

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

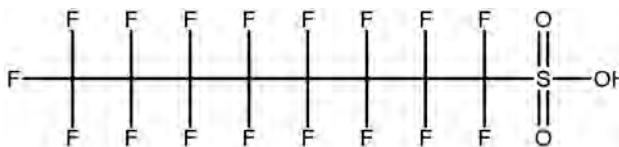
February 16, 2018

To: File for Perfluorooctanoic Sulfonic Acid (PFOS) (CAS No. 1763-23-1)
From: Michael Depa, Air Quality Division, Toxics Unit
Subject: Screening Level Derivation

The initial threshold screening level (ITSL) for perfluorooctanoic sulfonic acid (PFOS) is $0.07 \mu\text{g}/\text{m}^3$ with 24-hour averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), ECHA (European Chemical Agency) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), EPA Acute Exposure Guideline Levels (AEGLs), National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Levels (MRLs), U.S. EPA Provisional Peer Reviewed Toxicity Values (PPRTVs) for Superfund, International Agency for Research on Cancer (IARC) Monographs, California Office of Environmental Health Hazard Assessment (OEHHA), Chemical Abstract Service (CAS) - SciFinder (1967 – Nov. 2017), National Library of Medicine (NLM) Toxline, and National Toxicology Program (NTP) Status Report. The EPA has not established a reference concentration for PFOS. The EPA (2016) has established a reference dose (RfD) of $0.00002 \text{ mg}/\text{kg}/\text{day}$. The ACGIH has not derived a TLV.

The molecular formula for PFOS is $\text{C}_8\text{F}_{17}\text{HO}_3\text{S}$ and molecular weight is 500.12g.



Vapor Pressure: 0.002 mmHg at 25°C (MDEQ, 2016). The Danish EPA (2015) reported that the water solubility of PFOS is $519 \text{ mg}/\text{l}$ ($20 \pm 0.5^\circ\text{C}$) which is “moderately soluble” (EPA, 2013). The only inhalation toxicity study available is an acute lethality inhalation study in rats that found an LC_{50} of 5.2 ppm ($106 \text{ mg}/\text{m}^3$) (Rusch et al. 1979); no inhalation toxicity data are available in humans. Concerning the inhalation of PFOS, EPA (2016) states:

Inhalation of PFOS is possible; it has been measured in indoor air in residential, commercial, and office settings because of its use in carpets, textiles, paint, furniture, and other consumer products. Both air and dust can be a vehicle for volatile PFOSA¹ precursors that metabolically degrade to PFOS. Given the widespread commercial and industrial use of PFOS, as well as its physical properties, air is a potential source of exposure.

A thorough review of the literature using “lung”, and “inhalation” produced few studies; however, areas near wastewater treatment plants, waste incinerators, and landfills can be point sources for PFOS in outdoor air. Concentrations in air at wastewater treatment plants (43–171 pg/m³; 4.3E-11 g/m³ to 17.1E-11 g/m³) and landfills (3.9 pg/m³) are generally higher than for ambient air in cities (Ahrens et al. 2011).

A German occupational exposure limit (OEL) was listed as 0.01 mg/m³ (Wiley, 2011). The German OEL documentation showed that the derivation of the OEL was based on a no-observed-adverse-effect-level (NOAEL) of 0.03 mg PFOS/kg/day identified in a 6-month oral dose study in cynomolgus monkeys. The conversion of the oral dose to the inhalation dose was based on calculations equating the PFOS blood serum concentration in the monkeys at 15 mg/l to that in humans, which was then converted to an 8-hour time-weighted-average of 0.01 mg/m³. OELs are not available from OSHA, NIOSH, or ACGIH.

