Health Based Guidance for Air
Environmental Impacts Analysis Unit, Environmental Health Division
651-201-4899

Web Publication Date: June 2021

Air Toxicological Summary for: Perfluorooctane sulfonic acid

CAS: 1763-23-1
Synonyms: PFOS, Perfluorooctane sulfonate

Air Exposure Durations:
Acute - dosing duration 24-hours or less
Short-term - repeated dosing for more than 24-hours, up to approximately 30 days
Subchronic - repeated dosing for more than 30 days, up to approximately 8 years (10 percent of a lifespan in humans; more than 30 days up to approximately 90 days in typical laboratory rodent species)
Chronic = repeated dosing for more than approximately 8 years (10 percent of a life span in humans; more than approximately 90 days in typical laboratory rodent species)

Acute Non-Cancer Risk Assessment Advice ($nRAA_{Acute}$) = Not Derived (Insufficient Data)

Short-term, Subchronic, Chronic nRAA ($nRAA_{Short\text{-}term,\ Subchronic,\ Chronic}$) = 0.011 µg/m^3

= Reference Dose (mg/kg-d) x Route-to-route scaling factor (kg/m^3) x (1000 µg/mg)

= 0.0000031 (mg/kg-d) x (70 kg/20 m^3-d) x (1000 µg/mg)

= 0.0108 rounded to **0.011 µg/m^3**

Reference Dose:	HED/Total UF = 0.000307/100 = **0.0000031 mg/kg-d** (or 3.1 ng/kg-d) (adult C57BL/6 male mice)
Source of toxicity value:	Determined by MDH in 2018
Point of Departure (POD):	2.36 µg/mL (or mg/L) serum concentration (Dong et al 2011, NOAEL)
Dose Adjustment Factor (DAF):	Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.23 L/kg x (0.693/1241 days) = 0.00013 L/kg-day. (Half-life from Li et al 2018.)
Human Equivalent Dose (HED):	POD x DAF = 2.36 mg/L x 0.00013 L/kg-d = 0.000307mg/kg-d

Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (impacts on serum thyroxine (T4) in developing animals have been reported at serum concentrations ~3-fold lower than the POD. Additional studies regarding thyroid effects and a more complete assessment of developmental immune effects are warranted.)
Critical effect(s):	increased IL-4 and decreased SRBC specific IgM levels
Co-critical effect(s):	decreased pup body weight; increased fasting serum insulin and glucose in pups; suppressed SRBC response, increased NK cell activity and decreased IgM; decreased total and free T4 (maternal and pups); decreased adrenal weight, decreased serum corticosterone and adrenocorticotropic hormone levels in serum, and corticotropin-releasing hormone concentration in hypothalamus; and changes in cholesterol and histological changes in the liver (adults)
Additivity endpoint(s):	Adrenal, Developmental, Hepatic (liver) system, Immune, and Thyroid

Due to the highly bioaccumulative nature of PFOS within the human body, serum concentrations are the most appropriate dose metric and short-term exposures have the potential to stay in the body for an extended period of time (MDH 2020). In addition, accumulated maternal PFOS is transferred to offspring (i.e., placental and breastmilk transfer). A single HBV has therefore been recommended for short-term, subchronic, and chronic durations.

Further detail regarding the MDH 2020 PFOS RfD for water can be found in the Toxicological Summary for Perfluorooctane sulfonate (https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf).

Cancer Risk Assessment Advice = Not Applicable

Cancer classification:	Suggestive Evidence of Carcinogenic Potential (USEPA 2016)
Inhalation Unit Risk (IUR):	Not Determined
Source of IUR:	Not Applicable
Tumor site(s):	(via oral route) Liver and thyroid tumors were identified in both control and exposed animals at levels that did not show direct relationship to dose

Volatile: No

Summary of Guidance Value History: There are no previous air guidance values for PFOS.

Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity	Respiratory
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]	Yes[6]

Comments on extent of testing or effects:

[1] MDH 2020; Human epidemiological studies have examined a number of endocrine targets, including thyroid hormone levels and/or thyroid disease, reproductive hormones and insulin levels. Results from these studies have provided limited support for an association between PFOS and thyroid endpoints. Stronger associations were found in populations at risk for iodine deficiency or positive anti-TPO antibodies (a marker for autoimmune thyroid disease). Investigators from one laboratory have reported increased FSH and decreased LH and testosterone at doses similar in magnitude to the critical study LOAEL. However, there are concerns regarding the study design and these effects are not listed as co-critical at this time. Decreases in adrenal gland weight as well as serum corticosterone and adrenocorticotropic hormone levels have been observed at doses similar in magnitude to the critical study LOAEL. Changes in expression of POMC (proopiomelanocortin), ACTHr (adrenocorticotropic hormone receptor) and CRH (corticotropin-releasing hormone) genes were also observed. These effects have been included as co-critical effects. Multiple studies in laboratory animals have reported decreased serum thyroid levels, in particular, thyroxin (T4) in offspring and adult animals at exposure levels similar in magnitude to the critical effect. Transcriptional changes of genes, in part regulated by thyroid hormones, involved in neurodevelopment have also been reported. However, the biological or functional significance of these changes are not clear. A NOAEL for thyroid hormone impacts in offspring has not been identified. As a result, a database uncertainty factor has been incorporated into the RfD calculation. Changes in total and free T4 have been identified as co-critical effects and Thyroid (E) has been identified as an Additivity Endpoint.

[2] MDH 2020; Human epidemiology studies have evaluated associations for three categories of altered immune response: immunosuppression (altered antibody response, infectious disease resistance), hypersensitivity (asthma, eczema, allergies), and autoimmunity. The strongest evidence comes from fairly consistent associations with antibody response to vaccines.

However, consistent associations between serum PFOS and rates of infectious disease have not been reported.

Studies in laboratory animals have shown that PFOS exposure alters several immunologic measures (e.g., suppression of SRBC response and/or natural killer cell activity) in adult animals. A single developmental immune study evaluating effects resulting from in utero exposure only has been conducted. A database uncertainty factor was incorporated into the RfD calculation, in part, due to the need for a more comprehensive assessment of potential developmental immune effects. Immune suppression was identified as the critical effect and forms the basis of the RfD. Immune System has been identified as an Additivity Health Endpoint.

[3] MDH 2020; Human epidemiology studies have suggested an association between prenatal PFOS serum levels and lower birth weight, however, this association has not been consistent. Studies conducted in laboratory animals have identified several sensitive developmental effects, including decreased pup body weight, changes in energy metabolism (e.g., glucose levels, lipid metabolism) and decreased thyroid hormone levels. Some of these developmental effects were identified as co-critical effects and are included as an Additivity Health Endpoint. Additional effects, including increased pup death, were observed at higher exposure levels.

[4] MDH 2020; Human epidemiology studies have evaluated alterations in reproductive hormones, menstrual cycle length, onset of menopause, endometriosis, breastfeeding duration, effects on sperm, and fertility. Findings have not been consistent across studies or there are too few studies to interpret the results. Since menstruation, parturition and breastfeeding are elimination routes the possibility of reverse causation has been raised for several of the endpoints evaluated in females. An association between preconception serum PFOS, gestational diabetes, and pregnancy induced hypertension has been reported in populations with serum PFOS concentrations of 0.012-0.017 µg/mL (or 12 – 17 µg/L). Studies in laboratory animals indicate that fertility is not a sensitive endpoint, with postimplantation loss, decreases in male reproductive organ weights, decreased epididymal sperm count, and evidence of blood-testes-barrier disruption at exposure levels higher than those causing developmental or immune toxicity.

[5] MDH 2020; There have been limited evaluations of neurotoxicity in humans. Human epidemiological studies have not provided consistent associations between exposure to PFOS and neurobehavioral, neuropsychiatric or cognitive outcomes in childhood or adulthood. A limited number of developmental neurotoxicity and adult neurotoxicity studies have been conducted in laboratory animals. Increased motor activity and decreased habituation of male offspring was reported following gestational and lactational exposure at levels higher than those causing the critical effect. Results from studies using water maze tests for learning and memory in animals exposed during development or as adults have yielded inconsistent results or effects only at higher dose levels.

