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Toxicological Summary for: Perfluorooctanoic Acid

CAS: **335-67-1(free acid)**
335-66-0 (acid fluoride)
3825-26-1 (ammonium salt, APFO)
2395-00-8 (potassium salt)
335-93-3 (silver salt)
335-95-5 (sodium salt)
[Note: perfluorooctanoate anion does not have a specific CAS number.]
Synonym: PFOA

MDH conducted a focused re-evaluation which relied heavily upon EPA's hazard assessment and key study identification contained within the EPA Health Effects Support Document for Perfluorooctanoic Acid (PFOA) released in May 2016 (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.

Short-term, Subchronic and Chronic* - Non-Cancer Health Based Value (nHBV) = 0.035 µg/L**

*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 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. The 2017 HBV was derived using a toxicokinetic (TK) model developed by MDH with input from an external peer review panel. See details about the model presented below.

**Relative Source Contribution (RSC): based on current biomonitoring serum concentrations from local and national general populations to represent non-water exposures, an RSC of 0.5 (50%) was selected for water ingestion.

Intake Rate: In keeping with MDH's practice, 95th percentile water intake rates (Table 3-1 and 3-3, USEPA 2011) or upper percentile breastmilk intake rates (Table 15-1, USEPA 2011) were used. Breastmilk concentrations were calculated by multiplying the maternal serum concentration by a PFOA breastmilk transfer factor of 5.2%. The intake rates and breastfeeding period of one year were used as representative of a reasonable maximum exposure scenario.

MDH typically uses a simple equation to calculate HBVs at the part per billion level with results rounded to one significant digit. However, the toxicokinetic model used to derive the HBV for PFOA showed that serum concentrations were impacted by changes in water concentrations at the part per trillion level. As a result, the HBV contains two digits.

Reference Dose/Concentration:	HED/Total UF = 0.0053/300=0.000018 mg/kg-d (CD-1 Mice). *[The corresponding serum concentration is 38/300 = 0.13 mg/L (or µg/mL). NOTE: this serum concentration is inappropriate to use for individual assessment.***]*
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 (US EPA 2016a)
Human Equivalent Dose (HED):	POD x DAF = 38 mg/L x 0.00014 L/kg/day = 0.0053 mg/kg-day
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. In adult animals: liver weight changes accompanied by changes in liver enzyme levels, changes in triglyceride and cholesterol levels, and microscopic evidence of cellular damage, decreased spleen weight, decreased spleen lymphocytes, and decreased IgM response, and kidney weight changes.
Additivity endpoint(s):	Developmental, Hepatic (Liver) system, Immune system, and Renal (Kidney) system.

*** Serum concentration is useful for informing public health policy and interpreting population-based exposures. This value is based on population-based parameters and should not be used for clinical assessment or for interpreting serum levels in individuals.

Toxicokinetic Model Description:

Serum concentrations can be calculated from the dose and clearance rate using the following equation. This equation was used by EPA, to calculate the HEDs from the POD serum concentrations.

$$Serum\ Concentration\ \left(\frac{mg}{L}\right) = \frac{Dose\left(\frac{mg}{kg \cdot day}\right)}{Clearance\ Rate\left(\frac{L}{kg \cdot day}\right)}$$

Where:

Dose (mg/kg-day) = Water or Breastmilk Intake (L/kg-day) x Level in Water or Breastmilk (mg/L)

and

*Clearance (L/kg-d) = Volume of distribution (L/kg) x (Ln 2/half-life (days))*Two exposure scenarios were examined: 1) an infant fed with formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water. In both scenarios the simulated individuals began life with a pre-existing body burden through placental transfer (maternal serum concentration x 87%) based on average cord to maternal serum concentration ratios reported in the literature. The serum concentration of the mother at delivery was assumed to be at steady-state.

Consistent with MDH methodology, 95th percentile water intake and upper percentile breastmilk intake rates were used to simulate a reasonable maximum exposed individual. A breastmilk transfer factor of 5.2%, based on average breastmilk to maternal serum concentration ratios reported in the literature, was used to calculate breastmilk concentration. According to the 2016 Breastfeeding Report Card (CDC 2016) nearly 66 percent of mothers in Minnesota report breastfeeding at six months, with 31.4 percent exclusively breastfeeding. The percent breastfeeding dropped to 41% at twelve months. MDH selected an exclusive breastfeeding duration of one year for the breast-fed infant scenario.

Daily post-elimination serum concentration was calculated as:

$$Serum\ Conc.\left(\frac{mg}{L}\right) = \left[Prev.\ day\ Serum\ Conc.\left(\frac{mg}{L}\right) + \frac{Today's\ Intake(mg)}{V_d\left(\frac{L}{kg}\right) \times BW(kg)}\right] \times e^{-k}$$

To maintain mass balance, daily maternal serum concentrations and loss-of-chemical via transfer to the infant as well as excretion represented by the clearance rate, were calculated.

