DEPARTMENT OF HEALTH

CLEAN WATER LAND & LEGACY AMENDMENT

Background Document

Toxicokinetic Model for Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA) and Its Use in the Derivation of Human Health-Based Water Guidance Values

May 2017

NOTE: The following model was developed by the Minnesota Department of Health (MDH). Use of or reference to this model without proper attribution to MDH is prohibited. MDH is not responsible for changes or misuse of the model by others.

Table of Contents

List of Tables:

List of Figures:

List of Equations:

Acronyms

aci – as cited in
BIR – breastmilk intake rate
BW – body weight
CDC – Centers for Disease Control
CI – confidence interval
CR – clearance rate
HAs – health advisories
IR – intake rate
k – rate constant (Ln 2/half-life)
LOAEL – lowest observable adverse effect level
L/kg – liters per kilogram body weight
L/kg-d – liters per kilogram body weight per day
MDH – Minnesota Department of Health
mg/L – milligrams per liter
mg/kg-d – milligram per kilogram body weight per day
mg –milligram
MIR – mean intake rate
mL/day – milliliters per day
mL/kg-d – milliliters per kilogram body weight per day
ng/mL – nanogram per milliliter
NHANES – National Health and Nutrition Examination Survey
nHBG – noncancer health-based water guidance value
NOAEL – no observable adverse effect level
OAT – organic anion transporter
PBPK – physiologically-based pharmacokinetic
PFC – perfluorochemicals (also referred to as perfluoroalkyl substances or PFAS)
PFCAs – perfluorocarboxyletes
PFOA – perfluorooctanoic acid
PFOS – perfluorooctane sulfonate
PFSAs - perfluorosulfonates
PK – pharmacokinetic
POD – point of departure
PWS – public water system
RfD – reference dose
RME – reasonable maximum exposure
RSC – relative source contribution factor
t½ - half-life
TK – toxicokinetic
µg/L – microgram per liter (also known as parts per billion)
µg - microgram
UPIR – upper percentile intake rate
URAT – urate anion transporter
USEPA – United States Environmental Protection Agency
V_d – volume of distribution
V_d AF – volume of distribution adjustment factor
WIR – water intake rate

Executive Summary

The Minnesota Department of Health (MDH) evaluates human health risks from exposure to contaminants in drinking water. In May of 2016, the US Environmental Protection Agency (USEPA) issued lifetime health advisories (HAs) of 0.07 µg/L for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). As a result, MDH initiated a review of the basis of the USEPA HAs and a reassessment of MDH's own health-based guidance values for these two chemicals, which were derived in 2007.

Traditionally, noncancer health-based water guidance (nHBG) are derived by multiplying a reference dose (RfD, mg/kg-d) by a relative source contribution factor (RSC), divided by a water intake rate (L/kg-d). However, PFOS and PFOA have unique characteristics that are not adequately addressed when using this traditional approach.

PFOA and PFOS bioaccumulate in serum, cross the placenta, and are excreted into breastmilk. Research has shown that breastmilk can be a major source of exposure, resulting in infant serum concentrations that are higher than maternal concentrations. Although exposures during infancy are short-term, this particular life-stage is of particular concern because (1) PFOS and PFOA are developmental toxicants; (2) infants consume a much greater volume of liquid per unit body weight than older children and adults; and (3) due to the long elimination half-lives of PFOS and PFOA, the short-term exposures that occur during infancy can result in body burdens that take years to eliminate.

In deriving health-based guidance, MDH uses a reasonable maximum exposure (RME) approach. An RME scenario depicts a realistic but maximum exposure situation (e.g., 95th percentile water intake rate) to ensure that even the most heavily exposed individuals within the population will be protected. MDH used this RME approach in the context of a novel kinetic model to develop updated water guidance values for PFOS and PFOA.

In order to ensure that MDH's revised health-based water guidance values were adequately protective of infants, a one-compartment toxicokinetic (TK) model was developed to predict serum concentrations of PFOS and PFOA from birth through attainment of steady-state conditions. Two RME scenarios were evaluated: 1) an infant exclusively fed with formula reconstituted with contaminated water starting at birth, followed by a lifetime of drinking contaminated water; and 2) a breastfed infant exclusively breastfed for 12 months, followed by a lifetime of drinking contaminated water. In both scenarios, the simulated individuals began life with a pre-existing body burden through placental transfer from a mother at steady-state conditions.

MDH conducted an expedited and focused re-evaluation of the available toxicological information, relying in part on USEPA's 2016 health assessment documents ((USEPA, 2016a) (USEPA, 2016c)). Reference doses (RfDs) of 0.0000051 and 0.000018 mg/kg-d were derived for PFOS and PFOA, respectively. The corresponding serum concentrations are 0.063 and 0.13 mg/L for PFOS and PFOA, respectively.

Serum concentrations are the best measure of internal dose for PFOS and PFOA, and are therefore considered to be the most appropriate basis for deriving an RfD that is protective of potential health effects. It is important that total exposure from all sources, including potential ingestion of drinking water containing PFOS or PFOA, does not result in serum concentrations that exceed the serum concentration associated with the RfD for a toxicologically relevant period of time. The exposure contributed from non-water sources was addressed through the application of a Relative Source Contribution (RSC) factor, which allocates a fraction of the RfD (or in this case, the serum concentration associated with the RfD) to water exposures. MDH used the USEPA Exposure Decision Tree process (USEPA 2000) along with recent national (2013-2014 NHANES, CDC 2017) and local (new East Metro residents, Nelson 2016) biomonitoring results to identify an RSC apportionment of 50% for PFOS and PFOA.

The TK model developed by MDH predicts daily serum concentrations over a lifetime of exposure to a constant PFOA or PFOS concentration in drinking water. Since the excretion via breastmilk was significant, the calculation of daily maternal serum concentrations incorporated loss of chemical via transfer to the infant as well as excretion represented by the clearance rate. The infant's daily intake (and thus the mother's loss) was calculated from the breastmilk intake rate and the breastmilk concentration.

As part of the model development, predicted serum concentrations from the model were compared to empirical data from published studies, as well as published toxicokinetic models. In addition, MDH solicited input from six external peer reviewers for advice on how to improve the model predictions.

MDH derived RfDs of 0.0000051 and 0.000018 mg/kg-d for PFOS and PFOA, respectively. Based on the serum concentrations corresponding to the RfDs (0.063 and 0.13 mg/L for PFOS and PFOA, respectively[1]) and an RSC of 50%, the MDH TK model results indicate that water concentrations of 0.060 and 0.15 µg/L, respectively, are protective for the exclusively formula-fed infant scenario. However, due to the bioaccumulative nature of PFOS and PFOA, chronic exposure to mothers and subsequent transfer through breastmilk resulted in higher exposures to breastfed infants. Consequently, the model results indicate that lower health-based water concentrations of 0.027 and 0.035 µg/L for PFOS and PFOA, respectively, are necessary to be protective for the exclusively breastfed infant scenario. To ensure protection of all segments of the population, the final health-based values for PFOS and PFOA were set at 0.027 and 0.035 µg/L, respectively.

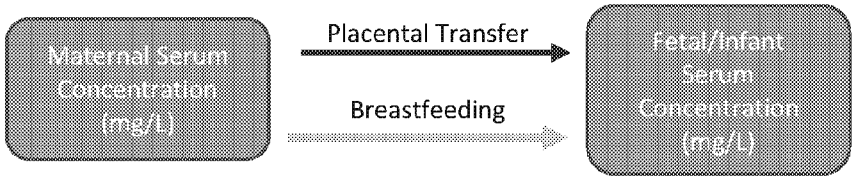
Breastfeeding is important for the short and long term health of both a mother and infant. As stated above an RME scenario was used in generating the health-based values. By design, an RME scenario depicts a realistic but maximum exposure situation to ensure that even the most heavily exposed individuals within the population will be protected. The majority of the population would experience lower exposure. MDH recommends that women currently breastfeeding, and pregnant women who plan to breastfeed, continue to do so. Exclusive breastfeeding is recommended by doctors and other health professionals. It is unlikely that potential health concerns exceed the known benefits of breastfeeding. Application of the final health-based values will ultimately result in lower body burdens and breastmilk concentrations of PFOS and PFOA so that infants can receive the optimal benefits from breastfeeding.

[1] Serum concentration corresponding to the RfD 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.

1.0 General Approach and Challenges for Estimating Water Guidance Values

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are bioaccumulative chemicals that have the potential to accumulate within the body over the years prior to pregnancy, cross the placenta, and partition into breastmilk. Therefore, serum and breastmilk concentrations will be higher than the concentrations in environmental media (e.g., contaminated water) to which a woman is exposed. In addition to being born with an existing body burden from placental transfer based on maternal accumulation, infants may also experience subsequent higher exposures, especially from breastfeeding (See Figure 1 below).

Figure 1. Maternal transfer to fetus/infant.



The MDH standard water guidance methodology, based on life-stage specific drinking water intake rates, does not incorporate body-burden at birth nor the concentration of environmental chemicals in breastmilk. This document, therefore, describes a framework developed by MDH that incorporates chemical-specific properties of PFOS and PFOA to derive sufficiently protective water guidance values.

A typical noncancer health-based water guidance value (nHBG) is calculated by combining a reference dose (RfD) with a water intake rate (IR) and relative source contribution factor (RSC), summarized by the following equation (MDH, 2008):

Equation 1. Standard equation for calculating noncancer health-based water guidance (nHBG).

$$\mathrm{n}HBG_{duration}\left(\frac{\mu g}{L}\right) = \frac{RfD_{duration}\left(\frac{mg}{kg \cdot day}\right) \times RSC_{duration} \times 1000\,\frac{\mu g}{mg}}{IR_{duration}\left(\frac{L}{kg \cdot day}\right)}$$

MDH HBGs represent a concentration of an environmental chemical in drinking water that is associated with negligible human health risk. It is standard US Environmental Protection Agency (USEPA) and MDH practice to incorporate upper-end exposure levels in order to ensure an adequate margin of safety for most of the exposed population ((USEPA, 2004), (MDH, 2008)). MDH's methodology for deriving health-based water guidance uses intake rates that approximate the 95th percentile (MDH, 2008) to ensure inclusion of most of the population and protection of individuals who consume a large percentage of their water from a single source, such as a private well or community water supply. MDH's goal, based on data availability, is to derive water guidance that is protective of short-term as well as chronic durations. Consistent with using data-supported higher-end exposure levels, RME scenarios have been determined and used in MDH's TK modeling.