[6] A human epidemiology cancer study reported no increases in the risk ratio episodes of care were found for the respiratory tract (estimated serum PFOS levels of 390–890 ng/mL) or high (estimated PFOS

serum levels of 1,300–1,970 ng/mL). Animal studies report inhalation exposure to PFOS nasal discharge, rales, and/or labored breathing at concentrations between 1890 – 45970 mg/m^3 for 1-hour in rats. Pulmonary congestion was reported for rats exposed to 5 mg/kg/d for 28 days. Rats dosed with up to 1.04 mg/kg/d in the diet for 104 weeks did not reveal significant effects in the lungs or trachea. Monkey dosed via ingested 2 mg/kg/d PFOS capsules for four weeks did had no gross or microscopic effects on the lungs. A lower dose of 0.75 mg/kg/d, also in monkeys, for 26 weeks also did not produce gross or microscopic effects on the lungs or trachea.

References and Resources Consulted

Agency for Toxic Substances and Disease Registry (ATSDR). 2021. Toxicological Profile for Perfluoroalkyls. https://www.atsdr.cdc.gov/ToxProfiles/tp200.pdf

Dong, G, MM Liu, D Wang, L Zheng, ZF Liang, YH Jin. 2011. Sub-chronic effect of perfluorooctanesulfonate (PFOS) on the balance of type 1 and type 2 cytokine in adult C57BL6 mice. *Archives of Toxicology* 85: 1235-1244. DOI: https://doi.org/10.1007/s00204-011-0661-x

Goeden, H. M., Greene, C. W., & Jacobus, J. A. 2019. A transgenerational toxicokinetic model and its use in derivation of Minnesota PFOA water guidance. *Journal of Exposure Science & Environmental Epidemiology*. https://doi.org/10.1038/s41370-018-0110-5

Hinderliter PM, DeLorme MP, and Kennedy GL. 2006. Perflurooctanoic acid: Relationship between repeated inhalation exposures and plasma PFOA concentration in the rat. *Toxiciology*. 222: 80 – 85. https://doi.org/10.1016/j.tox.2006.01.029

Kennedy GL, Hall GT, Brittelli MR, Barnes JR, and Chen HC. 1986. Inhalation toxicity of ammonium perfluorooctantoate. *Food and Chemical Toxicology*. 24:(12) 1325-1329. https://doi.org/10.1016/0278-6915(86)90066-9

Li, Y., T Fletcher, D Mucs, K Scott, CH Lindh, P Tallving, K Jakobsson. 2018. Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occupational and Environmental Medicine* 75: 46-51. DOI: https://doi.org/10.1136/oemed-2017-104651

Michigan Department of Environmental, Great Lakes, and Energy. 2018. File for Perfluorooctanoic Sulfonic Acid (PFOS) (CAS No. 1763-23-1). http://www.deq.state.mi.us/aps/downloads/ATSL/1763-23-1/1763-23-1_24hr_ITSL.pdf

Minnesota Department of Health. 2001. Statement of Need And Reasonableness; Proposed Permanent Rules Relating to Health Risk Values Minnesota Rules, Parts 4717.8000 to 4717.8600. https://www.health.state.mn.us/communities/environment/risk/docs/rules/hrvsonar.pdf

Minnesota Department of Health. 2020. Toxicological Summary for Perfluorooctane sulfonate. https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf

New Jersey Department of Environmental Protection. December 19, 2019. Memo--Evaluation of Michigan Department of Environmental Quality's derivation of Initial Threshold Screening Levels for Inhalation Exposure to PFOA and PFOS.

US Environmental Protection Agency (EPA). 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F. https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf

USEPA. 2016a. Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). EPA 822-R-16-002. https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf

USEPA. 2016b. US Environmental Protection Agency - Office of Water. Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS). https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final-plain.pdf