Pharmacokinetics

A study in occupationally exposed workers with probable inhalation exposure was performed by Olsen et al. (2007) to determine the elimination half-life of PFOS. Retirees from the 3M Company, Decatur, Alabama, facility were eligible for the study if they had retired between January 1995 and onset of the study in November 1998. The retirees were invited to participate based on having prior work assignments in fluorochemical production. Thirty-four individuals were identified and 24 (22 males, 2 females) agreed to participate (71%). In addition, 3 retirees from the 3M, Cottage Grove, Minnesota, chemical division were also directly invited to participate. Based on their work history records, their lifetime usual jobs at either the 3M Decatur or Cottage Grove facility were categorized as electrochemical fluorination cell operators (n = 3), chemical operators (n = 6), maintenance workers (n = 5), foremen (n = 6), laboratory technicians (n = 3), and other (n = 2: warehouseman and engineer). Their mean length of study follow-up was 1,849 days (range, 1,139–1,945 days) equivalent to a mean of 5.0 years (range, 3.1–5.3 years). The arithmetic and geometric mean half-lives of human serum elimination for three perfluoroalkyl substances (PFAS) are shown in Table 1. The two female subjects (subjects 7 and 25) had arithmetic mean serum elimination half-lives similar to those calculated for males, respectively, for PFOS (5.9 years vs. 5.4 years; p = 0.87).

Table 1. Serum Half-Life in Years in Occupationally Exposed Humans*

	Arithmetic Mean (95% CI)	Geometric Mean (95% CI)	Median	Range
PFOS	5.4 (3.9–6.9)	4.8 (4.0–5.8)	4.6	2.4–21.7
PFHS**	8.5 (6.4–10.6)	7.3 (5.8–9.2)	7.1	2.2–27.0
PFOA***	3.8 (3.1–4.4)	3.5 (3.0–4.1)	3.4	1.5–9.1

* Olsen et al., 2007. **Perfluorohexyl sulfonate. ***Perfluorooctanoic acid

¹ PFOSA = perfluorooctane sulfamide; PFOSA is often referred to as a precursor because PFOSA degrades in the environment to PFOS.

EPA (2016) used the pharmacokinetic model of Wambaugh et al. (2013), where average serum PFOS concentrations were derived from the Area Under the Curve, considering the number of days of exposure before sacrifice. Wambaugh et al. (2013) used a saturable renal resorption pharmacokinetic (PK) model. Saturable renal resorption of PFOS from the glomerular filtrate via transporters in the kidney tubules is believed to be a major contributor to the long half-life of this compound. Wambaugh's model is a two-compartment model in which a primary compartment describes the serum, and a secondary deep tissue compartment acts as a specified tissue reservoir. The human volume of distribution of 200 ml/kg was calibrated from actual human data on serum measurements and intake estimates. A calibration parameter obtained from human studies, where constant intake was assumed and blood levels were measured, is considered a more robust estimate for volume of distribution than that optimized within a model developed from animal data (EPA, 2016). Chang et al. (2012) estimated that the volume of distribution for monkeys, rats, and mice is likely in the range of 200–300 mL/kg. Seacat et al. (2002) calculated that a volume of distribution for cynomolgus monkeys was 220 ml/kg.

EPA (2006) stated that the Wambaugh et al. (2013) model allowed predictions across species, strains, and genders to identify serum levels associated with the no observed adverse effect level (NOAEL) and lowest observed adverse effect level (LOAEL) external doses. EPA (2016) stated, "There were no systematic differences between the experimental data and the model predictions across species, strain, or gender, and median model outputs uniformly appeared to be biologically plausible despite the uncertainty reflected in some of the 95th percentile credible intervals."

The predicted serum concentrations were then converted to oral HEDs in units of mg/kg/day for each corresponding serum measurement. Average serum PFOS concentrations were derived from the Area Under the Curve considering the number of days of exposure before sacrifice. The PK model predicted serum concentrations are converted into an oral equivalent dose by recognizing that, at steady state, clearance from the body equals the dose to the body. Clearance (CL) can be calculated if the rate of elimination (derived from half-life; $t_{1/2}$) and the volume of distribution (Vd) are both known. EPA used the Olsen et al. (2007) calculated human half-life of 5.4 years and the Thompson et al. (2010) volume of distribution (Vd) of 0.23 l/kg body weight (bw) to determine a clearance of 8.1×10^{-5} l/kg bw/day using the following equation:

$$CL = Vd \times (\ln 2 \div t_{1/2})$$

Where: Vd = 0.23 L/kg
 ln(2) = 0.693; and
 $t_{1/2}$ = 1971 days (from 5.4 years x 365 days/year)

$$CL = 0.23 \text{ L/kg bw} \times (0.693 \div 1971 \text{ days})$$

$$CL = 0.000081 \text{ liter/kilogram bw/day}$$

Multiplying the PK model derived average serum concentrations (in $\mu\text{g/ml}$) for the NOAELs and LOAELs identified in the key animal studies by the clearance value predicts oral HEDs in mg/kg/day for each corresponding serum measurement.

