Per- and Poly-fluoroalkyl Substances (PFAS)
February 14, 2023

CASRN	PFAS [1]	Acronym	Formula	RfD (mg/kg-day)	RfC (mg/m^3)
375-22-4	**Perfluorobutyric acid**	PFBA	$C_4HF_7O_2$	1.0E-03	3.5E-03
375-73-5	**Perfluorobutane sulfonate** (Perfluorobutane sulfonic acid)	PFBS	$C_4HF_9O_3S$	1.4E-03	4.9E-03
2706-90-3	Perfluoropentanoic acid	PFPeA	$C_5HF_9O_2$	5.0E-04	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	$C_6HF_{11}O_2$	5.0E-04	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**	PFDA	$C_{10}HF_{19}O_2$	1.5E-05	5.3E-05
335-77-3	Perfluorodecane sulfonate	PFDS	$C_{10}HF_{21}SO_3$	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

CASRN, Chemical Abstracts Services Registry Number; NA, not applicable; RfC, reference concentration; RfD, reference dose

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

REVISIONS:

On June 15, 2011, the TCEQ derived oral reference doses (RfDs) for sixteen PFAS. Later, the TCEQ updated these values to reflect changes in the 2012 revision of the TCEQ Guidelines to Develop Toxicity Factors (RG-442), which were subsequently updated again in 2015. With this 2023 update, the TCEQ is adopting RfDs recently derived by EPA's IRIS program for perfluorobutyric acid (PFBA) and perfluorohexanoic acid (PFHxA). These EPA RfDs underwent peer review by an external expert panel that included a TCEQ staff member (Joseph T. Haney, MS of the Texas Commission on Environmental Quality (TCEQ) Toxicology, Risk Assessment, and Research Division). The change to the RfD for PFBA results in a commensurate change to the RfC calculated through route-to-route extrapolation. Additionally, the RfD for PFHxA is now

used as a surrogate value for perfluoropentanoic acid (PFPeA), which has no useful toxicity data and was previously surrogated to perfluorohexane sulfonate (PFHxS). The previous *Background* and *Information Sources* sections from the 2011 version of this document, Appendix A (US EPA's provisional health advisory values) and references to it, as well as various value comparisons (e.g., to older EPA health advisories) have been omitted from this version as these are now outdated.

This assessment is yet to be fully updated scientifically but will be in the near future as the TCEQ has begun the process of systematically collecting PFAS data for the eventual derivation of toxicity factors in accordance with the most recent TCEQ toxicity factor guidelines (TCEQ 2015). The future development support document (DSD) will contain updated background information, a detailed description of the sources of information utilized, the most recent toxicity data and information available, etc. The revision of this document only represents an interim step in the TCEQ evaluation process as the PFAS DSD, expected within the next 1-2 years, will contain the latest scientific information and toxicity factor derivations.

ORAL TOXICITY FACTORS:

(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 (2009) used a benchmark dose 95% lower confidence limit at the 10% response level ($BMDL_{10}$) of 0.46 mg/kg-day based on increased maternal liver weight from a mouse developmental study (Lau et al. 2006). To this $BMDL_{10}$, EPA applied a toxicokinetic (TK) interspecies data-derived extrapolation factor of 81 (the half-life of PFOA 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 used 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 used results from other studies as well.

To investigate the low-dose effects of PFOA on offspring, in Macon et al. (2011) timed-pregnant CD-1 mice were dosed orally by gavage with PFOA for all or half of gestation. In the full gestation study, mice were administered 0, 0.3, 1.0, or 3.0 mg/kg-day from gestation days (GD) 1-17. In the late gestation study, mice were administered 0, 0.01, 0.1, or 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 lowest observed adverse effect level (LOAEL) for increased liver weight of offspring 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 that used by EPA (2009), 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 no-observed-adverse-effect-level [NOAEL] identified) significantly reduced mammary gland development in offspring that persisted into adulthood, and the NOAEL for these effects could be significantly lower as late gestation exposure to PFOA