Criteria for bioaccumulative contaminants are often based on long-term exposures and typically consider the resulting steady-state serum levels that arise from the net balance between daily intake and elimination. In 2016, USEPA derived RfDs of 0.00002 mg/kg-d for PFOS and PFOA. In deriving their Health Advisories (HAs) of 0.07 µg/L, USEPA chose to use the 90th percentile water intake rate for lactating women (0.054 L/kg-d). Using this intake rate along with an RSC of 0.2 in Equation 1 results in USEPA's lifetime health advisory of 0.07 µg/L.

For comparison, if MDH's typical chronic intake rate (95th percentile lifetime intake, 0.044 L/kg-d) is used to calculate a water value based on USEPA's RfD and RSC, the resulting water concentration would be 0.09 µg/L.

MDH determined that the traditional approach for deriving water guidance was not adequate to address the bioaccumulative nature of PFOS and PFOA, placental transfer, breast-milk transfer, and high early-life intake rates. The consideration of early-life exposure and kinetics is further reinforced by the developmental basis of the RfDs for both PFOS and PFOA. The time to reach steady-state conditions is typically equivalent to approximately five half-lives. However, this general principle is based on constant exposure. Given the significantly higher intake rates early in life, it is likely that long-term late life steady-state levels are reached faster, and exceedances (peak levels) of steady-state levels may occur, especially considering the body burden transferred from mother to offspring. Use of an infant intake rate (0.285 L/kg-d) and an RSC of 0.2 (since transplacental and lactational exposure occur) would result in a calculated water concentration of 0.014 µg/L. However, this short-term infant intake rate is based on an exposure duration of only two months, does not take into account the differences between PFOS and PFOA toxicokinetics (TK) nor the body burden at birth, and could be inconsistent with the dose metric used to derive the RfDs.

Fluid intake rates in infants are 7-10 fold higher per unit body weight than in older children and adults (USEPA, 2011). Given the long half-lives of PFOS and PFOA, these high, short-term exposures can result in prolonged elevations of internal body burden over several years, including critical times of development. Formula-fed and nursing infants consume a greater volume of liquid on a per body weight basis than older children and adults. The available literature (e.g., (Fromme, 2010), (Haug, 2011), (Mondal, 2014), (Mogensen, 2015)) reports higher PFOS and PFOA serum levels in breastfed infants than in maternal serum, providing direct evidence of higher exposures in breastfed infants compared to mothers. A physiologically-based pharmacokinetic (PBPK) model confirmed the importance of breastmilk as an important exposure pathway for PFOS and PFOA in infants (Loccasano, 2013). This model also showed that failing to account for both route of exposure (breastmilk) and increased fluid intake rates would result in an underestimation of serum concentrations throughout much of early life. A simpler pharmacokinetic (PK) model was developed by Verner and colleagues (Verner, 2016), which again documented breastmilk as a significant exposure pathway. Both models are coded using acslX, a modeling program which is no longer available or supported (http://acslx.com/). In order to address concerns regarding higher, early life exposures, MDH created a simple one-compartment toxicokinetic (TK) model in Microsoft Excel 2013 to evaluate the importance of high early life exposures in formula-fed and breastfed infants.

PFOS and PFOA are well absorbed into the body and are not metabolized. Therefore, the amount in the body is a function of how much goes into the body (dose) and how quickly the chemicals are eliminated (cleared) from the body. MDH agrees with USEPA and others that serum concentration is the best dose metric for dose-response, exposure, and risk characterization of PFOS and PFOA.

In deriving the RfDs for PFOS and PFOA, the USEPA ((USEPA, 2016a), (USEPA, 2016d)) used the following relationship to calculate the human equivalent doses that would correspond to the serum concentrations from animal studies.

Equation 2. Calculation of human equivalent dose corresponding to a specific serum concentration.

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

With continuous exposure to bioaccumulative chemicals, serum concentrations increase until steady-state is reached. Steady-state conditions, assuming a constant exposure rate, are achieved when the rates of absorption

and elimination from the body are equal. However, a constant exposure rate does not reflect reality during early life, where intake rates, body weight, volume of distribution, and exposure matrix (drinking water used in formula or breastfeeding) are all in constant flux. The adoption of adult chronic steady-state kinetics for deriving water guidance is difficult to justify when the most sensitive and highly exposed individuals are the very young. Therefore, MDH developed a one-compartment TK model incorporating the most reliable science and concepts to aid in the derivation of water guidance that is protective of all segments of the general population.

2.0 Simple One-Compartment TK Model

Serum concentrations are the best measure of exposure and basis for an RfD. Therefore, a water guidance value that results in a serum concentration at or below the serum concentration associated with the RfD, even when accounting for the contribution of non-water exposures, would be health protective. Equation 2, above, can be rearranged to calculate serum concentration based on dose and clearance.

Equation 3. Calculation of serum concentration from dose and clearance rate.

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

Where:

for water ingestion –

$$Dose\left(\frac{mg}{kg \cdot day}\right) = Water\ Intake\ Rate\left(\frac{L}{kg \cdot day}\right) \times Water\ Concentration\left(\frac{mg}{L}\right)$$

for breastmilk -

$$Dose\left(\frac{mg}{kg \cdot day}\right) = Breastmilk\ Intake\ Rate\left(\frac{L}{kg \cdot day}\right) \times Breastmilk\ Concentration\left(\frac{mg}{L}\right)$$

and

$$Clearance\ Rate\left(\frac{L}{kg \cdot day}\right) = V_d \times k$$

$$V_d = Volume\ of\ Distribution\left(\frac{L}{kg}\right)$$

$$k = \frac{ln(2)}{half - life\ (d)}$$

The volume of distribution (Vd), 0.23 and 0.17 L/kg for PFOS and PFOA, respectively, has been characterized by several researchers (see Section 2.5.3 in (USEPA, 2016c) and Section 2.6.3 in (USEPA, 2016a)). By combining these Vd estimates with the half-life of PFOS (5.4 years) and PFOA (2.3 years), USEPA (US EPA 2016a, c) calculated the following clearance rates:

$$PFOS: \quad 0.23\frac{L}{kg} \times \frac{0.693}{5.4\ yr \times 365\frac{d}{yr}} = 0.000081\frac{L}{kg \cdot d}$$

$$PFOA: \quad 0.17\frac{L}{kg} \times \frac{0.693}{2.3\ yr \times 365\frac{d}{yr}} = 0.00014\frac{L}{kg \cdot d}$$

When a lifetime mean water intake rate of 0.016 L/kg-d (USEPA, 2011) is applied to a water concentration of 1 mg/L (arbitrarily set for comparison purposes), the resulting steady-state serum to water concentration ratios are 198:1 and 114:1 for PFOS and PFOA, respectively:

$$PFOS: \quad 198\ \frac{mg}{L}(Serum\ Concentration) = \frac{0.016\left(\frac{L}{kg \cdot day}\right) \times 1\ \frac{mg}{L}(Water\ Concentration)}{0.000081\left(\frac{L}{kg \cdot day}\right)}$$

$$PFOA: 114\ \frac{mg}{L}(Serum\ Concentration) = \frac{0.016\left(\frac{L}{kg \cdot day}\right) \times 1\ \frac{mg}{L}(Water\ Concentration)}{0.00014\left(\frac{L}{kg \cdot day}\right)}$$

Increasing the lifetime water intake rate to the 95th percentile rate of 0.044 L/kg-d (USEPA, 2011) results in a steady-state serum to water concentration ratio of 543:1 and 314:1 for PFOS and PFOA, respectively, due to the increased daily exposure and absorbed dose:

$$PFOS: \quad 543\ \frac{mg}{L}(Serum\ Concentration) = \frac{0.044\left(\frac{L}{kg \cdot day}\right) \times 1\ \frac{mg}{L}(Water\ Concentration)}{0.000081\left(\frac{L}{kg \cdot day}\right)}$$

$$PFOA: 314\ \frac{mg}{L}(Serum\ Concentration) = \frac{0.044\left(\frac{L}{kg \cdot day}\right) \times 1\ \frac{mg}{L}(Water\ Concentration)}{0.00014\left(\frac{L}{kg \cdot day}\right)}$$

Very limited empirical data exist for comparison of the ratio between PFOS/PFOA water concentration and human serum concentration. The calculated average PFOA concentration in finished water in the city of Little Hocking, Ohio (3.55 µg/L, range 1.5 – 7.2) has been compared to measured serum levels (Emmett, 2006). Data from private well owners were also evaluated. Emmett's evaluation included only those residents who reported that their sole source of residential drinking water was the Little Hocking water system. It also excluded anyone with substantial occupational exposure. The median serum concentration to average drinking water concentration ratio for residents using only the Little Hocking water system (N=282) was 371 µg/L serum to 3.55 µg/L water, or 105, with an interquartile range between 62 and 162. For individuals who used a private well as their only source of residential drinking water, ratios varied from 142 to 855 (N=6).

In order to assess the impact of early life exposures, MDH created a single compartment, Excel-based TK model. The MDH model calculates a daily serum concentration in an infant born with an initial serum PFOS or PFOA concentration based on the mother's serum concentration at delivery. The model was used to examine the impact of an infant exclusively consuming breastmilk for one year, versus a formula-fed infant exclusively consuming contaminated water for one year. After this first year, both scenarios assumed a lifetime consumption of contaminated water. Daily intake, elimination, and serum concentration were calculated over a simulation period of 20,000 days.

Maternal serum concentration at delivery was calculated using Equation 3 above, a time-weighted (from birth to 30 years of age) 95th percentile water intake rate (0.044 L/kg-d), and the following chemical specific parameters:

- Half-life: PFOS 1,971 days and PFOA 840 days ,
- Volume of Distribution (V_d): PFOS 0.23 L/kg and PFOA 0.17 L/kg, and
- Clearance Rate (CR): PFOS 0.000081 L/kg-d and PFOA 0.00014 L/kg-d.