$$\text{Human dose} = \text{average serum concentration} \times CL$$

EPA's candidate RfDs (data not shown here) ranged from 0.00002 to 0.00005 mg/kg/day across multiple endpoints. The POD for the derivation of the RfD for PFOS is the HED of 0.00051 mg/kg/day that corresponds to a no-observed-adverse-effect-level (NOAEL; 0.1 mg/kg/day from Luebker et al, 2005a; see below for details of study) that represents approximately 30% of steady-state concentration. Analysis of steady state concentrations at different dose levels and serum concentrations revealed that the steady-state concentration was not a good indicator of toxicity. EPA (2016) states:

Despite the higher administered dose, the short 19-day study resulted in effects at a lower serum concentration than that for the longest duration of exposure, the one closest to steady state. In fact, the average serum values from the studies that do not approach steady state have lower average serum LOAELs for endpoints of toxicological concern. Thus, the data do not appear to indicate increasing sensitivity as steady-state is approached. If anything, the average serum values appear to be more protective than serum concentrations at steady state.

For comparison purposes, the measured average serum concentrations and modeled PK (EPA, 2016) predicted serum concentrations are shown in Table 2.

Table 2. Modeled and Predicted Serum PFOS Concentrations in Rats (EPA, 2016)

Value at the NOAEL of 0.1 mg/kg bw/day	µg/ml
Measured Mean Maternal Serum PFOS at Lactational Day 21	5.28
Modeled Rat Average Serum PFOS for "Duration of Dosing"*	4.52

Study: Luebker et al., 2006

*Table 4-6 from EPA, 2016

U.S Environmental Protection Agency: Reference Dose

The EPA (2016) derived an RfD based on a two-generation study in rats performed by Luebker et al. (2005a) where male and female rats were dosed via oral gavage at dose levels of 0, 0.1, 0.4, 1.6, and 3.2 mg/(kg day) for 6 weeks prior to mating, during mating, and, for females, through gestation and lactation, across two generations. Due to substantial F1 neonatal toxicity observed in the 1.6 and 3.2 mg/(kg day) groups, continuation into the second generation was limited to F1 pups from the 0, 0.1, and 0.4 mg/(kg day) groups. Neonatal toxicity in F1 pups, as demonstrated by reduced survival and body-weight gain through the end of lactation, occurred at a maternal dose of 1.6 mg/(kg day) and higher but not at dose levels of 0.1 or 0.4 mg/(kg day) or in F2 pups at the 0.1 or 0.4 mg/(kg day) dose levels tested. The LOAEL for pup body weight effects was 0.4 mg/kg/day. A NOAEL of 0.1 mg/kg/day was identified. See Table 3 for a description of uncertainty factors, human equivalent dose (HED) and the point of departure (POD).

Table 3. Derivation of the Oral Reference Dose (RfD) for PFOS (EPA, 2016)

POD	HED POD mg/kg/day	UFH	UFA	UFL	UFS	UFD	UFtotal	RfD (mg/kg)
PK-HED NOAEL (Luebker et al. 2005a): rat, for ↓ pup body weight	0.00051	10	3	1	1	1	30	0.00002

Abbreviations: POD = point of departure. PK-HED = pharmacokinetic human equivalent dose; NOAEL = no observed adverse effect level; UFH = intra-individual uncertainty factor; UFA = inter-species uncertainty factor; UFS = subchronic to chronic uncertainty factor; UFL = lowest-observed-adverse-effect to NOAEL uncertainty factor; UFD = incomplete database uncertainty factor; UFtotal = total (multiplied) uncertainty factor.

EPA applied a total UF of 30 (UFH of 10 for intra-individual / sensitive individual extrapolation, and UFA of 3 for inter-species / animal-to-human extrapolation) to the HED NOAEL to derive an RfD of 0.00002 mg/kg/day. A subchronic to chronic UFS was unnecessary because studies for developmental endpoints are not adjusted for lifetime exposures since they cover a critical window of exposure with lifetime consequences. This RfD is supported by another candidate RfD of 0.00002 mg/kg/day derived from the LOAEL for the same effect in the one-generation study by Luebker et al. (2005b) and the 0.00003 mg/kg/day value for neonatal neurodevelopmental effects in the Butenhoff et al. (2009) study. Low body weights in neonates are a biomarker for developmental deficits and are linked to problems that often manifest later in life (EPA, 2016).

