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Toxicological Summary for: Perfluorooctane sulfonate

CAS: 45298-90-6 (anion)
1763-23-1 (acid)
29081-56-9 (ammonium salt)
70225-14-8 (diethanolamine salt)
2795-39-3 (potassium salt)
29457-72-5 (lithium salt)

Synonyms: PFOS, Perfluorooctane sulfonic acid

MDH conducted a focused re-evaluation that used three recent state and federal comprehensive reviews (ATSDR 2018, New Jersey DWQI 2017, and USEPA 2016b) as a starting point. MDH identified additional studies and conducted supplemental analysis to comply with MDH's methodology.

Short-term, Subchronic and Chronic* Non-Cancer Health Based Value (nHBV) = 0.015 µg/L**

*Due to the highly bioaccumulative nature of PFOS within the human body, serum concentrations are the most appropriate dose metric and the standard equation to derive the HBV is not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. 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. The HBV was derived using a toxicokinetic (TK) model previously developed by MDH (Goeden et al. 2019). Model details and results are presented below.

**Relative Source Contribution (RSC): Using the most recent publications regarding PFOS serum levels in infants and young children as well as the National Report on Human Exposure to Environmental Chemicals (CDC, 2017) for older children and adults, RSCs of 0.5 (50%) and 0.2 (20%) were selected for infants/young children and chronic steady-state conditions, respectively.

Intake Rate: In keeping with MDH's peer-reviewed and promulgated methodology, 95th percentile water intake rates (Table 3-1, 3-3 and 3-5, USEPA 2019) 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 1.7%. 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. [Note: "exclusively breast-fed" intake rates refers to infants whose sole source of milk comes from human breastmilk, with no other milk substitutes (USEPA 2011, page 15-2).]

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 are impacted by changes in water concentrations at the part per trillion level. As a result, the HBV contains two digits.

Reference Dose/Concentration: $\text{HED/Total UF} = 0.000307/100 = 0.0000031 \text{ mg/kg-d}$ (or 3.1 ng/kg-d) (adult C57BL/6 male Mice). *[The corresponding serum concentration is $2.36/100 = 0.024 \text{ mg/L}$. Note: this serum concentration is inappropriate to use for individual assessment.***]*

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): $\text{POD} \times \text{DAF} = 2.36 \text{ mg/L} \times 0.00013 \text{ L/kg-d} = 0.000307 \text{ mg/kg-d}$

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 adrenocorticotrophic 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 (E), Developmental, Hepatic (liver) system, Immune, and Thyroid (E)

***Serum concentration is useful for informing public health policy and interpreting population-based exposure potential. 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 (Goeden 2019):

PFOS is well absorbed and is not metabolized. Serum concentrations can be calculated from the dose and clearance rate using the following equation.

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

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 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 40%) 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 and was calculated by using the equation above with a time-weighted 95th percentile intake from birth to 30 years of age (0.048 L/kg-d). During lactation a 95th percentile water intake rate of 47 mL/kg-d and a body weight of 65.1 kg ((USEPA 2019), Table 3-3) was used to calculate daily maternal serum concentrations.

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 1.7%, 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, dropping to 41% at twelve months. MDH chose to use the breastmilk intake rates for exclusively breastfed infants, as reported in USEPA 2011, for one year for the breast-fed infant scenario.

Daily post-elimination serum concentration was calculated as:

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

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 Reasonable Maximum Exposure (RME) Scenario Model Parameters

Model Parameter	Value Used
Half-life	1241 days (mean value for all ages, Li et al 2018) (5 th to 95 th percentile range: 803 – 2263 days)
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)	0.00013 L/kg-d, calculated from Vd x (Ln 2/half-life)
Placental transfer factor (% of maternal serum level)	40% (mean of mean paired maternal:cord blood ratios reported in the literature. Range of mean values 30 – 60%.) (Mean 95 th percentile value 81%, range 70 – 106%.)
Breastmilk transfer factor (% of maternal serum level)	1.7% (mean of mean paired maternal serum:breastmilk ratios reported in the literature. Range of mean values 1 – 3%.) (No 95 th percentile values reported in literature.)
Water Intake Rate (L/kg-d)	95 th percentile consumers only (default values, MDH 2008) (Table 3-1 (for ages ≥ 2 yrs), 3-3 (for lactating women), and 3-5 (for ages < 2yr)) (USEPA 2019)
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). **In the case of PFOS, the RSC concept must be applied in a framework recognizing the long elimination half-life of PFOS, 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 (serum concentrations) from the general population (National Report on Human Exposure to Environmental Chemicals (CDC 2017) and new residents who were not historically exposed to contaminated water in the East Metro (Nelson, 2016) can be used to represent non-water or background exposures for older children and adults. For infants and young children, MDH conducted a review of the literature to identify appropriate background serum concentrations.

