use a TK interspecies extrapolation factor of 81 and a TD interspecies UF of 3. Additionally, the following UFs are appropriate: an intrahuman UF of 10, a UF of 10 for extrapolation from acute to subchronic, a UF of 10 for extrapolation from subchronic to chronic, and a database UF of 10 for significant insufficiency in the inhalation database (e.g., no subchronic or chronic studies, or even subacute).

PFNA RfC = 67 mg/m^3 / (81 x 3 x 10 x 10 x 10 x 10) = 2.8E-05 mg/m^3

Given the limited inhalation data available, this RfC shows reasonable agreement with the derived oral RfD extrapolated to the inhalation pathway (i.e., 1.2E-05 mg/kg-day x 70 kg / 20 m^3-day = 4.2E-05 mg/m^3, within a factor of 1.5).

(3) For PFBA, PFBuS, PFHxS, PFOS, PFDeA, and PFDoA, all of which had toxicity data, RfC values will be derived using route-to-route extrapolation from their RfD values because the effects of PFCs in laboratory animals do not appear to be route-specific. That is, because the health effects of these substances are independent of the route of exposure (ATSDR 2009), route-to-route extrapolation is supported. Assuming equal absorption in the absence of inhalation absorption data, the following general equation is used:

RfD in mg/kg-day x 70 kg / 20 m^3-day = RfC in mg/m^3

PFBA RfC = 2.9E-03 mg/kg-day x 70 kg / 20 m^3-day = 1.0E-02 mg/m^3
PFBuS RfC = 1.4E-03 mg/kg-day x 70 kg / 20 m^3-day = 4.9E-03 mg/m^3
PFHxS RfC = 3.8E-06 mg/kg-day x 70 kg / 20 m^3-day = 1.3E-05 mg/m^3
PFOS RfC = 2.3E-05 mg/kg-day x 70 kg / 20 m^3-day = 8.1E-05 mg/m^3
PFDeA RfC = 1.5E-05 mg/kg-day x 70 kg / 20 m^3-day = 5.3E-05 mg/m^3
PFDoA RfC = 1.2E-05 mg/kg-day x 70 kg / 20 m^3-day = 4.2E-05 mg/m^3

(4) As RfDs typically drive cleanup values and surrogate RfDs were assigned to PFCs with no toxicity data (PFPeA, PFHxA, PFHpA, PFDS, PFUA, PFTrDA, and PFTeDA), no surrogate RfC values are necessary for these PFCs.

Joseph "Kip" Haney, MS
Senior Toxicologist
(reviewed by Michael E. Honeycutt, Ph.D.)

Key References:

ATSDR. 2009. Draft Toxicological Profile for Perfluoroalkyls. May 2009.

Cui L, Liao CY, Zhou QF, et al. 2011. Excretion of PFOA and PFOS in male rats during a subchronic exposure. Arch Environ Contam Toxicol 58(1): 205-13.

Emmett EA, Shofer FS, Zhang H, et al. 2006. Community exposure to perfluorooctanoate: Relationships between serum concentrations and exposure sources. J Occup Environ Med 48:759-770.

Fang X, Fenga Y, Wang J, et al. 2010. Perfluorononanoic acid-induced apoptosis in rat spleen involves oxidative stress and the activation of caspase-independent death pathway. Toxicology 267: 54-59.

Harris MW, Birnbaum LS. 1989. Developmental toxicity of perfluorodecanoic acid in C57BL/6N mice. Fundam Appl Toxicol 12:442-448.

Hinderliter PM, DeLorme MP, Kennedy GL. 2006. Perfluorooctanoic acid: Relationship between repeated inhalation exposures and plasma PFOA concentration in the rat. Toxicology 222:80-85.

Hoberman AM, York RG. 2003. Oral (gavage) combined repeated dose toxicity study of T-7706 with the reproduction/developmental toxicity screening test. Argus Research.

Kawashima Y, Kobayashi H, Miura H, et al. 1995. Characterization of hepatic responses of rat to administration of perfluorooctanoic and perfluorodecanoic acids at low levels. Toxicology 99(3):169178.

Kennedy GL, Hall GT, Brittelli MR, et al. 1986. Inhalation toxicity of ammonium perfluorooctanoate. Food Chem Toxicol 24(12):1325-1329.

