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

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# Air Toxicological Summary for: Perfluorooctanoic Acid (PFOA)

CAS: 335-67-1
Synonyms: Perfluorooctanoate, PFOA

**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 ($RAA_{Acute}$) = Not Derived (Insufficient Data)**

**Non-Cancer Short-term, Subchronic, Chronic RAA ($RAA_{Short\text{-}term,\ Subchronic,\ Chronic}$) = 0.063 µg/m$^3$*** 

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

= 0.000018 (mg/kg-d) x (70 kg/20 m$^3$-d) x (1000 µg/mg)

= 0.063 µg/m$^3$

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| Reference Dose/Concentration: | HED/Total UF = 0.0053/300 = 0.000018 mg/kg-d (CD-1 Mice) |
| Source of toxicity value: | Determined by MDH in 2017 |
| Point of Departure (POD): | 38 mg/L serum concentration (EPA 2016a predicted average serum concentration for maternal animals from Lau et al 2006) |
| Dose Adjustment Factor (DAF): | 0.00014; Toxicokinetic Adjustment based on Chemical Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.17 L/kg x (0.693/840 days) = 0.00014 L/kg-day. (Half-life from US EPA 2016a) |

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| Human Equivalent Dose (HED): | POD x DAF = 38 mg/L x 0.00014 L/kg/day = 0.0053 mg/kg-d |
| Total uncertainty factor (UF): | 300 |
| Uncertainty factor allocation: | 3 for interspecies differences (for toxicodynamics); 10 for intraspecies variability. With the exception of accelerated preputial separation (PPS), the effects observed at the LOAEL were mild. A LOAEL-to-NOAEL uncertainty factor of 3 was used, along with a database uncertainty factor of 3 for the lack of an acceptable 2-generation study |
| Critical effect(s): | Delayed ossification, accelerated PPS in male offspring, trend for decreased pup body weight, and increased maternal liver weight |
| Co-critical effect(s): | In offspring exposed during development: changes in liver weight, histology, and triglycerides, and delayed mammary gland development.<br><br>In adult animals: liver weight changes accompanied by changes in liver enzyme levels, changes in triglyceride and cholesterol levels, microscopic evidence of cellular damage and bile duct hyperplasia; decreased spleen weight and spleen lymphocytes; decreased IgM response; kidney weight changes and papilla urothelium hyperplasia; increased pancreatic acinar cell hyperplasia; and decreased serum thyroid hormone levels. |
| Additivity endpoint(s): | Developmental, Hepatic (Liver) system, Immune system, and Renal (Kidney) system, Pancreas, and Thyroid |

*MDH 2018; Due to the highly bioaccumulative nature of PFOA and human half-life of approximately 2- 3 years, serum concentrations are the most appropriate dose metric and the standard equation to derive the Health Based Value (HBV) was not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. Therefore, a single HBV has been recommended for short-term, subchronic, and chronic durations. Further detail regarding the MDH 2018 PFOA RfD can be found in the Toxicological Summary for Perfluorooctanoate (https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfoa.pdf)

**Cancer Risk Assessment Advice = Not Applicable**

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| Cancer classification: | Suggestive Evidence of Carcinogenic Potential (EPA 2016b)<br>Likely to be carcinogenic at high doses (MDH 2018, based on US EPA 2005 Cancer Guidelines). |
| Inhalation Unit Risk (IUR): | Not Determined** |
| Source of IUR: | Not Applicable |
| Tumor site(s): | Leydig Cell Tumors, Liver, and Pancreas (via oral route) |

**MDH 2018; EPA derived a slope factor of 0.07 (mg/kg-d)-1, however, this slope factor cannot be used to derive quantitative guidance because it was based on body weight scaling rather than established chemical-specific toxicokinetic differences.

**Volatile: No**

**Summary of Guidance Value History:** There are no previous PFOA air guidance values.

**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 2018; Three large epidemiological studies provide support for an association between PFOA exposure and incidence or prevalence of thyroid disease in female adults or children, but not in males. In addition, associations between PFOA and Thyroid Stimulating Hormone (TSH) have also been reported in some populations of pregnant females. However, no significant associations were found between PFOA and TSH or thyroid hormones (T4 or T3) in people who have not been diagnosed with thyroid disease.

Effects of PFOA on thyroid hormones in animals are generally not as well characterized as those of PFOS. Reduced total and free T4 were reported in adult male rats and monkeys at serum levels > 500-fold higher than the serum level corresponding to the RfD. However, these doses were the lowest doses tested within the study and the dose-response relationship of serum total T4 with PFOA exposure has yet to be fully evaluated. As a result, the lowest effective dose remains unknown.

Other endocrine effects beyond thyroid have not been well-studied, and study results are not entirely consistent. A few studies reported sperm abnormalities, decreased testosterone and increased estradiol in male rats and mice at PFOA levels similar to those which form the basis of the RfD, whereas other studies only reported these effects at higher doses.