Serum concentrations in the general population have decreased over time, but appear to increase with age, with older children and adults exhibiting higher serum levels. This trend direction is in the opposite direction than MDH's RME model serum predictions. However, it is

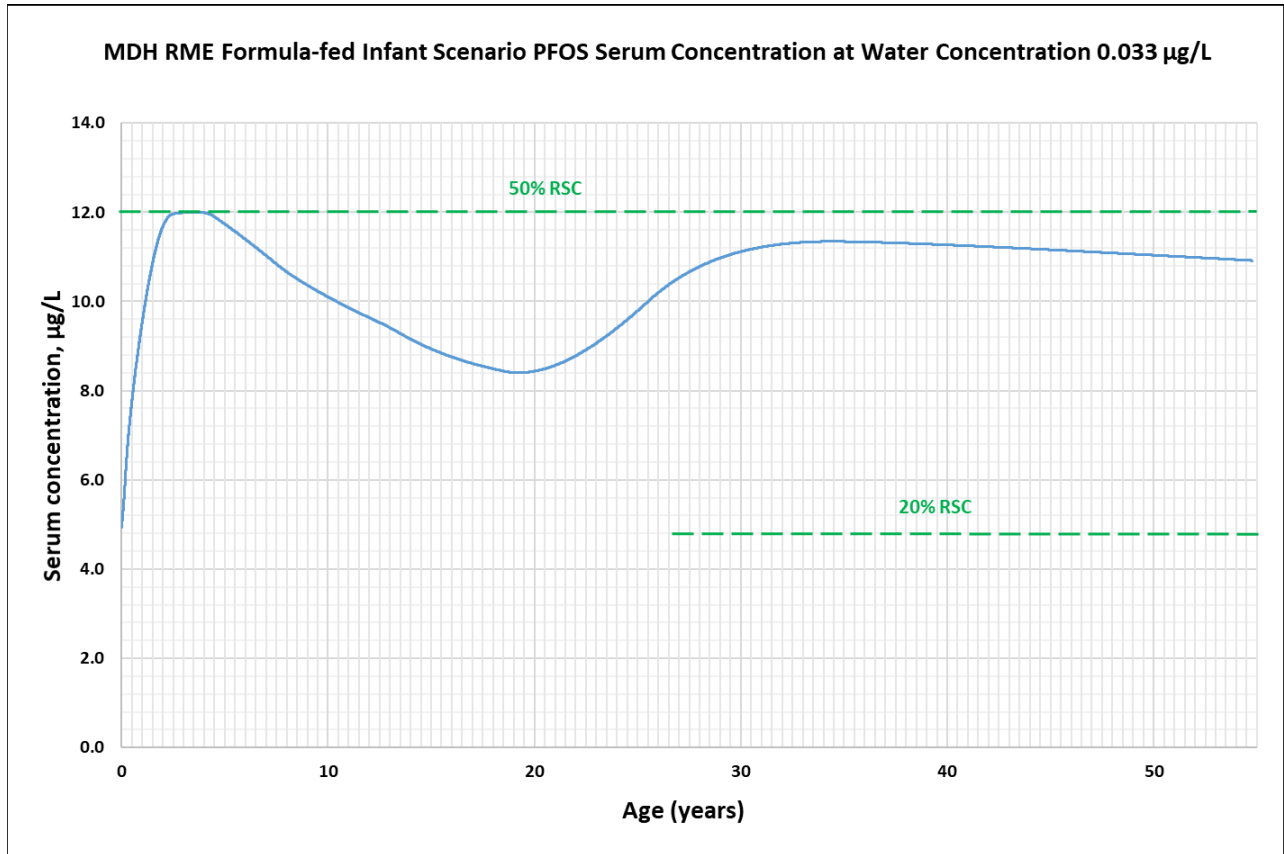
critical to note that background exposure levels are the result of decreasing historical exposure while MDH's model predicts serum concentrations resulting from a constant contaminated water source over time.