The infant's serum concentration at birth was calculated based on maternal serum concentrations and placental transfer:

Equation 4. Calculation of infant serum concentration at birth.

$$Serum\ Conc.\left(\frac{mg}{L}\right) = Maternal\ serum\ conc.\left(\frac{mg}{L}\right) \times placental\ transfer\ factor$$

For all subsequent days, the daily post-elimination serum concentration was calculated as:

Equation 5. Calculation of infant's daily serum concentration.

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

Due to the magnitude of the loss via lactation, the calculation of daily maternal serum concentrations incorporated the amount of chemical transferred to the infant as well as excretion represented by the clearance rate. The infant's daily intake (and thus the mother's loss) was calculated from the breastmilk intake rate and the breastmilk concentration:

Equation 6. Calculation of breastmilk concentration.

$$Breastmilk\ conc.\left(\frac{mg}{L}\right) = Maternal\ serum\ conc.\ \left(\frac{mg}{L}\right) \times breastmilk\ transfer\ factor$$

The various model input parameters and the values used are described in Section 2.1 below.

2.1 Model Inputs

2.1.1 Elimination (Half-life)

Centers for Disease Control (CDC) scientists found PFOS and PFOA in the serum of nearly all of the people tested, indicating widespread exposure in the U.S. population (CDC, 2017). It is important to consider background exposures because chemical half-lives can be overestimated if background exposures are not taken into account (Bartell, 2012). Accurately accounting for ongoing background exposures is very difficult and most studies estimating half-life have not taken it into account, resulting in potential overestimations.

Empirical data regarding the half-life of PFOS is limited to occupationally exposed workers (see Section 2.5.2 of (USEPA, 2016c). The arithmetic and geometric mean half-lives of PFOS in humans have been estimated to be 5.4

years (95% confidence interval (CI) 3.9-6.9 years) and 4.8 years (95% CI 4.0-5.8 years), respectively, based on occupational workers (Olsen, 2007). This population consisted of 26 individuals (24 male, 2 female) with a mean age of 61 years at the time of initial blood collection. Half-life information across different age groups, in particular infants, is not available. The half-life value of 5.4 years was used by USEPA (USEPA, 2016c) and by several researchers in developing TK models (Loccisano, 2011), (Verner, 2016)).

The decline of PFOS in infants was indirectly evaluated using newborn blood spots collected by New York State (Spliethoff, 2008). Blood spot cards from 11 different dates were selected from an archive spanning 1997 to 2007. Two hundred and forty individual infant blood spots were selected for each of the 11 dates, representing a total of 2,640 newborn infants. According to the authors, the temporal trends observed were consistent with a half-life of 4.4 years for PFOS. This value is reasonably close to the adult half-life estimate derived from occupational exposure studies. Due to the limitations of this blood spot analysis, MDH used the adult half-life estimates for the TK model throughout all life stages.

Unpublished data from the East Metro biomonitoring study, conducted by MDH, noted that decreasing serum concentrations over time were consistent with elimination rates of 6.3 years based on geometric mean serum concentration and 7.2 years based on individual results for PFOS ((Nelson, 2016) and (MDH, 2015)). This population consisted of 149 individuals (67 male, 82 female) and a mean age of 53 years. No data on half-life of PFOS in the general population were identified in the published literature. Background exposures from the East Metro study were not taken into account in these calculations.

There are several publications evaluating half-life of PFOA in human populations exposed either occupationally or via contaminated drinking water. The following half-life estimates were summarized by EPA and are presented below ((USEPA, 2016a)):

- 3.8 years (median 3.5, range 1.5 – 9.1) –based on decreasing serum concentrations in twenty-six retired 3M workers (Burris et al. 2000, 2002 aci (USEPA, 2016a)).
- 2.3 years - based on a series of serum concentrations from 200 adults taken over time after treatment of drinking water in West Virginia and Little Hocking, OH (Bartell et al. 2010). Covariates included the water treatment system, the time exposed before and after filtration, public versus bottled water, gender, age, consumption of local or homegrown vegetables, and exposure to the public water supply at work.
- 3.3 years (geometric mean, range 1.0 – 14.7) - based on differences in plasma concentrations from a population (n=66) in Arnsberg, Germany, that was exposed to a contaminated drinking water supply (Brede et al. 2010). Exposure was estimated from drinking water monitoring results and intake estimates based on questionnaires and interviews. The total population evaluated (2,008 subjects from the exposed area and 73 from a reference area) included children, as well as adults.
- 2.5 – 3.0 years (average 2.9) for former Little Hocking residents and 5.9 – 10.3 years (average 8.5) for former Lubeck, WV, residents [note initial levels in Lubeck residents were lower than Little Hocking residents] - based on a decline in serum levels in individuals who changed residential location (Seals et al. 2011). The authors identified three potential limitations of their analysis: the cross-sectional design, the assumption that exposure was uniform within a water district, and a potential bias introduced by the exclusion of individuals with serum values <15 ng/mL.

The decreasing serum concentrations of PFOA were also evaluated in infants based on newborn blood spots collected in New York State (Spliethoff, 2008). The temporal trends observed were consistent with a half-life of 4.1 years. This value is reasonably close (within a factor of 2) to the adult half-life estimates of 2.3 to 3.8 years. Due to the limitations of this blood spot analysis, MDH used the adult half-life estimate of 2.3 years for the TK model throughout all life stages.

Results from the East Metro biomonitoring study showed that decreasing serum concentrations over time were consistent with PFOA elimination rates of 3.2 years based on geometric mean serum concentrations and 3.4 years based on individual results (Nelson, 2016 and (MDH, 2015)). Background exposures were not taken into account in these calculations.

The elimination half-lives of PFOS and PFOA vary greatly among different species. Renal excretion is one of the routes of elimination. The underlying mechanism appears to involve glomerular filtration with active renal tubular secretion and reabsorption (Han, 2012). Biliary excretion also occurs but does not seem to be a major factor contributing to species differences. Serum albumin has been identified as the primary binding protein in the plasma. Species appear to have similar binding affinities and; therefore, it does not seem to play an important role in differentiating renal elimination among various mammalian species. Levels of albumin and total proteins are approximately 70 percent lower in young infants than in adults (Sethi, 2016), however, the potential impact of this difference on elimination is unknown at this time.

Humans appear to have the slowest PFOS and PFOA renal elimination rate and longest half-lives among the species studied thus far (Han, 2012). To date, renal organic anion transporter (OAT) proteins have been studied both indirectly and directly for their potential interactions with perfluorinated chemicals. Perfluorocarboxylates (PFCAs) have been studied to a greater extent than perfluorosulfonates (PFSAs). Among the confirmed PFCA renal uptake transporters, OAT1 and OAT3 reside in the basolateral membrane of the proximal tubular cells, and their PFCA uptake would facilitate PFCA renal tubular secretion. In contrast, due to their expression in the apical membrane of the proximal tubular cells, OAT4, and URAT1 would be the transporters involved in PFCA renal tubular reabsorption (Han, 2012). It appears that a key reason for the long PFCA plasma half-life in humans is the high percentage of renal tubular reabsorption (>99%).

Excretion of PFOS and PFOA also occurs through biliary excretion. Renal clearance of PFOA has been estimated to be roughly 90 percent of the total clearance in male rats, whereas it is estimated to be only 40 percent of the total clearance in male and female Japanese macaques. The significance of the biliary pathway compared to renal elimination in humans is not clear and could be significant. Increased fecal elimination of PFOS and PFOA in adult humans was demonstrated after administration of a bile acid sequestering agent (Genuis, 2013).

The serum half-lives estimated to-date likely represent both enterohepatic and renal processes, rather than renal processes alone. While limited insights have been gained regarding species differences in elimination mechanisms, an understanding of potential life-stage differences in humans continues to be an area of considerable uncertainty. In the absence of life-stage specific renal and biliary excretion information, and the lack of high quality estimates of PFOA and PFOS half-lives for infants, the MDH model uses the same half-life values across all life-stages.

A half-life value of 5.4 years (1,971 days) for PFOS was selected by MDH for use in our model. This is the same value utilized by Verner and colleagues (Verner, 2016) and by EPA in their assessments.

A half-life value of 2.3 years (840 days) for PFOA was selected by MDH for use in our model. This is the same value utilized by EPA in their assessments. Verner and colleagues (Verner, 2016) utilized the higher half-life value of 3.8 years.

2.1.2 Volume of Distribution

The volume of distribution (Vd, L/kg body weight) for PFOS and PFOA is believed to largely represent the body's extracellular fluid volume ((USEPA, 2016c) and (Han, 2012)). The values used for Vd by USEPA for PFOS and PFOA were 0.23 and 0.17 L/kg, respectively (USEPA, 2016c) and (USEPA, 2016a). These Vd values are used for long-term exposure and are most applicable to older children and adults. Identical or similar values were utilized

by Verner and colleagues (Verner, 2016) (0.23 and 0.17 for PFOS and PFOA, respectively) and Loccisano and colleagues (Loccisano, 2013) (0.22 and 0.17 for PFOS and PFOA, respectively).

MDH agrees with the Vd values of 0.23 and 0.17 L/kg for PFOS and PFOA, respectively, for older children and adults. Infants, however, have higher water content and should, therefore, have a higher Vd based on extracellular volume potential. The volume of extracellular fluid as a percent of body weight roughly plateaus around 3 years of age (Friis-Hansen, 1961). The MDH model includes an early-life stage Vd adjustment factor based on information from Table I of Friis-Hansen (1961) regarding the extracellular water as a percentage of body weight (BW). Age-specific Vd adjustment factors were calculated by MDH and are presented in the table below:

Table 1. Age-specific volume of distribution (V_d) adjustment factors.