Kennedy GL. 1987. Increase in mouse liver weight following feeding of ammonium perfluorooctanoate and related fluorochemicals. Toxicol Lett 39(2-3):295-300.

Kinney LA, Chromey NC, Kennedy Jr GL. 1989. Acute inhalation toxicity of ammonium perfluorononanoate. Food Chem Toxicol 21(1):46-68.

Lau C, Thibodeaux JR, Hanson RG, et al. 2006. Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. Toxicol Sci 90(2):510-518.

Leider PH, SC Chang, RG York, JL Butenhoff. 2009. Toxicological evaluation of potassium perfluorobutanesulfonate in a 90-day oral gavage study with Spraque-Dawley rats. Toxicology 255:45-52.

Loccisano AE, Campbell JL, Andersen ME, Clewell HJ. 2011. Evaluation and prediction of PFOA and PFOS in the monkey and human using a PBPK model. Reg Tox Pharmacol 59(1): 157-75.

Loveless SE, Finlay C, Everds NE, et al. 2006. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). Toxicology 220(2-3):203217.

Macon MB, Villanueva LR, Tatum-Gibbs K, et al. 2011. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low dose developmental effects and internal dosimetry. Toxicol Sci First published online: April 11, 2011 (doi: 10.1093/toxsci/kfr076).

Mollenhauer MA, Bradshaw SG, Fair PA, et al. 2011. Effects of perfluorooctane sulfonate (PFOS) exposure on markers of inflammation in female B6C3F1 mice. J Environ Sci Health Part A 46(2): 97-108.

Onishchenko N, Fischer C, Ibrahim WNW, et al. 2011. Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. Neurotox Res 19(3): 452-61.

Post GB, Cooper KR, Louis JB, et al. 2009. Response to Comment on "Occurrence and Potential Significance of Perfluorooctanoic Acid (PFOA) Detected in New Jersey Public Drinking Water Systems." Environ Sci Technol 43 (22): 8699-8700.

Seacat AM, Thomford PJ, Hansen KJ, et al. 2002. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in cynomolgus monkeys. Toxicol Sci 68(1):249-264.

Shi Z, Zhang H, Liu Y, et al. 2007. Alterations in gene expression and testosterone synthesis in the testes of male rats exposed to perfluorododecanoic acid. Toxicol Sci 98(1):206-215.

Staples RE, Burgess BA, Kerns WD. 1984. The embryo-fetal toxicity and teratogenic potential of ammonium perfluorooctanoate (APFO) in the rat. Fundam Appl Toxicol 4:429-440.

Tardiff RG, Carson ML, Sweeney LM, et al. 2009. Derivation of a Drinking Water Equivalent Level (DWEL) Related to the MaximumContaminant Level Goal for Perfluorooctanoic Acid (PFOA), a Persistent Water Soluble Compound. Food Chem Toxicol 47: 2557–2589.

Tatum-Gibbs K, Wambaughb JF, Das KP, et al. 2011. Comparative pharmacokinetics of perfluorononanoic acid in rat and mouse. Toxicology 281: 48-55.

Trudel D, Horowitz L, Wormuth M, et al. 2008. Estimating consumer exposure to PFOS and PFOA. Risk Anal 28(2):251-269.

van Otterdijk FM. 2007. Repeated dose 90-day oral toxicity study with MTDID 8391 by daily gavage in the rat followed by a 3-week recovery period. 3M.

White SS, Stanko JP, Kato K, et al. 2011. Gestational and Chronic Low-Dose PFOA Exposures and Mammary Gland Growth and Differentiation in Three Generations of CD-1 Mice. Environ Health Perspect First published online: April 18, 2011 (doi: 10.1289/ehp.1002741).

York RG 2003. Oral (Gavage) Repeated Dose 90-Day Toxicity Study of Potassium Perfluorobutane Sulfonate (PFBS) in Rats. Argus Research Protocol Number 418-026.

Zeng HC, Li YY, Zhang L, et al. 2011. Prenatal exposure to perfluorooctanesulfonate in rat resulted in long-lasting changes of expression of synapsins and synaptophysin. Synapse 65(3): 225-33.