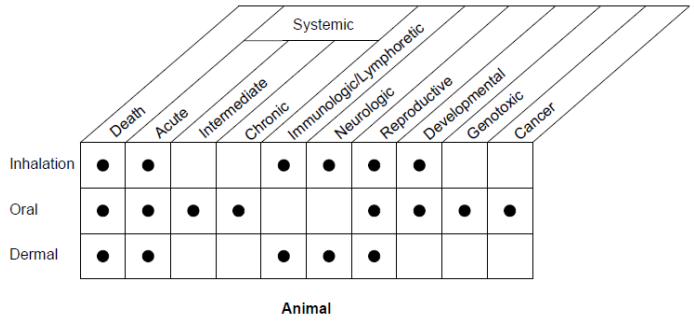
produced these effects at a LOAEL of 0.01 mg/kg-day, although late gestational-exposed mice were evaluated at postnatal day 21 and not in adulthood. As the mammary gland effects from full gestational exposure are known not to have reversed by the time they were evaluated in adulthood, the LOAEL of 0.3 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 Male Crl:CD®(SD)IGS BR rats and Crl:CD®-1(ICR)BR mice by oral gavage with 0.3-30 mg/kg-day for 29 days. Overall body weight gains (test days 0-13) were 55% and 22% of control, respectively, in rats dosed with 10 or 30 mg/kg linear/branched ammonium perfluorooctanoate (APFO), and 74% and 15% of control, respectively, in rats dosed with 10 or 30 mg/kg linear APFO, and increases in serum corticosterone levels to 135 and 196% of control, respectively. In mice dosed with 10 or 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 relative to control), an ~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% relative to control 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)[1] and intrahuman uncertainty factor (UF) of 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 dams during a 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 because liver effects have also been observed 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

[1] Calculating the toxicokinetic portion of the interspecies on the basis of plasma CL: CL animal / CL human = 8.07 ml/kg/day / 0.10 ml/kg/day = 80.7 or 81

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 (because TK already adjusted for as per 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 from ATSDR 2009).



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

NA, not applicable; POD, point of departure

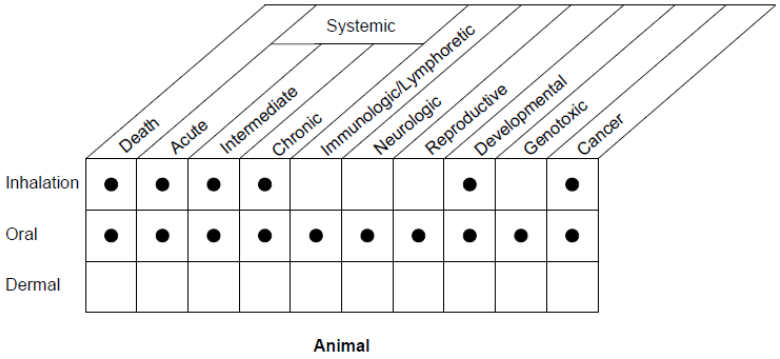
The potential chronic RfDs based on liver effects (4.1E-05 to 1.9E-04 mg/kg-day) are very similar and seem reasonable compared to EPA's 2009 subchronic RfD (2.0E-04 mg/kg-day), which was also based on liver effects. However, examination of the potential RfDs based on mammary gland developmental effects 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 PFAS. 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 because use of that lower LOAEL (0.01 mg/kg-day) with a lower intrahuman UF of 3 results in a similar RfD (see the table above). 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 (2009) used a cynomolgus monkey NOAEL of 0.03 mg/kg-day for increased levels of thyroid-stimulating hormone (TSH) in males, reduced total triiodothyronine (T3) levels in males and females, and reduced levels of high-density lipoproteins (HDL) in females (Seacat et al. 2002). EPA (2009) also used a TK interspecies data-derived extrapolation factor of 13 (the half-life of PFOS in humans is years, as opposed to days for laboratory animals), a TD interspecies UF of 3, and an intrahuman UF of 10. TCEQ used 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), differences in interspecies TK 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, or 2.0 mg/kg-day orally by gavage from GD 0 to GD20. PFOS concentration in the hippocampus of offspring was evaluated 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 habituation, 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 (i.e., 0.1 mg/kg-day, which is 6 times lower than the POD of 0.6 mg/kg-day used by EPA 2009), TCEQ will use a LOAEL-to-NOAEL UF of 10 along with the TK factor of 263, animal-to-human UF of 1 (because TK already adjusted for as per 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). 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 PFAS. Thus, the RfD will be based on Zeng et al. (2011).