Age	Extracellular Water as % of BW*	Calculated V_d Adjustment Factor**
0-1 day	44.5	44.5/18.7 = **2.4**
1-30 days	39.7	39.7/18.7 = **2.1**
1-3 months	32.2	32.2/18.7 = **1.7**
3-6 months	30.1	30.1/18.7 = **1.6**
6-12 months	27.4	27.4/18.7 = **1.5**
1-2 years	25.6	25.6/18.7 = **1.4**
2-3 years	26.7	26.7/18.7 = **1.4**
3-5 years	21.4	21.4/18.7 = **1.1**
5-10 years	22.0	22.0/18.7 = **1.2**
10-15 years	18.7	18.7/18.7 = **1**

*from Table I of Friis-Hansen, 1961.
** calculated by MDH

The above estimate for young infants (0 – 30 days of age) is consistent with newborns having a 2-fold higher extracellular water content than adults (Felter, 2015). To avoid abrupt changes within the model, the midpoint in time for each age group was set equal to the age-specific volume of distribution adjustment factor (Vd AF) value. The daily Vd AF between one midpoint and the next were calculated by linear interpolation. Overall, use of the Vd AF improved model results in comparison to empirical data (see section 2.2 and Tables 3 and 4).

2.1.3 Placental Transfer

Several studies measured maternal and cord serum levels of PFOS and PFOA near the time of delivery ((Cariou, 2015), (Kim, 2011), (Liu, 2011), (Fromme, 2010), (Monroy, 2008), (Midasch, 2007), and (Fei, 2007)), thereby permitting an estimation of placental transfer and initial body burden in the newborn infant. See Appendix I for more information.

The reported mean ratios of cord to maternal concentrations ranged from 0.31 (Fromme, 2010) to 0.60 (Midasch, 2007) for PFOS and from 0.69 (Kim, 2011) to 1.24 (Midasch, 2007) for PFOA. The average of the reported mean ratios from these studies were 0.42 and 0.87 for PFOS and PFOA, respectively. These values were used in the MDH TK model. The placental transfer values used by Loccisano and colleagues (Loccasino, 2012) and Verner and colleagues (Verner, 2016) were 0.46 and 0.45, respectively, for PFOS and 0.46 and 0.78, respectively, for PFOA.

2.1.4 Breastmilk Intake and Body Weight

Intake rates for exclusively breastfed infants, and data used to calculate corresponding body weights for the first year of life, were obtained from Table 15-1 of USEPA's 2011 Exposure Factors Handbook (EPA 2011).

Table 2. Human milk intake for exclusively breastfed infants and calculated corresponding body weights (BW).

Age Group	Mean			Upper Percentile**		
	mL/day	mL/kg-day	*Calculated BW (kg)**	mL/day	mL/kg-day	*Calculated BW (kg)**
< 1 month	510	150	*3.4*	950	220	*4.3*
1 to < 3 month	690	140	*4.9*	980	190	*5.2*
3 to < 6 months	770	110	*7.0*	1000	150	*6.7*
6 to < 12 months	620	83	*7.5*	1000	130	*7.7*

Mean and upper percentile intake rates taken from Table 15-1, USEPA 2011
*(mL/day) ÷ (mL/kg-day)
**Upper percentile is reported as mean plus 2 standard deviations.

Consistent with MDH's current methodology of using an RME scenario for deriving protective health-based guidance (MDH 2008), the upper percentile intake rates and corresponding body weights were selected for use in the TK model. Upper percentile breastmilk intake rates represent a compilation of measured or estimated values intended to approximate the 95th percentile by adding two standard deviations to the mean value (USEPA, 2011).

Within the model, the midpoint in time for each age group was set equal to the mean body weight value. The daily body weights between one midpoint and the next were calculated by linear interpolation. This approach avoids abrupt body weight changes and keeps the overall body weight time series close to the discrete values in the USEPA Exposure Factors Handbook. The body weight at birth was set at 3.38 kg, the mean birth weight for singleton births at 37 to 41 weeks of gestation in the year 2005, using data from the National Center for Health Statistics (Donahue, 2010). Body weights in the last age group were calculated by extending the sloped line from the center of the two previous groups (11 to <16 and 16 to <21) until it reached the 80 kg value for the 22 and older age group. Water intake rates were interpolated in a similar manner.

2.1.5 Breastmilk partitioning

Several studies measured maternal serum and breastmilk concentrations of PFOS and PFOA ((Cariou, 2015), (Kim, 2011), (Haug, 2011), (Liu, 2011), (Fromme, 2010), and (Karrman, 2007)), thereby permitting an estimate of partitioning from maternal serum into breastmilk and prediction of breastmilk concentrations. The reported mean ratios of breastmilk to maternal serum concentration range from 0.01 (Karrman, 2007) to 0.018 (Liu, 2011) for PFOS and from 0.026 (Kim, 2011) to 0.109 (Liu, 2011) for PFOA. The averages of the reported mean ratios from these studies were 0.013 and 0.052 for PFOS and PFOA, respectively. MDH selected the average of the mean values across studies (see Appendix I for more information) to calculate PFOS and PFOA breastmilk concentrations from corresponding maternal serum concentrations in our model. The breastmilk transfer values used by Loccisano and colleagues (Loccisano, 2013) and Verner and colleagues (Verner, 2016) were 0.0122 and 0.014, respectively, for PFOS and 0.038 and 0.058, respectively, for PFOA.

The maternal serum concentration at delivery was calculated as a steady-state concentration based on the proposed water guidance value using Equation 3 (see Section 2.0). Due to the magnitude of excretion via breastmilk, the calculation of daily maternal serum concentrations incorporated loss of chemical via transfer to the infant as well as ongoing maternal exposure via drinking water and excretion represented by the clearance rate:

Equation 7. Calculation of maternal daily serum concentration.

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

Pregnancy and lactation are significant maternal elimination routes for PFOS and PFOA that greatly impact maternal serum concentrations and breastmilk concentrations. According to Loccisano and colleagues, maternal serum concentrations at the end of a six month lactation period are approximately 14 and 40 percent lower for PFOS and PFOA, respectively, than during early pregnancy (Loccisano, 2013). The empirical data reported in several publications also document a decrease in maternal serum concentrations, in general confirming the greater loss of PFOA from maternal serum versus PFOS.

Maternal serum PFOS concentrations decreased by about nine percent after six months of breastfeeding relative to concentrations at delivery (mean during pregnancy and at delivery 3.5 µg/L and 3.2 µg/L at six months) (Fromme, 2010). For PFOA, maternal serum concentrations decreased by 11.5 percent at delivery (mean during pregnancy 2.6 µg/L and at delivery 2.3 µg/L) and decreased an additional 26 percent after six months of breastfeeding (mean at delivery 2.3 µg/L and 1.7 µg/L at six months). Overall, the total maternal PFOA serum concentrations decreased by about 38 percent from pregnancy through six months of lactation.

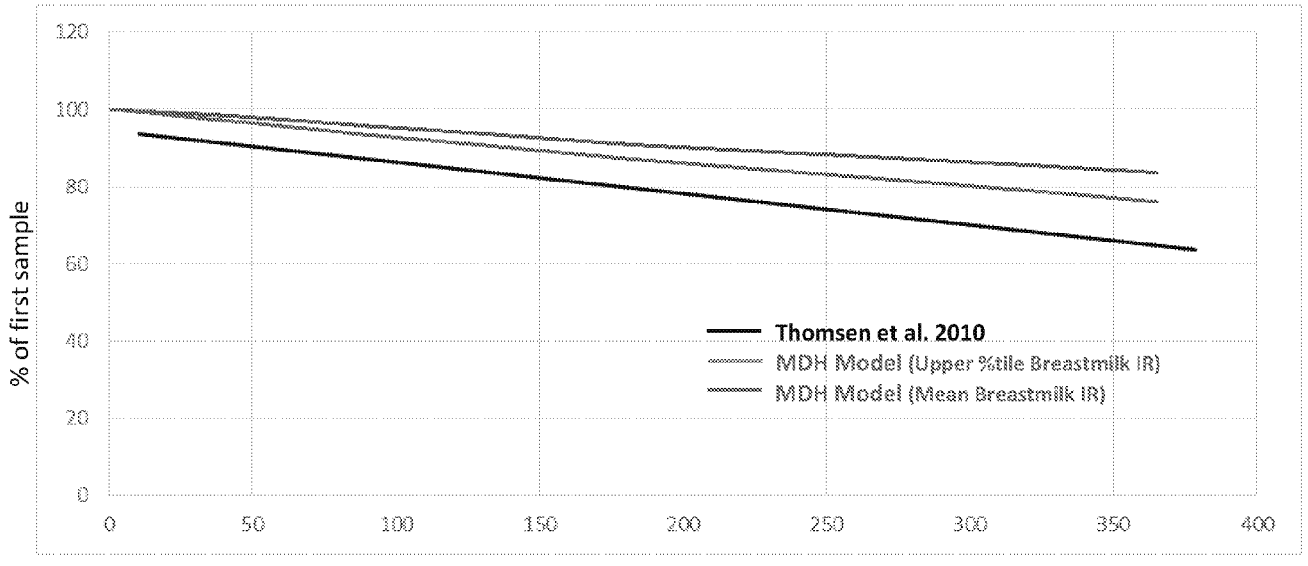
Decreases in maternal PFOS and PFOA serum concentrations have also been reported by others. Mondal and colleagues (Mondal, 2014) reported an average of three percent per month of breastfeeding, which would result in an 18 and 36 percent decrease over six and twelve months, respectively. When upper percentile infant breastmilk intake rates (see Table 2) were incorporated into the MDH model, maternal PFOS serum concentration decreased by 12 percent after six months of breastfeeding and 24 percent after one year of breastfeeding. Adjustment of the model to use mean infant breastmilk intake rates (see Table 2) resulted in smaller decreases in maternal PFOS serum concentration (9 and 17 percent after six and twelve months, respectively).

Incorporation of upper percentile infant breastmilk intake rates (see Table 2) in the MDH model for PFOA produced a 48 percent decrease in maternal serum concentration after six months of breastfeeding and a 73 percent decrease after one year. When the model was adjusted to consider mean infant breastmilk intake rates (see Table 2), smaller decreases in maternal PFOA serum concentration were observed (40 and 61 percent after six and twelve months, respectively).