Appendix A: EPA Provisional Health Advisory Values

The Office of Water (OW) has developed Provisional Health Advisory values for PFOA and PFOS to assess potential risk from exposure to these chemicals through drinking water. Other PFCs have been found at this site. However, information on the toxicity of PFCs other than PFOS and PFOA is limited and therefore no attempt is made at the present time to develop Provisional Health Advisory values for these other PFCs.

Summary of Data for PFOA

Epidemiological studies of exposure to PFOA and adverse health outcomes in humans are inconclusive at present.

Several animal toxicological studies have been conducted using PFOA. These include subchronic, developmental/reproductive, and chronic toxicity/carcinogenicity studies in several animal species, in both sexes. An evaluation of these studies was conducted by the European Food Safety Authority (EFSA) and no-observed-adverse-effect level (NOAEL), lowest-observed-adverse-effect level (LOAEL), and critical endpoints identified (EFSA, 2008).

Among these studies, a recent and well conducted developmental toxicity study in mice was selected by the Office of Water (OW) as the critical study for the derivation of therovisional Health Advisory for PFOA (Lau et al., 2006). In this study, CD-1 mice were given the ammonium salt of PFOA by oral gavage from gestational day (GD) 1 to 17 at doses of 0, 1, 3, 5, 10, 20 or 40 mg/kg/day. Significant increase in the incidence of full-litter resorption occurred at 5 mg/kg/day and higher doses. Weight gain in dams that carried pregnancy to term was significantly lower in the 20-mg/kg/day 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/day 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/day groups compared to 96% for controls. Postnatal survival was severely compromised at 10 or 20 mg/kg/day, and moderately so at 5 mg/kg/day. Dose-dependent growth deficits were detected in all PFOA-treated litters except the 1-mg/kg/day group. Significant delays in eye-opening (up to 2–3 days) were noted at 5 mg/kg/day 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 (Lau et al., 2006).

Toxicity endpoints identified in the Lau et al. (2006) study included a number of developmental landmarks: neonatal eye opening, neonatal survival and body weight at weaning, reduced phalangeal ossification at term, live fetus weight at term, maternal liver weight at term, and maternal weight gains during pregnancy. The most sensitive endpoint was for increased maternal

liver weight at term. This endpoint for liver effects was identified in a number of other studies described in EFSA (2008).

Benchmark dose (BMD10) and the 95% lower bound on the BMD (BMDL10) were calculated for these toxicity endpoints by the EFSA on the basis of raw data provided by the principal author (Lau, personal communication, November 18, 2008). The lowest BMDL10 in the Lau et al. (2006) study was 0.46 mg/kg/day for increase in maternal liver weight at term. This value was used as the point of departure for the derivation of the Provisional Health Advisory value for PFOA. It should be noted that liver effects were also reported in studies in rats and monkeys. BMDL10 values for increased liver weight in studies in mice and rats ranged from 0.29 to 0.74 mg/kg/day (EFSA, 2008). The BMDL10 for Lau et al. (2006) was in the middle of this range.

Summary of Data for PFOS

Epidemiological studies of exposure to PFOS and adverse health outcomes in humans are inconclusive at present.

Several animal toxicological studies have been conducted with PFOS. These include subchronic, developmental/reproductive, and chronic toxicity/carcinogenicity studies in several animal species, in both sexes. An evaluation of these studies was conducted by the EFSA (2008) and NOAEL, LOAEL and critical endpoints identified.

The subchronic toxicity study in Cynomolgus monkeys (Seacat et al., 2002) was selected by the OW as the critical study for the derivation of the Provisional Health Advisory value for PFOS. In the study by Seacat et al. (2002), groups of male and female monkeys received orally potassium PFOS at doses of 0, 0.03, 0.15 or 0.75 mg/kg/day for 183 days. Compound-related mortality in 2 of 6 male monkeys, decreased body weights, increased liver weights, lowered serum total cholesterol, lowered triiodothyronine (T3) concentration, and lowered estradiol levels were seen at the highest dose tested. At 0.15 mg/kg/day, increased levels of thyroid-stimulating hormone (TSH) in males, reduced total T3 levels in males and females, and reduced levels of high-density lipoproteins (HDL) in females were seen. A NOAEL of 0.03 mg/kg/day was identified in this study.