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, heptafluorobutyric acid or perfluorobutanoic acid), the EPA IRIS program has finalized a chronic RfD that the TCEQ has adopted. The following is a summary of USEPA (2022a). From the identified human health hazards of potential concern (liver, thyroid, developmental toxicity), hepatocellular hypertrophy and increased relative liver weight (i.e., liver hypertrophy) and decreased thyroxine (T4) in adult male rats after subchronic (90-day) exposure, as reported in Butenhoff et al. (2012), were selected as the basis for the RfD. A NOAEL of 6 mg/kg-day PFBA ammonium salt was identified for liver hypertrophy, and a NOAEL of 6 mg/kg-day PFBA ammonium salt was identified for decreased T4. These values were used as the points of departure

(PODs). After converting the PODs from units of mg/kg-day PFBA ammonium salt to units of mg/kg-day PFBA (by multiplying by the ratio of the molecular weights of the free acid and the ammonium salt), the ratio of serum clearance values between rats and humans was used to account for toxicokinetic differences between species, resulting in the human equivalent doses (POD_{HED}) of 1.15 mg/kg-day and 1.27 mg/kg-day for liver hypertrophy and decreased T4, respectively. The RfD for PFBA was calculated by dividing the POD_{HED} values by a composite uncertainty factor of 1,000 to account for residual toxicokinetic and toxicodynamic uncertainty in the extrapolation from rats to humans (UF_A of 3), interindividual differences in human susceptibility (UF_H of 10), extrapolation from a subchronic-to-chronic exposure duration (UF_S of 10), and deficiencies in the toxicity database (UF_D of 3). The RfD for PFBA was derived based on liver and thyroid effects and is 1.0E-03 mg/kg-day.

PFBA RfD = 1.15 and 1.27 mg/kg-day / (3 x 10 x 10 x 3) = **1E-03 mg/kg-day**

(4) For perfluorobutane sulfonate (PFBS), the Minnesota Department of Health previously 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 (for extrapolation from male rats to humans; detailed calculation not provided by Minnesota Department of Health). 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).

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

(5) For perfluorooctane sulfonamide (PFOSA), only LD_{50} data were found in the Registry of Toxic Effects of Chemical Substances (RTECS). The rodent oral LD_{50} of > 172 mg/kg for PFOSA may be similar to that for PFOA (LD_{50} of 189 mg/kg), another 8-carbon PFAS 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 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 (8.5% lower than control, $p < 0.01$) in the 5 mg/kg-day group. Significantly increased levels of pro-inflammatory cytokines interleukin-1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α,149.4%, 140.5%, 130.1% of the control values, 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), dietary dosing of male and female mice with approximately 5.3 mg/kg-day PFNA for 14 days resulted in increased absolute liver weight by 178–190% relative to control. 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 sex 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 sex-specific rat half-lives for PFNA that when combined average approximately 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 that in rats. Furthermore, although PFNA half-life information for humans was not available, 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.

Potential PFNA RfD = 1 mg/kg-day / (81 x 1 x 10 x 10 x 10)
= 1.2E-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 rats 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 (PFDA), 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 PFDA exhibits teratogenic effects or is a developmental toxicant, time-mated C57BL/6N mice were administered PFDA orally 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 were assessed. Fetuses were examined for external, visceral, or skeletal malformations. No hydronephrosis, cleft palate, or edema was observed, nor were any other soft tissue or skeletal malformations detected. Note that only the fetuses in the control and 12.8 mg/kg-day groups were examined for visceral malformations or variations. Maternal body weight gain (corrected for the weight of the gravid uterus) was significantly reduced as a result of PFDA treatment at 6.4 and 12.8 mg/kg-day (GD 6–15), and at 16.0 and 32.0 mg/kg-day (GD 10–13). Fetal viability was decreased only in those groups showing 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 because they are a potentially susceptible subpopulation (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) cited 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 PFDA (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. Based on administered dose, PFDA was 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. PFDA lowered the activity of glutathione (GSH)-related enzymes in the same manner as PFOA. The LOAEL for increased liver weight (≈ 30% greater than control) 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 PFDA 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 PFDA 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 PFAS

as a surrogate for PFDA (i.e., the TK interspecies extrapolation factor of 81 for PFOA [8-carbon] is the most conservative surrogate value for PFDA [10-carbon]). That is, in order to derive an RfD for a chemical that may otherwise go unaddressed at a site, TCEQ will assume the ratio of human-to-rodent half-lives for PFDA is the same as that for PFOA (i.e., the PFDA 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 PFDA 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 PFDA 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 PFDA:

PFDA 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 as assessed by clinical chemistry, hematology, and organ histopathology. PFHxS did induce hematology findings in male rats at ≥ 0.3 mg/kg-day and liver and thyroid effects at ≥ 3 mg/kg-day. More specifically, male rats receiving doses ≥ 0.3 mg/kg-day for at least 42 days had significantly increased prothrombin time, doses ≥ 1 mg/kg-day had significantly decreased hemoglobin concentration, and doses ≥ 3 mg/kg-day had decreased erythrocyte count and hematocrit. Female rats receiving up to 10 mg/kg-day PFHxS did not have any significant hematology findings. The thyroid effects in male rats (i.e., hypertrophy-hyperplasia of thyroid follicular cells) were thought to be a compensatory response to liver hypertrophy. The dose of 0.3 mg/kg-day is the LOAEL for hematology findings 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 PFAS (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 PFAS with reported human half-lives (Table 3-8 of ATSDR 2009). Therefore, to derive an RfD for a chemical that 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 of 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 oral 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 PFAS 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]). Therefore, to derive an RfD for a chemical that 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) For perfluorohexanoic acid (PFHxA), the EPA IRIS program has derived a draft chronic RfD (USEPA 2022b). The draft RfD underwent peer review by an external expert panel that included a TCEQ staff member (Joseph T. Haney, MS, of the TCEQ Toxicology, Risk Assessment, and Research Division), who determined that the value was scientifically up-to-date and defensible. Accordingly, the TCEQ has adopted the draft EPA RfD as a final TCEQ RfD. The following is a summary of USEPA (2022b). From

the identified hazards of potential concern (i.e., hepatic, hematopoietic, and developmental toxicity), decreased offspring body weight in neonatal mice (Loveless et al., 2009) was selected as the basis for the RfD of 5E-04 mg/kg-day. A benchmark dose 95% lower confidence limit at the 5% relative deviation response level ($BMDL_{5RD}$) of 10.62 mg/kg-day PFHxA sodium salt was identified for this endpoint and was used as the POD. The POD_{HED} of 0.048 mg/kg-day was derived by applying the ratio of the clearance between female rats and humans and a calculation based on the differences in molecular weights of the free acid and sodium salt. The RfD for PFHxA was calculated by dividing the POD_{HED} by a composite uncertainty factor of 100 to account for toxicodynamic and toxicokinetic uncertainty in the extrapolation from rats to humans (UF_A of 3), interindividual differences in human susceptibility (UF_H of 10), and deficiencies in the toxicity evidence base (UF_D of 3).

PFHxA RfD = 0.048 mg/kg-day / (3 x 10 x 3) = **5E-04 mg/kg-day**

(11) No toxicity data were found for perfluoropentanoic acid (PFPeA), perfluoroheptanoic acid (PFHpA), perfluorodecane sulfonate (PFDS), perfluoroundecanoic acid (PFUA), perfluorotridecanoic acid (PFTrDA), and perfluorotetradecanoic acid (PFTeDA). Recognizing that elimination rate for PFAS generally decreases as carbon chain length increases and there is uncertainty associated with assigning surrogate values, an RfD from a PFAS with the same or longer carbon chain length was conservatively assigned as the surrogate RfD value for these PFAS, except for PFTrDA and PFTeDA. For PFTrDA (13 carbon) and PFTeDA (14 carbon), there is no PFAS of the same or longer carbon chain length with an RfD, so the RfD for PFDoA (12 carbon) was used.

PFPeA RfD = RfD for PFHxA = **5.0E-04 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 TOXICTY FACTORS:

(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 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 (i.e., increased absolute and relative liver weight; hepatocellular hypertrophy and necrosis); 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 findings 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 also resulted in 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**

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 compared to controls (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**

(3) For PFBA, PFBS, PFHxS, PFOS, PFDA, and PFDoA, all of which had toxicity data in 2011 when the TCEQ originally derived toxicity values, RfC values were derived using route-to-route extrapolation from their RfD values because the effects of PFAS in laboratory animals do not appear to be route-specific. That is, because the health effects of these substances appear to be 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 where the human adult body weight is 70 kg and the human daily ventilation volume is 20 m^3:

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

PFBA RfC = 1.0E-03 mg/kg-day x 70 kg / 20 m^3-day = **3.5E-03 mg/m^3**
PFBS 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**
PFDA 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 PFAS with no toxicity data (PFPeA, PFHpA, PFDS, PFUA, PFTrDA, and PFTeDA), no surrogate RfC values were derived for these PFAS.

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(2023 updates reviewed by Janet Hamilton, Ph.D. and Sabine Lange, Ph.D.)

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