Thomsen and colleagues specifically studied the impact of breastfeeding on PFOS and PFOA breastmilk concentrations in ten Norwegian mothers (Thomsen, 2010). Breastmilk samples were collected monthly from about two weeks up to twelve months after birth. Depuration rates of PFOS and PFOA were estimated to be 3.8 and 7.8 percent per month of breastfeeding. MDH used WebPlotDigitizer (WebPlotDigitizer, 2017) to approximate the data in Figure 2 from the paper by Thomsen and colleagues (Thomsen et al., 2010). WebPlotDigitizer is a web-based tool used to extract data from plots, images, and maps. The approximated data

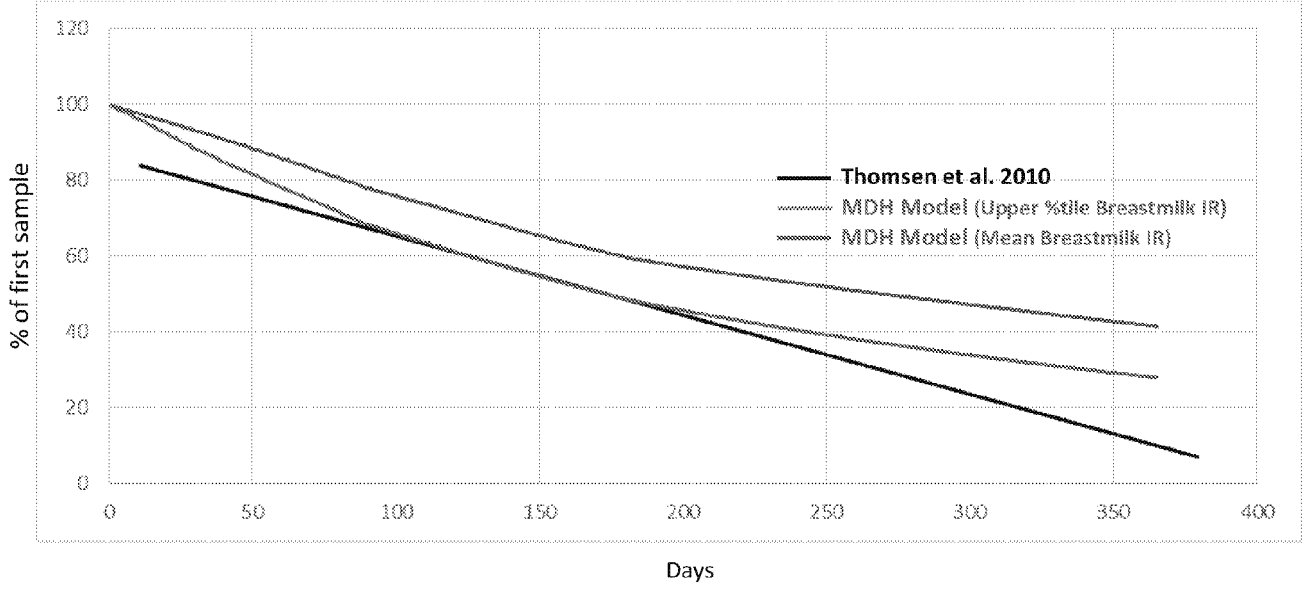
was then compared to the depuration rates predicted by the MDH model (see Figures 2 and 3 below). The MDH model predictions closely resembled the empirical data.

Figure 2. Relative concentration comparisons of PFOS in breastmilk, Thomsen, 2010 and MDH TK model results.*



**normalized to concentration in first sample*

Figure 3. Relative concentration comparison of PFOA in breastmilk, Thomsen, 2010 and MDH TK model results.*



**normalized to concentration in first sample*

2.2 Preliminary Evaluation of Model

MDH used available empirical data, as well as results, from other models of PFOS and PFOA ((Fromme, 2010), (Mogensen, 2015)) during chronic and early life exposure conditions to ascertain whether the simple, one-compartment MDH model produces appropriate results. For each model comparison, the mother's serum concentration at delivery was assumed to be at steady-state and her ongoing exposure (estimated from the published maternal serum concentration) during the lactation period was included in the MDH model. MDH also made special requests for data in some cases, but not all data were available for use, including individual maternal:child paired data.

2.2.1 Comparison with empirical data from Fromme and colleagues (2010)

Fromme and colleagues investigated maternal and infant body burdens of PFOS and PFOA during the six months following birth. There were 50 participants, the majority of which exclusively breastfed their infants (37 infants were exclusively breastfed, 6 predominantly breastfed, 6 partially breastfed, and 1 infant received no breastmilk). Blood concentrations were collected from 38 – 47 mothers during pregnancy, at delivery, and at six months post-delivery. Median and 95th percentile breastmilk concentrations were reported for 44 mothers.

The MDH model was evaluated by inserting the mean or 95th percentile maternal serum concentration at delivery and allowing the model to predict the infant serum concentration at delivery and at 6 months. The MDH model incorporated either the mean or the upper percentile breastmilk intake rates and corresponding body weights for exclusively breastfed infants (Table 2).

Blood concentrations were reported for 33 fetal cord samples, 40 infants at six months after birth, and 24 infants at 19 months after birth. The mean and 95th percentile maternal and infant blood concentrations at six months of age reported by Fromme and colleagues (Fromme, 2010) and those predicted by the MDH model are summarized below for PFOS (Table 3, Figure 4).

Table 3. Results of comparing MDH-modeled PFOS infant serum concentrations to Fromme et al. (2010) data.

Concentration	Fromme et al. 2010	MDH TK Model*		Ratio of Model to Measured	
Maternal – serum					
At birth Mean	3.5 µg/L	3.5 µg/L			
95th Percentile	6.1 µg/L	6.1 µg/L			
		(set to measured value)			
At 6 months Mean	3.2 µg/L	2.9 µg/L[a]		0.91[a]	
95th Percentile	6.3 µg/L	4.9 µg/L[b]		0.78[b]	
Breastmilk					
At 6 months Median	0.04 µg/L (median)	0.038 µg/L[#a]		0.95	
95th Percentile	0.08 µg/L	0.064 µg/L[#b]		0.80	
Infant – serum					
At birth Mean	1.1 µg/L	1.47 µg/L[#]		1.34	
95th Percentile	2.2 µg/L	2.56 µg/L[#]		1.2	
		With Vd AF	*Without Vd AF*	*With Vd AF*	*Without Vd AF*
At 6 months Mean	3.3 µg/L	3.7 µg/L[a]	5.45 µg/L[a]	1.12[a]	1.65[a]
95th Percentile	8.1 µg/L	7.9 µg/L[b]	11.3 µg/L[b]	0.98[b]	1.4[b]
Infant:Maternal serum Ratio @6 months		*With Vd AF*	*Without Vd AF*		
Mean	1.03	1.3[a]	1.9[a]		
95th Percentile	1.29	1.6[b]	2.3[b]		

**MDH model included maternal loss via breastmilk as well as ongoing exposure during lactation. Ongoing exposure was estimated by back calculating a dose based on maternal serum concentration at time of delivery.*

#Breastmilk concentration and infant serum concentration calculated by multiplying the maternal serum concentration by the breastmilk transfer factor and placental transfer factor, respectively.
[a]Model utilized mean breastmilk intake rate for infant (see Table 2).
[b]Model utilized upper percentile breastmilk intake rate for infant (see Table 2).

PFOS concentrations were obtained for 14 individual infants from cord blood and at age 6 months (Fromme et al. 2010, Figure S5). Study data collected at 19 months after birth was not used because breastfeeding had ceased and ongoing exposures were uncertain. MDH used WebPlotDigitizer to create an approximation of the data presented in Figure S5 and compared the approximated results to the MDH model based on upper percentile intake rates (UPIR) and mean breastmilk intake rates (MIR), and with and without the incorporation of a Vd AF. Results are presented in Figure 4.

Figure 4. Infant PFOS serum concentrations predicted for exclusively breastfed infants by MDH's model vs. estimated individual data points from Figure S5, Fromme et al. (2010).

** UPIR - upper percentile breastmilk intake rates (see Table 2), with and without incorporating a Vd AF.*
*** MIR – mean breastmilk intake rates (see Table 2), with and without incorporating a Vd AF.*
Data points are individual serum measurements estimated from Fromme et al, 2010 at birth and 6 months.

MDH also evaluated its model outputs for PFOA by comparing them to data presented in Fromme, 2010. Blood concentrations of PFOA were reported for 33 fetal cord samples, 40 infants at six months after birth, and 24 infants at 19 months after birth. The mean and 95th percentile maternal and infant blood concentrations at six months of age reported by Fromme and colleagues (Fromme, 2010), and those predicted by the MDH model, are summarized below for PFOA (Table 4, Figure 5).

Table 4. Results of comparing MDH-modeled PFOA infant serum concentrations to Fromme et al. (2010) data.

Concentration	Fromme et al. 2010	MDH TK Model*	Ratio of Model to Measured
Maternal –			
At birth Mean	2.3 µg/L	2.3 µg/L	
95th Percentile	5.2 µg/L	5.2 µg/L *(set to measured value)*	
At 6 months Mean	1.7 µg/L	1.1 µg/L[a]	0.65[a]
95th Percentile	3.9 µg/L	1.9 µg/L[b]	0.49[b]
Breastmilk		*@6 months*	*@6 months*
At 6 months Mean	NA (only detected in 2% of samples)	0.057 µg/L[#a]	--
95th Percentile	0.25 µg/L	0.10 µg/L[#b]	0.40[b]

Concentration	Fromme et al. 2010	MDH TK Model*		Ratio of Model to Measured	
Infant –					
At birth Mean	1.7 µg/L	2.0 µg/L[#]		1.2	
95th Percentile	3.7 µg/L	4.5 µg/L[#]		1.2	
		With Vd AF	*Without Vd AF*	*With Vd AF*	*Without Vd AF*
At 6 months Mean	8.0 µg/L	7.9 µg/L[a]	12.7 µg/L[a]	0.99[a]	1.6[a]
95th Percentile	19.5 µg/L	21.2 µg/L[b]	33.1 µg/L[b]	1.1[b]	1.7[b]
Infant:Maternal serum Ratio @6 months		*With Vd AF*	*Without Vd AF*		
Mean	4.7	7.2[a]	11.5[a]		
95th Percentile	5.0	11.2[b]	17.4[b]		