Calculation of Provisional Health Advisories for PFOA and PFOS

The general equation for the derivation of a Provisional Health Advisory is:

(NOAEL or BMDL10) x BW x RSC UF x Extrapolation Factor x Water intake

Where BW = body weight; RSC = relative source contribution; UF = uncertainty factors

The OW is using the exposure scenario of a 10-kg child consuming 1 L/day of drinking water to calculate the Provisional Health Advisories for PFOA and PFOS. This population subgroup was used because children, who consume more drinking water on a body weight basis than adults, have a higher exposure on a body weight basis than adults. The selection of children's exposure parameters will help to ensure that this Provisional Health Advisory is protective of sensitive

populations potentially exposed. A default relative source contribution (RSC) of 20% was used to allow for exposure from other sources such as food, dust and soil. The relevant period of exposure for the Health Advisory is a short-term exposure. This time period is consistent with the toxicity data used for PFOA and PFOS, both of which rely upon subchronic data. The value should be protective of all population subgroup and lifestages.

Data derived extrapolation factors for toxicokinetics were developed to better approximate internal doses for PFOA and PFOS. This step was deemed important because of the marked differences in retention time among humans and the test species in which toxicological data were collected. Available data for PFOA from female mice indicate a half-life of 17 days and from humans, a half-life of 3.8 years (1387 days). Critically, measures of internal exposure should be used as the basis for interspecies extrapolation; the assessment is somewhat complicated by the lack of area under the curve (AUC) or clearance (CL) data. However, the one-compartment model foundation is useful to convert half-life data to clearance data, assuming steady-state has been reached (Equation 1).

Half-life = (ln 2 or 0.693) x Volume of Distribution / CL (1)

The volume of distribution of 198 + 69 ml/kg has been estimated in female monkeys (Butenhoff et al., 2004). Olsen et al. (2007) summarized other findings on PFOS and PFOA as indicating primarily an extracellular distribution volume. Olsen et al. (2007) also cited other reports that these agents were highly bound to plasma proteins in rats, monkeys and humans. Together, these data support using the same volume of distribution for rodents and humans, based on the findings (198 ml/kg) in monkeys.

The mouse half-life of 17 days converts:
CL = (0.693 x 198 ml/kg) / 17 days = 8.07 ml/kg/day

The human half-life of 1387 days converts:
CL = (0.693 x 198 ml/kg) / 1387 days = 0.10 ml/kg/day

Calculating the toxicokinetic portion of the interspecies on the basis of plasma CL would be:

CL animal / CL human = 8.07 ml/kg/day / 0.10 ml/kg/day = 80.7

The total interspecies correction derived from using a 3X for toxicodynamics and 81X for toxicokinetics is 243X.

To calculate the Provisional Health Advisory for PFOA, a default intraspecies uncertainty factor of 10 was applied to the BMDL10 of 0.46 mg/kg/day to account for variation in susceptibility within the human population. A default uncertainty factor of 3 was used for toxicodynamic differences between animals and humans.

The following Provisional Health Advisory is obtained:

PFOA Provisional Health Advisory = 0.46 x 1000 x 10 x 0.2 / 10 x 3 x 81 x 1 = 0.4 μg/L

Similarly, a data-derived extrapolation factor was developed for PFOS. The half-lives of PFOS in humans and in male and female monkeys were estimated by Lau et al., (2007) to be 5.4 years and 150 days, respectively.

The monkey half-life of 150 days converts:
CL = (0.693 x 198 ml/kg) / 150 days = 0.915 ml/kg/day

The human half-life of 1971 days converts:
CL = (0.693 x 198 ml/kg) / 1971 days = 0.07 ml/kg/day

Calculating the toxicokinetic portion of the interspecies on the basis of plasma clearance would be:

CL animal / CL human = 0.915 ml/kg/day / 0.07 ml/kg/day = 13.1

The total interspecies correction derived from using a 3X for toxicodynamics and 13X for toxicokinetics is 39X.

To calculate the Provisional Health Advisory for PFOS, a default intraspecies uncertainty factor of 10 was applied to the NOAEL of 0.03 mg/kg/day to account for variation in susceptibility within the human population. A default uncertainty factor of 3 was used for toxicodynamic differences between animals and humans.

The following value is obtained:

PFOS Provisional Health Advisory = 0.03 x 1000 x 10 x 0.2 / 10 x 3 x 13 x 1 = 0.2 μg/L