Using the HED from Luebker et al. (2005b), the EPA (2016) RfD was calculated as follows:

$$\text{RfD} = (\text{HED POD})/(\text{UFH} \times \text{UFA})$$

$$\text{RfD} = (0.00051 \text{ mg/kg/day})/30 \cong 0.00002 \text{ mg/kg/day}$$

Agency for Toxic Substances and Disease Registry: Minimal Risk Level

The Agency for Toxic Substances and Disease Registry (ATSDR, 2015) calculated a draft intermediate-duration oral Minimal Risk Level (MRL) for PFOS of 3×10^{-5} mg/kg/day. The draft MRL was based on results from Seacat et al. (2002). In the PFOS monkey study (Seacat et al. 2002), groups of male and female Cynomolgus monkeys were administered via capsule 0, 0.03, 0.15, or 0.75 mg/kg/day potassium PFOS for 26 weeks; there were four monkeys/sex in the 0.03 mg/kg/day group and six monkeys/sex/group in the other groups. The serum levels of PFOS was measured at the end of the study (see Table 4). Two monkeys/sex in the 0, 0.15, and 0.75 mg/kg/day were allowed to recover for 1 year. Significant increases in relative liver weight were observed in the male and females exposed to 0.75 mg/kg/day and absolute liver weight was significantly increased in females at 0.75 mg/kg/day. Centrilobular vacuolation, hypertrophy, and mild bile stasis were observed in some monkeys in the 0.75 mg/kg/day group (incidence not reported). Lipid-droplet accumulation in two of four males and two of four females and increased glycogen content were noted in the electron microscopic examination of the liver. No histological alterations were observed in the other major tissues and organs. Clinical chemistry alterations consisted of decreases in total cholesterol in the second half of the study in the 0.75 mg/kg/day group.

Table 4. Effect Levels and Serum Concentration of PFOS from Seacat et al. 2002*

Effect	Dose (mg/kg/day)	Serum Concentration** (µg/ml)
NOAEL	0.15	36.4
Increased Liver Weight	0.75	131.0

* As reported by ATSDR, 2015.

** Time-weighted average of mean serum concentrations for the 6-month period (Figure 1. Seacat et al, 2002).

ATSDR (2015) stated:

Because decreases in body weight were observed, increased absolute liver weight was selected as the critical effect.

Using serum PFOS level as the internal dose metric, the absolute liver weight data in female monkeys were fit to all available continuous models in EPA's BMDS². Using a benchmark response of 10% relative deviation (RD), the exponential model 2 produced the best data fit, and yielded a POD for serum concentration of 36.4 µg/ml (ATSDR, 2015).

ATSDR (2015) used the following equations to calculate the human equivalent dose. The relationship between the elimination rate constant (k_e , day⁻¹) and the elimination half-time ($t_{1/2}$, day), is given in Equation 1:

$$\text{Equation 1: } k_e = \frac{\ln(2)}{t_{1/2}}$$

Estimates of the half-time ($t_{1/2}$) based on Olsen et al. (2007a) were derived from longitudinal measurements of serum concentrations of PFOS in a group of fluorochemical production workers (24 males, 2 females) observed over a 5-year period; the estimated $t_{1/2}$ was 5.4 yrs. Equation 2 below was used to calculate an external oral dosage as D_{ss} (mg/kg/day) that would be equivalent to any given steady-state blood serum concentration, C_{ss} (mg/l).

$$\text{Equation 2: } D_{ss} = \frac{C_{ss} \times k_e \times V_d}{AF}$$

Estimates of volume of distribution (V_d) are based on non-compartmental modeling of serum concentration kinetics in monkeys and are assumed to be applicable to humans (ATSDR, 2015). The gastrointestinal absorption fraction (AF) of 1 was based on studies in rodents and non-human primates.