**MDH model included maternal loss via breastmilk as well as ongoing exposure during lactation (using back calculated dose based on maternal serum concentration at time of delivery).*

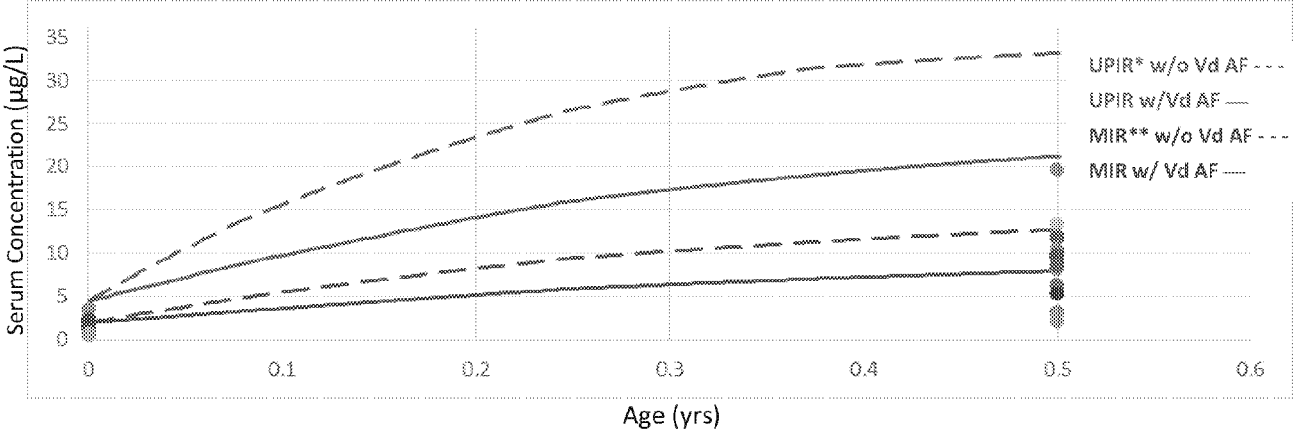
[#]Breastmilk concentration and infant serum concentration calculated by multiplying the maternal serum concentration by the breastmilk transfer factor and placental transfer factor, respectively.

[a]Model utilized mean breastmilk intake rate for infant (see Table 2).

[b]Model utilized upper percentile intake rate for infant (see Table 2).

PFOA concentrations were obtained from the cord blood of 14 individual infants at birth and from blood samples at age 6 months (Fromme et al. 2010, Figure S6). MDH used WebPlotDigitizer to create an approximation of the data and compared the approximated results to the MDH model results based on upper percentile breastmilk intake rates with (solid line) and without (dotted line) inclusion of the Vd AF.

Figure 5. Infant PFOA serum concentrations for exclusively breastfed infants predicted by MDH's model vs. estimated individual data points from Figure S6, Fromme et al. (2010).



** UPIR - upper percentile breastmilk intake rates (see Table 2), with and without incorporating a Vd AF.*

*** MIR – mean breastmilk intake rates (see Table 2), with and without incorporating a Vd AF.*

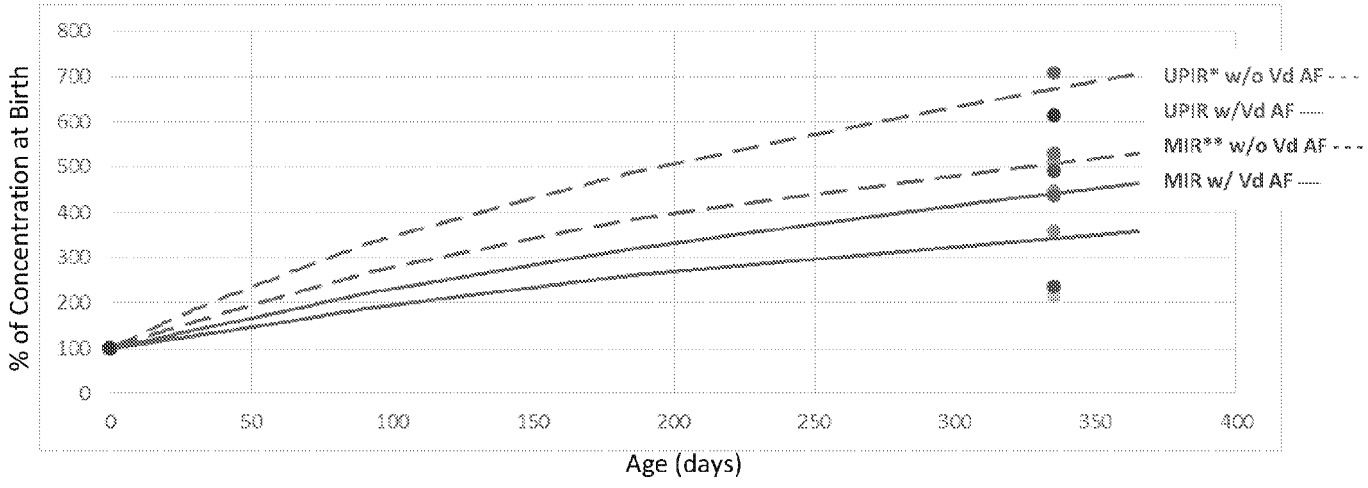
Data points are individual serum measurements estimated from Fromme et al, 2010 at birth and 6 months.

2.2.2 Comparison with empirical data from Mogensen and colleagues (2015)

Estimated or measured serum concentrations of PFOS and PFOA were examined in a Faroese birth cohort at delivery and at ages 11, 18, and 60 months to determine the impact of breastfeeding (Mogensen, 2015). The authors estimated serum concentrations at birth from maternal serum concentrations using factors of 0.72 and 0.34 for PFOS and PFOA, respectively, based on ratios between cord and maternal pregnancy serum concentrations previously estimated for the same cohort. Children were breastfed exclusively for a median duration of 4.5 months, followed by partial breastfeeding with supplementary baby food for a median of 4

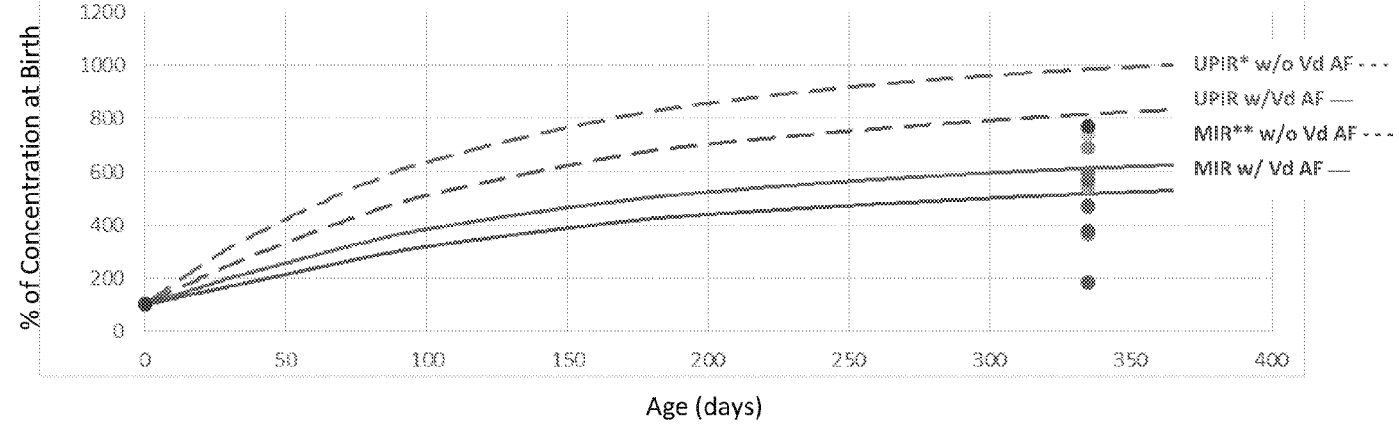
months. MDH used WebPlotDigitizer to estimate serum concentrations for PFOS and PFOA at birth and at 11 months of age from trajectories presented in Figure 1 of Mogensen et al. 2015. The relative magnitude change in serum concentrations from birth to 11 months of age for the eleven children who were at least partially breastfed was compared to the magnitude in relative change predicted by the MDH model (exclusive breast feeding). The comparisons for PFOS and PFOA are presented below in Figures 6 and 7, respectively.

Figure 6. Relative increase in infant PFOS serum concentration at 11 months of age normalized to concentration at birth - MDH model results for exclusively breastfed infant vs. estimated individual data points from Figure 1, Mogensen et al. (2015).



** UPIR - upper percentile breastmilk intake rates (see Table 2), with and without incorporating a Vd AF.*
*** MIR – mean breastmilk intake rates (see Table 2), with and without incorporating a Vd AF.*
Data points are individual serum measurements estimated from Mogensen et al, 2015 at 11 months, relative to concentration at birth

Figure 7. Relative increase in infant PFOA serum concentration at 11 months of age normalized to concentration at birth - MDH model results for exclusively breastfed infant vs. estimated individual data points from Figure 1, Mogensen et al. (2015).



** UPIR - upper percentile breastmilk intake rates (see Table 2), with and without incorporating a Vd AF.*
*** MIR – mean breastmilk intake rates (see Table 2), with and without incorporating a Vd AF.*
Data points are individual serum measurements estimated from Mogensen et al, 2015 at 11 months, relative to concentration at birth

2.2.3 Comparison with modeling results from Verner

Dr. Marc Verner, of the University of Montréal, developed a draft Excel-based model to estimate serum concentrations for nursing infants up to 3 years of age and generously provided a draft copy of this model to MDH. The Verner model includes Monte Carlo simulations and requires only three inputs: 1) number of iterations, 2) compound selection (PFOS, PFOA, or PFHxS), and 3) maternal dose (µg/kg-day). MDH conducted an additional evaluation, which compared the results from the MDH model with results produced by the Verner model.