The apportionment to water ingestion can be calculated by taking a ceiling of 80% and subtracting a conservative (high-end) serum value from the most recent biomonitoring data. Eighty percent of the serum concentration associated with the RfD would be $19.2 \mu\text{g/L}$ ($24 \mu\text{g/L} \times 0.8$). Subtracting the 95th percentile serum level ($8.82 \mu\text{g/L}$) for three to five year olds (Ye et al 2018) as non-water background exposure for infants and young children from the 80% ceiling leaves a residual serum concentration of $10.4 \mu\text{g/L}$ ($19.2 - 8.82$) for ingestion of contaminated water. This residual concentration is approximately 43% of the serum concentration at the RfD ($24 \mu\text{g/L}$) and approximately 54% of the 80% ceiling value ($19.2 \mu\text{g/L}$), supporting the use of an RSC of 50% for infants and young children.

Since exposures take years to eliminate it is also important to consider the higher-background steady-state serum levels in older age groups. To determine the appropriate RSC for steady-state conditions the 95th percentile ($18.26 \mu\text{g/L}$) from the most recent NHANES data (2015-2016, (Nelson 2018)) was used to determine that the floor value of 20% is the appropriate RSC for steady-state conditions.

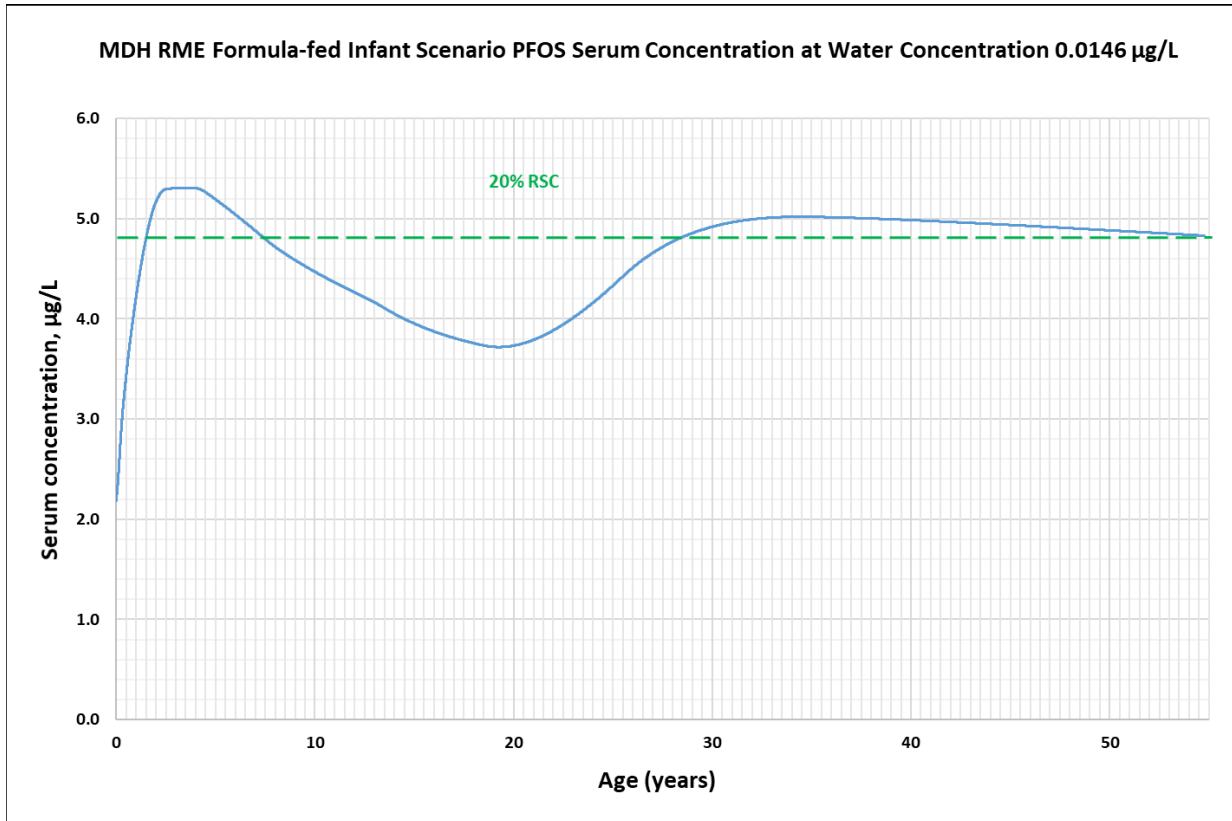
As mentioned above, two exposure scenarios were examined: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water through life. For the first scenario, the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water at or below an RSC of 50% in infants and young children is $0.033 \mu\text{g/L}$ (Figure 1).