Summary of Model Parameters

Model Parameter	Value Used
Half-life	840 days (US EPA 2016a)
Volume of distribution (Vd)	0.17 L/kg (US EPA 2016a)
Vd Age Adjustment Factor	2.1 age 1-30 days decreasing to 1.2 age 5-10 years and 1.0 after age 10 years (Friis-Hansen 1961)
Clearance Rate (CR)	0.00014 L/kg-d, calculated from Vd x (Ln 2/half-life)
Placental transfer factor *(% of maternal serum level)*	87% (MDH 2017b)

Model Parameter	Value Used
Breastmilk transfer factor *(% of maternal serum level)*	5.2% (MDH 2017b)
Water Intake Rate (L/kg-d)	95th percentile consumers only (default values, MDH 2008) (Table 3-1 & 3-3, USEPA 2011)
Breastmilk Intake Rate (L-kg-d)	Upper percentile exclusively breast-fed infants (Table 15-1, US EPA 2011)
Body weight (kg)	Calculated from water intake and breastmilk intake rate tables

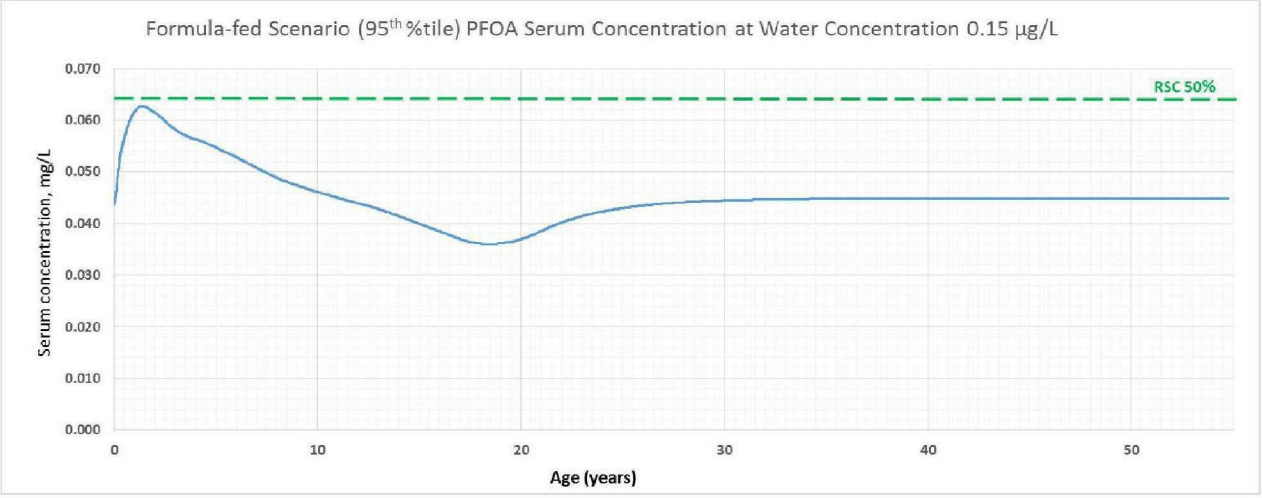
A relative source contribution factor (RSC) is incorporated into the derivation of a health-based water guidance value to account for non-water exposures. MDH utilizes the Exposure Decision Tree process presented in US EPA 2000 to derive appropriate RSCs. MDH relied upon the percentage method to reflect relative portions of water and non-water routes of exposure. The values of the duration-specific default RSCs (0.5, 0.2, and 0.2 for short-term, subchronic, and chronic, respectively) are based on the magnitude of contribution of these other exposures that occur during the relevant exposure duration (MDH 2008). However, in the case of PFOA, application of an RSC needs to account for the long elimination half-life, such that a person's serum concentration at any given age is not only the result of his or her current or recent exposures within the duration of concern, but also from exposure from years past.

Serum concentrations are the best measure of cumulative exposure and can be used in place of the RfD in the Decision Tree process. Biomonitoring results for the general public reported in the most recent National Report on Human Exposure to Environmental Chemicals (CDC 2017) can be used to represent non-water exposures. MDH selected an RSC of 50% for exposure from water ingestion based on:

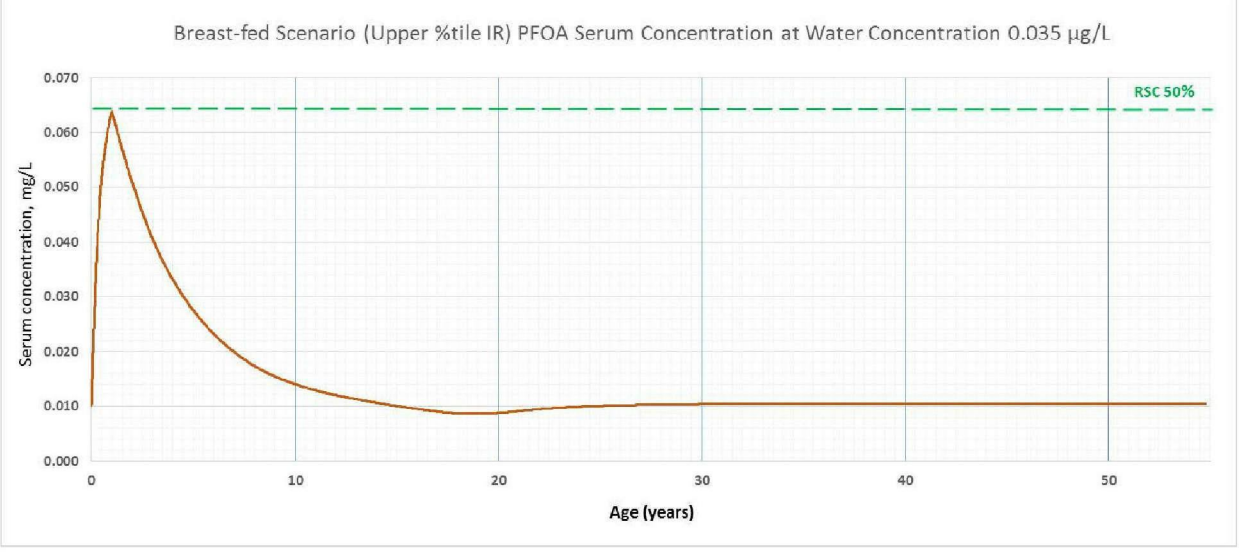
- A high-end, conservative estimate of background, non-water exposures represented by the 95th percentile serum concentration from 2013-14 NHANES (0.00557 mg/L serum), and
- The USEPA Decision Tree RSC ceiling of 80% to ensure a margin of safety to account for possible unknown sources of exposure

As mentioned above, two exposure scenarios were examined: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water through life.

For the first scenario, the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water below an RSC of 50% throughout life is 0.15 µg/L. Because of the long half-life, the serum concentration curve is very flat and even a small increment increase in the water concentration (0.16 µg/L) raises the serum concentration above the 50 percent threshold for over a year.



Applying this water concentration of 0.15 µg/L in the context of a breast-fed infant resulted in not only an exceedance of the 50% RSC threshold, but of the entire reference serum concentration for more than four years. In order to maintain a serum concentration at or below an RSC of 50% for breast-fed infants, the water concentration should not exceed 0.035 µg/L.



Due to chronic bioaccumulation in the mother and subsequent transfer to breastmilk, the breast-fed infant exposure scenario is the most limiting scenario in terms of water concentrations. To ensure protection of all segments of the population, the final health-based value for PFOA is set at 0.035 µg/L.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Suggestive Evidence of Carcinogenic Potential (EPA 2016b)
Slope factor (SF):	Not Applicable. [EPA derived a slope factor of 0.07 (mg/kg-d)$^{-1}$. However, this slope factor cannot be used to derive

quantitative guidance for PFOA because it was based on body weight scaling rather than established chemical-specific toxicokinetic differences.]

Source of cancer slope factor (SF): Not Applicable (see above)

Tumor site(s): Leydig Cell Tumors*

*An increased incidence of Leydig Cell Tumors (LCT) was observed in male rats. MDH considers the existing database to be inadequate for assessing carcinogenic potential of PFOA. No mode of action(s) (MOAs) has been identified, however, PFOA is not genotoxic and a hormonal cancer mechanism has been suggested. It is likely that the MOA(s) would have a threshold. Leydig cell turmors are common in rats but rare in humans. In addition, the MOA for LCTs in rats has questionable relevance to humans (Cook 1999) (Steinbach 2015). Some epidemiology studies reported a possible link between PFOA and testicular cancer in humans. Most human testicular cancers are not Leydig cell tumors and the type of testicular tumor associated with PFOA in humans was not characterized in the published literature. MDH considers the noncancer-based water guidance value of 0.035 µg/L to be protective for potential cancer effects, based on currently available data.

Volatile: No

Summary of Guidance Value History:

A chronic nHBV of 7 µg/L was first derived in 2002. A revised chronic nHBV of 0.3 µg/L was derived in 2007 and promulgated as an nHRL in 2009. In 2016, EPA released a Health Advisory of 0.07 µg/L for PFOA. MDH conducted a re-evaluation and derived a revised nHBV (applicable to all durations) of 0.035 µg/L in 2017. The 2017 nHBV is lower than the previous value as the result of: 1) incorporating the most recent toxicological information and 2) addressing chemical-specific exposure concerns from breastmilk.

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
Tested for specific effect?	Yes	Yes	Yes	Yes	Yes
Effects observed?	Yes[1]	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Comments on extent of testing or effects:

[Note: MDH conducted a focused re-evaluation which relied upon EPA's hazard assessment and key study identification (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.]

[1] 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] 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] 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] 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] 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.

Resources Consulted During Review:

[Note: MDH conducted a focused re-evaluation which relied upon EPA's hazard assessment and key study identification (EPA 2016a). A complete evaluation of the toxicological literature was not conducted.]

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