It should be noted that the Verner model used different input values for several parameters:

- Half-lives used within the Verner model are the same as the MDH model for PFOS but differ for PFOA (Verner used 3.8 years whereas MDH used 2.3 years). Rather than attempting to change the Verner model to MDH's selected half-life of 2.3 years, the MDH model was modified to incorporate a half-life for PFOA of 3.8 years for comparison purposes.
- The breastmilk intake rates used by Verner and colleagues (Verner, 2016) for the first 12 months were calculated (Intake (g/kg-d) = −0.312 × age (days) + 157.7) and are similar in magnitude to the mean breastmilk intake rates for exclusively breastfed infants presented in Table 2 above. MDH selected upper percentile intakes to represent a reasonable maximum exposure scenario.
- MDH's model uses an age-specific adjustment factor for volume of distribution (Vd AF) whereas the Verner model does not. MDH's model was run with and without the Vd AF for comparison purposes. (See Section 2.1.2 for more information regarding the basis of the Vd AF).

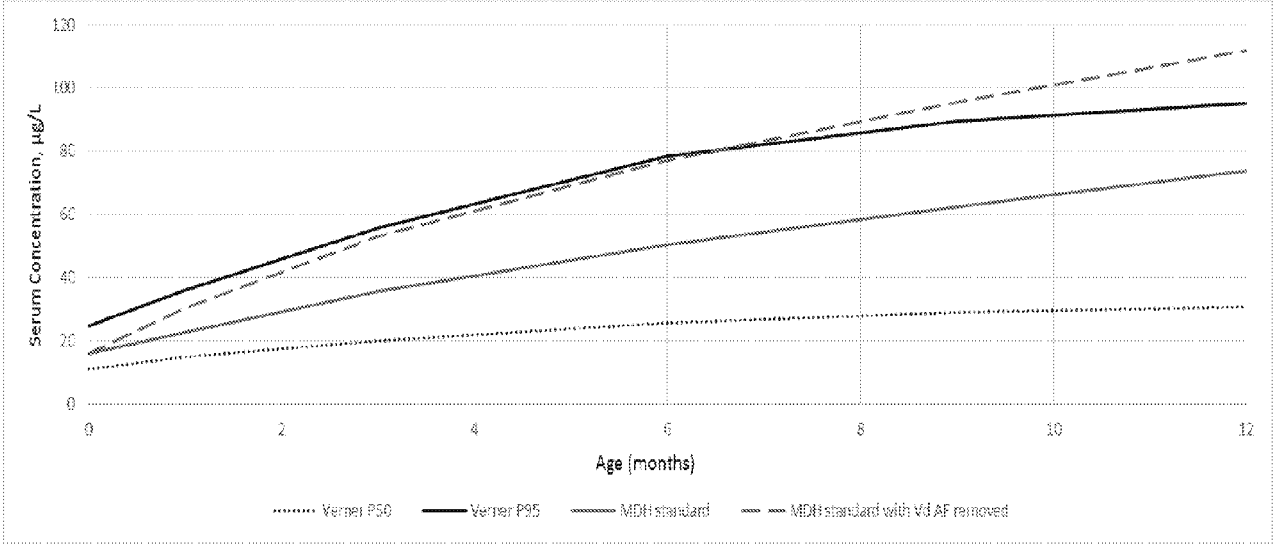
MDH conducted separate model runs for PFOS and PFOA using the draft Verner model with 1,000 iterations and a maternal dose of 0.00308 µg/kg-day. The maternal dose was based on a water concentration of 0.07 µg/L (the 2016 USEPA Health Advisory value) and a 95th percentile water intake rate of 0.044 L/kg-d. These same inputs for water concentration and adult water intake rates were used in model runs based on the MDH model.

The MDH model was run for an infant exclusively breastfed for one year, the duration for which the USEPA Exposure Factors Handbook provides breastmilk intake rates and body weights for exclusively breastfed infants. The results of the model runs and a comparison of resulting infant serum concentrations at birth, 1 month, 3 month, 6 month, 9 month, and 12 month time-points are presented below in Table 5/Figure 8 (PFOS) and Table 6/Figure 9 (PFOA).

Table 5. Comparison of MDH PFOS model results for exclusively breastfed infant (using upper percentile intake rates) vs. Verner model results.

Model	Predicted Serum Concentration (µg/L)					
	Birth	**1 Mon**	**3 Mon**	**6 Mon**	**9 Mon**	**12 Mon**
Verner 50th & 95th percentile	11.0 24.5	14.8 35.9	20.0 55.8	25.6 78.3	29.1 89.3	30.5 95.1
MDH model *(ratio vs. Verner 95th %tile)*	16.0 *(0.65)*	22.6 *(0.63)*	35.5 *(0.64)*	50.5 *(0.64)*	62.5 *(0.70)*	73.6 *(0.77)*
MDH model with Vd AF removed *(ratio vs. Verner 95th %tile)*	16.0 *(0.65)*	30.2 *(0.84)*	53.0 *(0.95)*	77.1 *(0.98)*	95.5 *(1.1)*	111.9 *(1.2)*

Figure 8. Comparison of MDH PFOS model results for 1-yr exclusively breastfed infant (using upper percentile intake rates) vs. Verner model results.



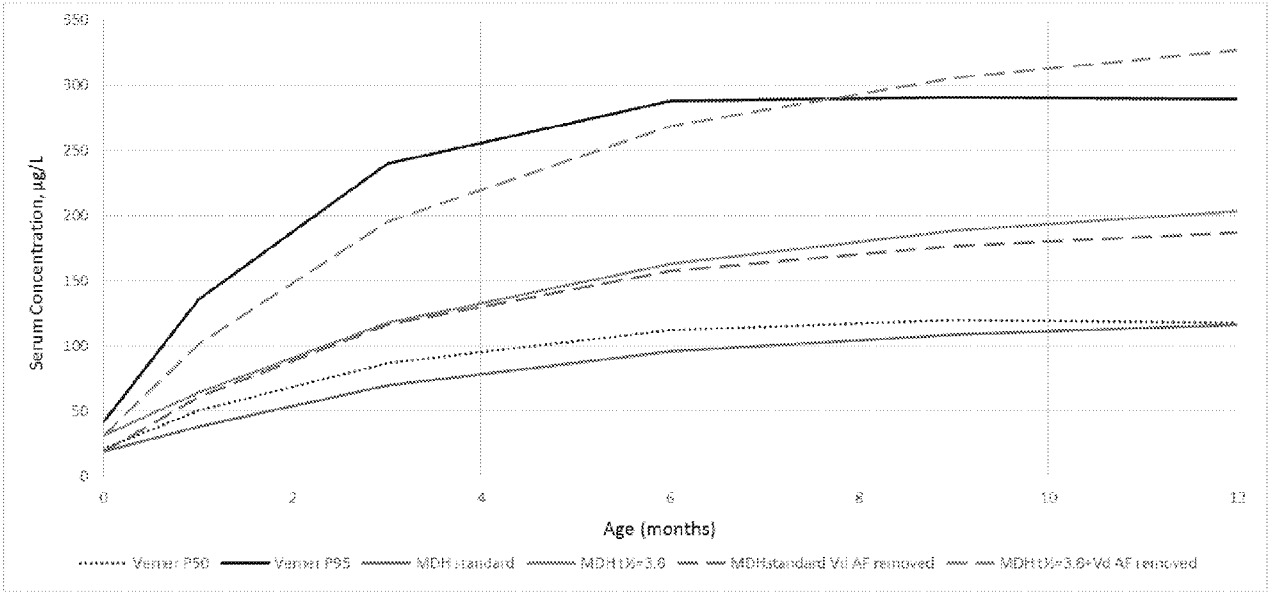
The serum concentrations estimated by the MDH model at the early time-points were between the 50th and 95th percentile values generated by the Verner model. Both models used similar half-life values for PFOS. However, there were differences in several other parameters used within each model. For example, MDH used higher breastmilk intake rates and applied age-specific Vd AFs, whereas the Verner model used breastmilk intake rates that were similar to mean intake rates and did not apply a Vd AF.

MDH performed a similar comparison to the Verner model for PFOA, shown below in Table 6 and Figure 9.

Table 6. Comparison of MDH PFOA model results for exclusively breastfed infant (using upper percentile intake rates) vs. Verner model results.

Model	Predicted Serum Concentration (µg/L)					
	Birth	**1 Mon**	**3 Mon**	**6 Mon**	**9 Mon**	**12 Mon**
Verner 50th & 95th percentile	21.4 42.0	50.6 135.6	87.1 239.9	112.1 288.0	119.7 290.6	117.6 289.6
MDH model [2.3 yr $t_{1/2}$] *(vs. Verner 95th %tile)*	19.1 *(0.45)*	38.7 *(0.29)*	71.9 *(0.30)*	100.3 *(0.35)*	114.1 *(0.39)*	121.1 *(0.42)*
MDH model with 3.8 yr $t_{1/2}$ *(vs. Verner 95th %tile)*	31.5 *(0.75)*	64.4 *(0.47)*	120.9 *(0.50)*	171.1 *(0.59)*	197.4 *(0.68)*	212.2 *(0.73)*
MDH model with Vd AF removed *(vs. Verner 95th %tile)*	19.1 *(0.45)*	61.3 *(0.45)*	119.7 *(0.50)*	164.9 *(0.57)*	185.2 *(0.64)*	194.4 *(0.67)*
MDH model with 3.8 yr half-life + Vd AF removed *(vs. Verner 95th %tile)*	31.5 *(0.75)*	101.8 *(0.75)*	201.0 *(0.84)*	281.4 *(0.98)*	320.9 *(1.1)*	341.5 *(1.18)*

Figure 9. Comparison of MDH PFOA model results for 1-yr exclusively breastfed infant (using upper percentile intake rates) vs. Verner model results.



MDH and Verner models used different half-life values for PFOA (MDH used 2.3 years whereas Verner used 3.8 years). When the MDH model was run using a half-life of 3.8 years, the predicted serum concentrations fell between Verner's 50th and 95th percentile estimates. When the Vd AF parameter was removed from the MDH model, the predicted PFOA serum concentrations for later time points exceeded the 95th percentile values predicted by the Verner model.

Comparisons between empirical data as well as modeling results from Verner and MDH model results were within a factor of 2 for all time points when comparable half-life values were utilized.

