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Toxicological Summary for: Perfluorooctane Sulfonate

CAS: **1763-23-1 (acid)**
29081-56-9 (ammonium salt)
70225-14-8 (diethanolamine salt)
2795-39-3 (potassium salt)
29457-72-5 (lithium salt)
[Note: perfluorooctanoate anion does not have a specific CAS number.]
Synonyms: PFOS, Perfluorooctane sulfonic acid

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 Perfluorooctane Sulfonate (PFOS) 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) = 0.027 µg/L**

*Due to the highly bioaccumulative nature of PFOS and human half-life of nearly 5.4 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. Model details are 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 PFOS breastmilk transfer factor of 1.3%. For the breast-fed infant exposure scenario, a period of exclusive breastfeeding for one year was used as representative of a reasonable maximum exposure scenario.

A simple equation is typically used 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 PFOS showed that serum concentrations were impacted by changes in water concentrations at the part per trillion level. As a result, the 2017 HBV contains two digits.

Reference Dose/Concentration:	HED/Total UF = 0.00051/100 = 0.0000051 mg/kg-d (Crl:CD(SD)IGS VAF Rats). *[The corresponding serum concentration is 6.26/100 = 0.063 mg/L. Note: this serum concentration is inappropriate to use for individual assessment.***]*
Source of toxicity value:	Determined by MDH in 2017

Point of Departure (POD):	6.26 mg/L serum concentration (EPA 2016a predicted average serum concentration for F2 generation. NOAEL from Luebker et al 2005b)
Dose Adjustment Factor (DAF):	0.000081; Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half-life, days) = 0.23 L/kg x (0.693/1971 days) = 0.000081 L/kg-day (US EPA 2016a)
Human Equivalent Dose (MDH, 2017):	POD x DAF = 6.26 mg/L x 0.000081 L/kg/day = 0.00051 mg/kg-day
Total uncertainty factor (UF):	100
Uncertainty factor allocation:	3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability and 3 for database uncertainty (additional studies regarding immunotoxicity are warranted)
Critical effect(s):	Decreased pup body weight
Co-critical effect(s):	In offspring exposed during development: delayed eye opening, increased sternal defects, changes in lung development, decreased glucose tolerance, increased motor activity and decreased habituation, decreased levels of thyroxine (T4), and decreased survival. In adult animals: liver weight changes accompanied by changes in cholesterol levels and histology; decreased levels of thyroxine (T4); decreased SRBC response, increased NK cell activity, decreased spleen and thymus weight and cellularity
Additivity endpoint(s):	Developmental, Hepatic (Liver) system, Immune system, Thyroid (E)

*** 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 of PFOS (maternal serum concentration x 46%) 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 PFOS breastmilk transfer factor of 1.3%, 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	1971 days (US EPA 2016c)
Volume of distribution (Vd)	0.23 L/kg (US EPA 2016c)
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)	0.000081 L/kg-d, calculated from Vd x (Ln 2/half-life)
Placental transfer factor *(% of maternal serum level)*	46% (MDH 2017b)
Breastmilk transfer factor *(% of maternal serum level)*	1.3% (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)

Model Parameter	Value Used
Body weight (kg)	Calculated from water intake and breastmilk intake rate tables

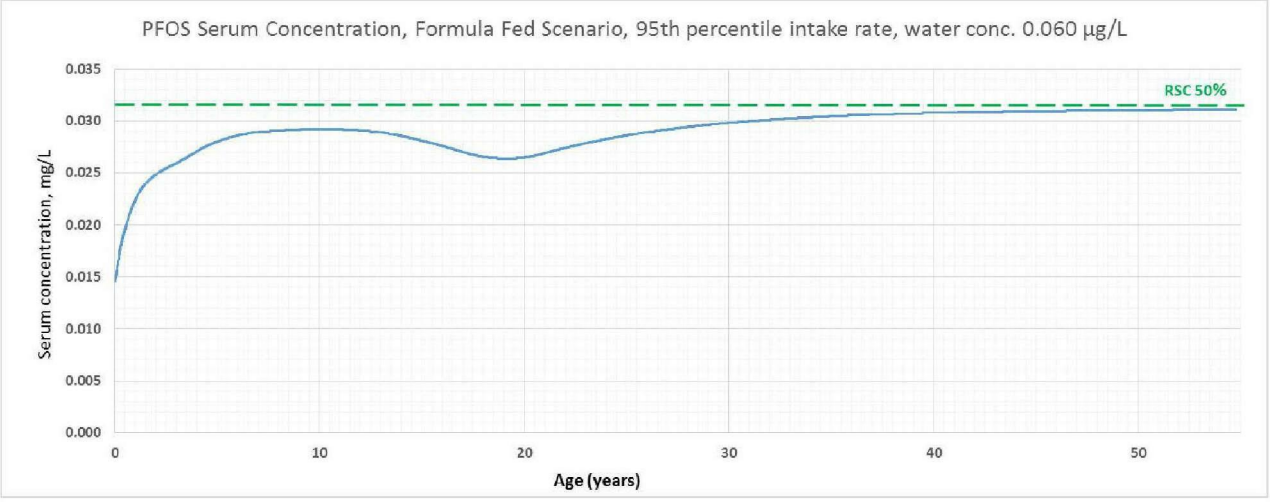
A relative source contribution factor (RSC) is incorporated into the derivation of a health-based water guidance value to account for non-water exposures. MDH utilizes the Exposure Decision Tree process presented in US EPA 2000 to derive appropriate RSCs. MDH relied upon the percentage method to reflect 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 PFOS, 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 from new residents who were not historically exposed to contaminated water in the East Metro can be used to represent non-water exposures (Nelson, 2016). The serum concentrations in these residents were similar in magnitude to those for the general public reported in the most recent National Report on Human Exposure to Environmental Chemicals (CDC 2017). MDH selected an RSC of 50% for exposure from water ingestion based on:

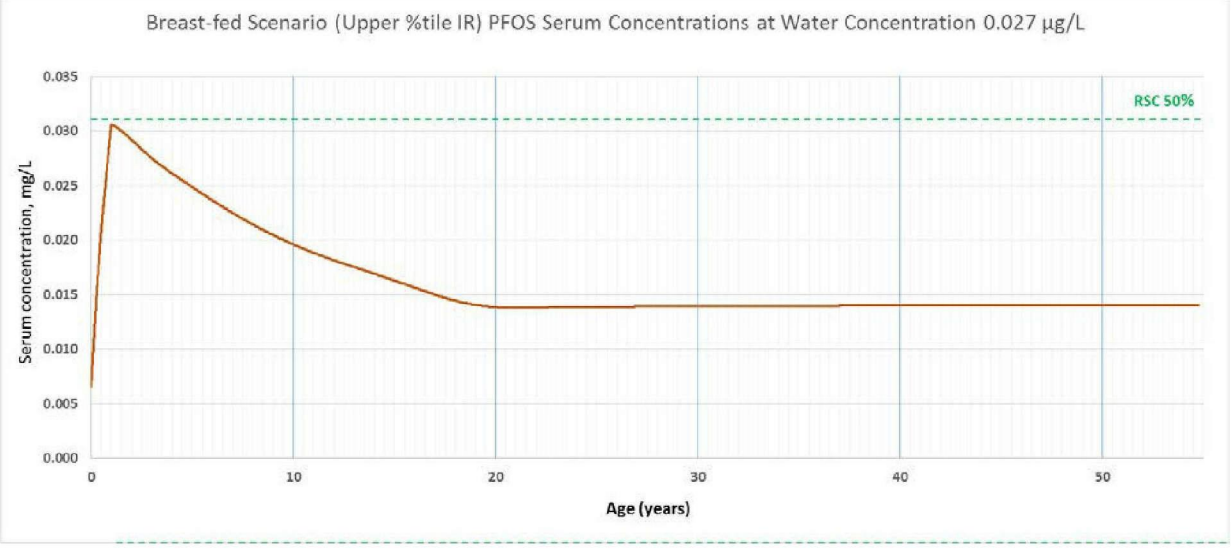
- A high-end, conservative estimate of background, non-water exposures represented by the 95th percentile serum concentration for new East Metro residents (0.021 mg/L serum), and
- The USEPA Decision Tree RSC ceiling of 80% to ensure a margin of safety to account for possible unknown sources of exposure

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 0.060 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 (0.061 µg/L) raises the serum concentration above the 50 percent threshold for nearly 9 years.



Applying this water concentration of 0.060 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 one year. In order to maintain a serum concentration at or below an RSC of 50% for breast-fed infants, the water concentration should not exceed 0.027 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 PFOS is set at 0.027 µg/L.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification:	Suggestive Evidence of Carcinogenic Potential (EPA 2016b)
Slope factor (SF):	Not Applicable
Source of cancer slope factor (SF):	Not Applicable

Tumor site(s): Liver and thyroid tumors were identified in both control and exposed animals at levels that did not show a direct relationship to dose.

Volatile: No

Summary of Guidance Value History:

A chronic nHBV of 1 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 PFOS. MDH conducted a re-evaluation and derived a revised nHBV (applicable to all durations) of 0.027 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) 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] Numerous human epidemiological studies have evaluated thyroid hormone levels and/or thyroid disease in association with serum PFOS. Results from these studies have provided limited support for an association. Stronger associations were found in populations at risk for iodine deficiency or positive anti-TPO antibodies (a marker for autoimmune thyroid disease).

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. Decreased T4 has been identified as a co-critical effect and Thyroid has been identified as an Additivity Endpoint.

[2] A few human epidemiology studies have evaluated associations between immunosuppression measures and serum PFOS. However, no clear associations were reported between serum PFOS and rates of infectious disease.

Studies in laboratory animals have shown that PFOS exposure alters several immunologic measures (e.g., suppression of SRBC response, and/or increased natural killer cell activity). Some of these effects occur at exposure levels similar to the POD. As a result the immune system has been identified as an Additivity Endpoint and a database uncertainty factor has been incorporated into the derivation of the RfD.

[3] 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. Decreased pup body weight appears to be among the most sensitive effects and, in part, forms the basis of the Reference Dose and corresponding serum concentration of concern. A limited number of studies have also reported changes in male reproductive development and changes in energy metabolism (e.g., glucose levels, lipid metabolism) following exposure during development. Additional effects, including increased pup death, were observed at higher exposure levels.

[4] A small number of human epidemiology studies have reported an association between preconception serum PFOS and gestational diabetes and pregnancy-induced hypertension. There has also been some evidence of associations between serum PFOS and decreased fertility, however, concerns have been raised over the possibility that this is due to reverse causation.

Studies in laboratory animals do not indicate that fertility is a sensitive endpoint, with decreases in male reproductive organs weights, decreased epididymal sperm count, and evidence of disruption of the blood-testes-barrier occurring at exposure levels higher than those causing developmental toxicity (see above). Therefore, the RfD would be protective of these effects.

[5] 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 similar to the critical effect and have been included as co-critical effects. These effects are encompassed by the Developmental Additivity Endpoint. 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 at higher dose levels.

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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