[2] MDH 2018; Associations between prenatal, childhood, or adult PFOA exposure and risk of infectious diseases (as a marker of immune suppression) have not been consistently seen in epidemiological studies, although there was some indication of effect modification by gender (i.e., associations seen in female children but not in male children). Three studies examined associations between maternal and/or child serum PFOA levels and vaccine response (measured by antibody levels) in children and adults. The study in adults reported that a reduction in antibody response to one of the three influenza strains tested after receiving the flu vaccine was associated with increasing levels of serum PFOA. While decreased vaccine response was associated with PFOA levels in these studies, similar results

were also observed with other perfluorinated chemicals and, therefore, could not be attributed specifically to PFOA.

Several animal studies demonstrate effects on the spleen and on thymus weights as well as decreased immune response. These effects were observed at serum concentrations similar to the critical study LOAEL. The immune system is listed as one of the co-critical effects and Additivity Endpoints.

[3] MDH 2018; There have been numerous human epidemiological studies examining PFOA exposure and developmental effects. Some studies reported an association between PFOA and birth weight, while others have not. Two epidemiological studies examined development of puberty in females in relation to prenatal exposure to PFOA, however, the results of these two studies are conflicting.

Among the animal studies, decreased postnatal growth leading to developmental effects (e.g., lower body weight, delayed eye opening, delayed vaginal opening, and accelerated preputial separation) have been observed. These effects form the basis of the RfD and were observed at serum concentrations ~300-fold higher than the serum concentration corresponding to the RfD.

Delayed mammary gland development in female mice exposed in utero has been reported. Qualitative and quantitative scoring assessments have identified different thresholds for this effect. MDH had more confidence in using quantitative measurements of mammary gland development and these measures were used in identifying mammary gland development as a co-critical effect. An additional study evaluated the correlation between mammary duct branching patterns and the ability to support pup growth through lactation. No significant impacts were found.

Doses resulting in serum concentrations >700-fold higher than the serum concentration corresponding to the RfD resulted in decreased neonatal survival.

[4] MDH 2018; A series of studies in a high-exposure study population reported associations between PFOA exposure and pregnancy-induced hypertension or preeclampsia. Limited data suggest a correlation between higher PFOA levels in females and decreases in fecundity and fertility, however, loss of body burden via birth and lactation could impact this correlation. No clear effects of PFOA on male fertility endpoints have been identified.

Among the animal studies, there was no effect of PFOA on reproductive or fertility parameters in female rats. However, it should be noted that female rats have a very high elimination rate compared to male rats or other species. Increased full litter resorptions and increased stillbirths were observed in pregnant mice exposed at serum concentrations >700-fold higher than the serum concentration corresponding to the RfD.

No evidence of altered testicular and sperm structure or function was reported in adult male rats exposed to doses producing serum concentrations >350-fold higher than the serum concentration corresponding to the RfD. Increased sperm abnormalities and decreased testosterone have been reported, but typically at serum concentrations 100-fold higher than the serum concentration corresponding to the RfD.

[5] MDH 2018; The human data pertaining to neurotoxicity (including neurodevelopmental effects) of PFOA are limited, but do not indicate the presence of associations between PFOA and a variety of

outcomes. Epidemiology studies of children found a weak statistical association between serum PFOA and parental reports of ADHD.

Information from animal studies is also quite limited. The offspring of mice fed PFOA throughout gestation had detectable levels of PFOA in their brains at birth. Locomotor activity, anxiety-related or depression-like behavior, or muscle strength were not altered. Circadian activity tests revealed gender related differences in exploratory behavior patterns. These data suggest a need for additional studies to fully understand the neurological effects of PFOA.

[6] PFOA studies investigated respiratory effects are limited in animals. Reported acute effects included excessive salivation and eye and nose irritation in rats exposed to 18,600 mg/$m^3$ for one hour and weight loss and pulmonary edema (disappeared within one week of exposure) in rats exposed to 380 mg/$m^3$ for four hours. No changes to the lungs or trachea were reported from rats exposed head-only to up to 84 mg/$m^3$ ammonium perfluorononanoate (APFO) dusts 6 hours/day, 5 days/week for two weeks. Male CD rats exposed nose-only to ≥590 mg/$m^3$ APFO for four hours exhibited lung noise and labored breathing during exposure and throughout a 12-day recovery period. A monkey study exposure to APFO via up to 20 mg/kg/d via capsule for 26 weeks reported no sign of respiratory issues or gross or microscopic effects in the lungs and trachea.

Pulmonary function tests and chest roentgenograms conducted on workers potentially exposed to PFOA at the Washington Works fluoropolymers production facility were within normal limits. Another study of workers at this facility did not find an association between estimated cumulative serum PFOA levels and the risk of chronic obstructive pulmonary disease; however, residents living near the facility had an increased risk of chronic bronchitis and shortness of breath (based on health surveys).

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