Figure 1. Formula-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and an RSC of 50% for infants and young children.



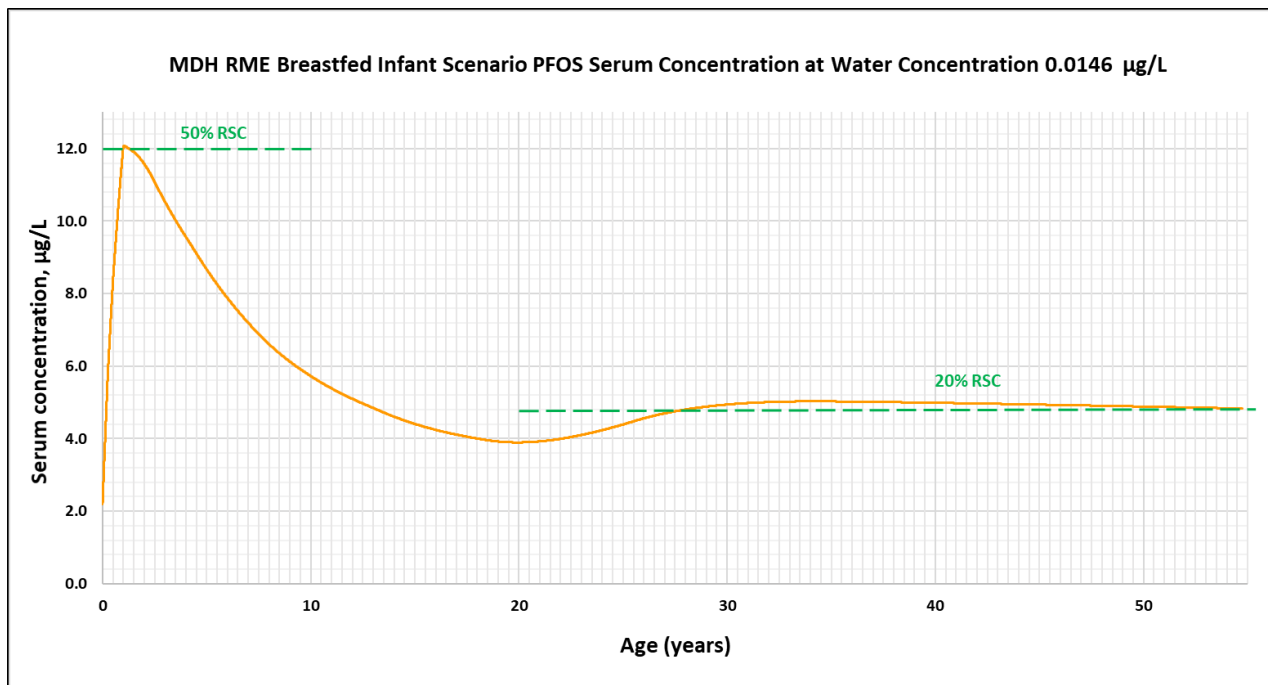
However, because of the long half-life the serum concentration curve is very flat, and serum levels in older children and adults exceeds the steady state RSC of 20%. In order to keep serum concentrations at steady state at or below 20% the water concentration had to be lowered to 0.0146 µg PFOS/L water (Figure 2).

Figure 2. Formula-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and an RSC of 20% for steady-state.



For the second scenario, the breast-fed infant, the water concentration that maintains a serum concentration attributable to drinking water at or below an RSC of 50% in infants and young children is 0.0146 µg/L (Figure 3).

Figure 3. Breast-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and an RSC of 50% for infants and young children.



The water concentration of 0.0146 µg/L also maintains serum concentrations at steady state at or below 20%.

To ensure protection of all segments of the population, the final health-based value for PFOS is set at 0.0146, rounded to 0.015 µg/L.

Cancer Health Based Value (cHBV) = Not Applicable

Cancer classification: Suggestive Evidence of Carcinogenic Potential (USEPA 2016b,d)
 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 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 2017, MDH derived a revised nHBV (applicable to all durations) of 0.027 µg/L. In 2018, MDH revised the nHBV (applicable to all

durations) to 0.015 µg/L. The 2018 value is lower than the previous value as the result of: 1) incorporating a more recent, community-based shorter half-life value and 2) additional toxicological information. In 2020 MDH incorporated updated water intake rates (US EPA 2019). Using the updated intake rates did not change the HBV value.

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:

¹ 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 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 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 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 post-implantation 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 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.

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