The draft intermediate-duration oral MRL for PFOS was derived by dividing the HED of 2.52×10^{-3} mg/kg/day by a total uncertainty factor (UF_{tot}) of 90, composed of an UFA of 3 for animal to human extrapolation with a dosimetric adjustment, 10 for human variability, and UFD of 3 for uncertainties in the database, particularly the lack of developmental and immunological data in monkeys (ATSDR, 2015).

$$\begin{aligned} \text{MRL} &= \text{HED}/(\text{UFA} \times \text{UFH} \times \text{UFD}) \\ \text{MRL} &= (2.52 \times 10^{-3} \text{ mg/kg/day})/(3 \times 10 \times 3) \\ \text{MRL} &= 3 \times 10^{-5} \text{ mg/kg/day} \end{aligned}$$

The lowest LOAEL for developmental effects in mice (0.4 mg/kg/day; Luebker et al. 2005a) was slightly higher than the lowest LOAEL for liver effects (Seacat et al. 2002). ATSDR (2015) used a database uncertainty factor to account for the lack of studies examining the possible developmental and immune toxicity of PFOS in monkeys which would allow for a more thorough evaluation of the most sensitive target of PFOS toxicity in humans.

Comparison of the EPA (2016) RfD and ATSDR (2015) Draft MRL

EPA's RfD and ATSDR's draft MRL were derived from well conducted animal studies. Table 5 describes the major factors used to calculate the health protective reference values.

² Benchmark Dose Software (version 2.4.0). National Center for Environmental Assessment. Available from: <http://bmds.epa.gov>

Table 5. Key Attributes of the EPA (2016) and ATSDR (2015) Reference Values

Attribute	EPA RfD	ATSDR Draft MRL
Key Study Author (year)	Luebker et al. (2005a)	Seacat et al. (2002)
Key Study Type, species (duration)	Oral, rat, Two-generation Reproductive (pre-mating+gestation+lactation; 84 days)	Oral, monkey (182 days)
Internal Dose Metric (units)	Serum (µg/l)	Serum (µg/l)
Dosimetric Adjustment for Animal to Human Extrapolation	PBPK	PBPK
LOAEL Oral Dose	0.4 mg/kg/day	0.75 mg/kg/day
NOAEL Oral Dose	0.1 mg/kg/day	0.15 mg/kg/day
NOAEL Blood Serum (measured)	5.28 µg/ml	66.8 µg/ml
HED Point of Departure Blood Serum	6.26 µg/ml	36.4 µg/ml
HED Point of Departure Oral Dose	0.00051 mg/kg/day	0.0025 mg/kg/day
Total Uncertainty Factor	30	90
Reference Value	0.00002 mg/kg/day	0.00003 mg/kg/day

* Mean maternal serum PFOS values at LD 21

The EPA (2016) RfD of 0.00002 mg/kg/day was selected as the most appropriate reference value because the critical effect of low birth weight observed in the Luebker et al. (2005a) rat study was lower than the liver effects observed in the monkey study by Seacat et al. (2002). The ATSDR (2015) draft MRL is designed to be protective for liver effects from PFOS exposures from 15–364 days. The short exposure period during the Luebker et al. (2005a) study occurs during a sensitive window of exposure (i.e., pregnancy) and yields a reference value that would also be protective of the adverse liver effects addressed with the MRL value.

Conversion of RfD to Initial Threshold Screening Level (ITSL)

$$\text{ITSL} = \text{RfD} \times (\text{average body weight}) / (\text{inhalation rate per day})$$

$$\text{ITSL} = (0.00002 \text{ mg/kg/day}) \times (70\text{kg}) / (20\text{m}^3/\text{day}) \times 1000\mu\text{g}/\text{mg}$$

$$\text{ITSL} = 0.07 \mu\text{g}/\text{m}^3 \text{ with 24-hr averaging time}$$

The averaging time is 24-hr based on short-term exposures during a two-generation reproductive toxicity study (critical effect: reduced pup body weight) (Luebker et al. 2005a).

If PFOS and perfluorooctanoic acid (PFOA, CAS No. 335-67-1) are co-emitted, then the proposed emission rates should be evaluated together such that the impacts of PFOS and PFOA combined shall be less than or equal to 0.07 µg/m³ with a 24-hr averaging time, for Rule 225 acceptability evaluations.

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