2.3 Expansion of Model to Steady-State Duration

Due to the long half-lives of PFOS and PFOA, early life exposures will take many years to be eliminated from the body. After encouraging results were obtained from initial testing of the model, the modeling duration was extended to long-term exposure. MDH sought input from six external experts regarding the adequacy (e.g., fit for purpose) of the model and how to enhance accuracy of serum predictions. Each reviewer submitted preliminary comments regarding the draft model and participated in a web-based meeting discussion. MDH responded to comments and made improvements to the model based on reviewer input. Reviewers were not explicitly asked to endorse or approve of the final model. See Appendix II for biographical information on each of the reviewers.

The expanded model was designed to predict serum concentration profiles for two exposure scenarios: 1) an infant fed exclusively with formula reconstituted with contaminated water starting at birth, followed by a lifetime of drinking contaminated water (Figure 10); and 2) an infant exclusively breastfed for 12 months, followed by a lifetime of drinking contaminated water (Figure 11). In both scenarios, the simulated individuals began life with a pre-existing body burden through placental transfer. Upper percentile intake rates were used for the breastfed infant scenario and 95th percentile intake rates were used for water intake to simulate an RME individual.

Figure 10. Scenario #1 schematic - Exclusively Formula-Fed Infant.

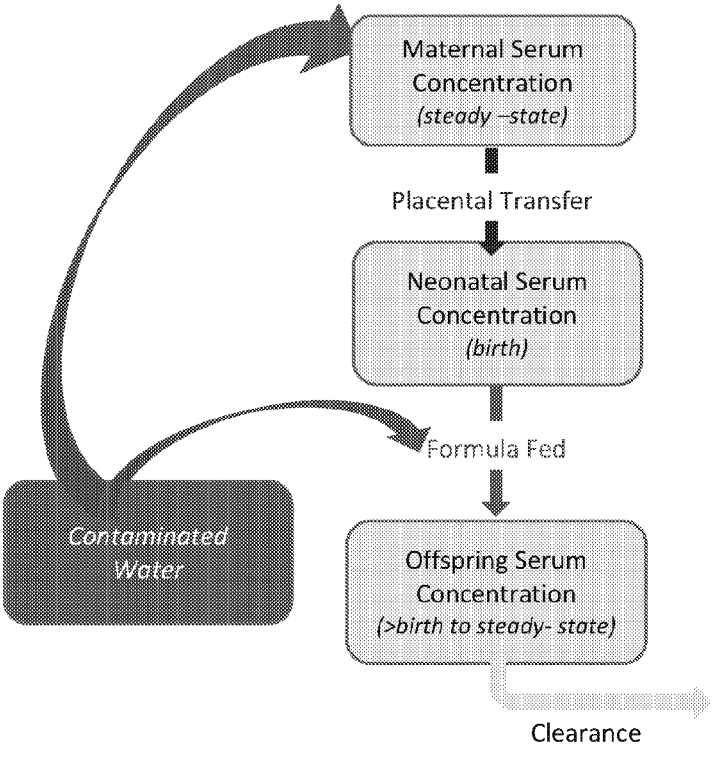
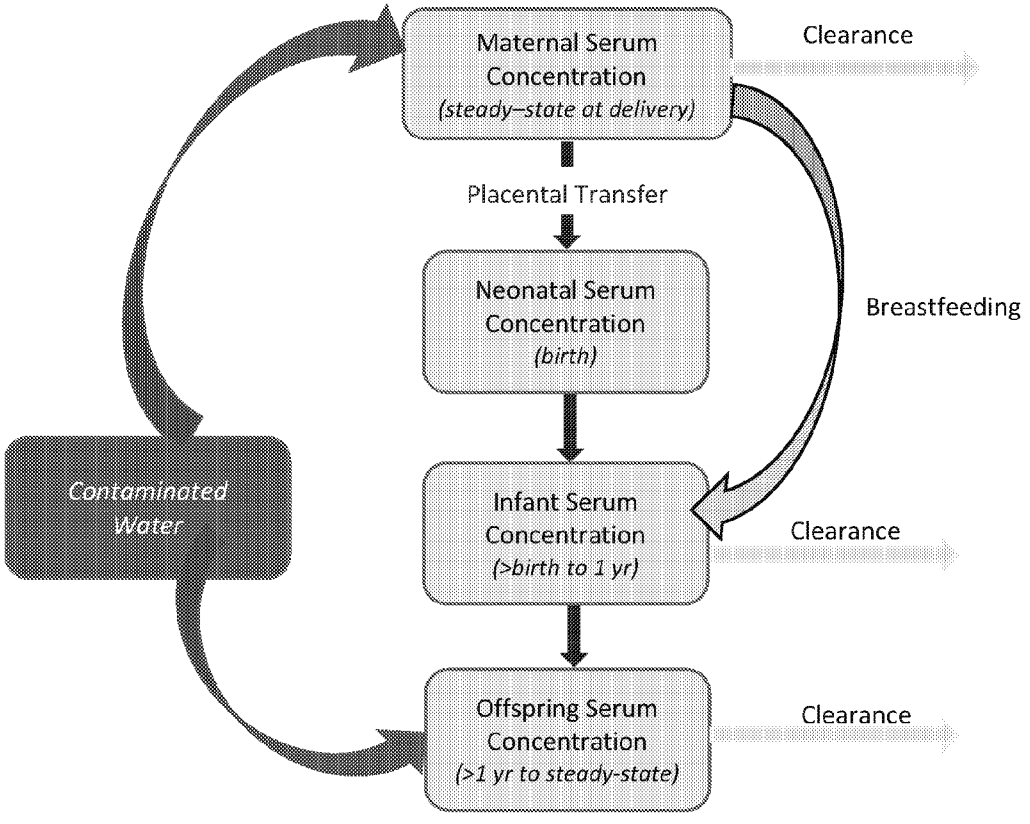


Figure 11. Scenario #2 schematic - Exclusively Breastfed Infant.



As noted above, infants born to exposed mothers will be born with an existing body burden resulting from maternal exposures only. Placental transfer factors of 0.42 and 0.87 were used for PFOS and PFOA, respectively, to calculate the initial infant serum concentration from the maternal serum concentration (see Section 2.1.3.) The maternal serum concentrations were assumed to be at steady-state and Equation 3 (repeated below, see Section 2.0 for additional information) was used to calculate the steady-state serum concentration.

$$Serum\ Concentration\left(\frac{mg}{L}\right) = \frac{Water\ Intake\ Rate\left(\frac{L}{kg \cdot day}\right) \times Water\ Concentration\left(\frac{\mu g}{L}\right)\ x\ \frac{1\ mg}{1000\ \mu g}}{Clearance\ Rate\left(\frac{L}{kg \cdot day}\right)}$$

Clearance rates of 0.000081 and 0.00014 L/kg-d for PFOS and PFOA, respectively (see Section 2.0), were applied to the equation above. A time-weighted average (95th percentile) water intake rate of 0.047 L/kg-d, calculated from birth to 30-35 years of age, was used as the water intake rate. An iterative approach was engaged to identify the water concentration that would result in maternal and offspring serum concentrations that would never exceed a level of concern identified by MDH. See Section 3 below for results.

The input values for breastmilk partitioning, breastmilk intake rate, body weight, elimination (half-life), and volume of distribution (Vd) were the same as those presented above in Section 2.2. A complete summary of model parameters is provided below in Table 8.

2.3.1 Additional Model Inputs

2.3.1.1 Duration of Breastfeeding

Breastfeeding has many clearly established health benefits for infants, children, and mothers and is a key strategy to improve public health. The American Academy of Pediatrics (AAP) recommends that infants be exclusively breastfed for about the first 6 months with continued breastfeeding alongside introduction of complementary foods for at least 1 year. 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 RME scenario. Upper percentile breastmilk intake rates from Table 15-1 of the USEPA 2011 Exposure Factors Handbook (see Table 2 in Section 2.1.4 above) were used from birth up to 12 months of age. At 12 months of age, fluid intake was switched from breastmilk to water, and an age-specific water intake at the 95th percentile (see Table 7 below) was used through the rest of life.

2.3.1.2 Water Intake Rate

Newborns derive all, or nearly all, of their nutrition from liquids. Liquid intake rates per unit body weight fall rapidly with age, and by age seven are nearly the same as those of adults. MDH methodology (Minnesota Department of Health (MDH), 2008) for deriving health-based water guidance uses age specific 95th percentile water intake rates, which are found in Table 3-1 of USEPA's 2011 Exposure Factors Handbook (EPA 2011) and are replicated in Table 7 below. These water intake rates were used 1) for infants exclusively formula-fed and 2) for breastfed infants following one year of exclusive breastfeeding. The information in EPA's Table 3-1 also provides data that allows for calculation of corresponding body weights for the corresponding age group.

Table 7. Drinking water ingestion rates for consumers-only and calculated corresponding body weights (BW).

Age Group	Mean			95th Percentile		
	mL/day	mL/kg-day	*Calculated BW (kg)**	mL/day	mL/kg-day	*Calculated BW (kg)**
< 1 month	470	137	*3.4*	858	238	*3.6*
1 to < 3 month	552	119	*4.6*	1053	285	*3.7*
3 to < 6 months	556	80	*7.0*	1171	173	*6.8*
6 to < 12 months	467	53	*8.8*	1147	129	*8.9*
1 to < 2 years	308	27	*11.4*	893	75	*11.9*
2 to < 3 years	356	26	*13.7*	912	62	*14.7*
3 to < 6 years	382	21	*18.2*	999	52	*19.2*
6 to < 11 years	511	17	*30.1*	1404	47	*29.9*
11 to < 16 years	637	12	*53.1*	1976	35	*56.5*
16 to < 18 years	702	10	*70.2*	1883	30	*62.8*
18 to < 21 years	816	11	*74.2*	2818	36	*78.3*
≥ 21 years	1227	16	*76.7*	3092	42	*73.6*

Mean and 95th percentile intake rates taken from Table 3-1, USEPA 2011
*(mL/day) ÷ (mL/kg-day)

2.4 Summary of MDH Model Parameters

Serum concentrations are the best metric for determining internal doses for PFOA and PFOS and served as the basis of the RfD. An RfD is an estimate of a daily oral dose to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects. It is important that total

exposure from all sources, including potential ingestion of drinking water containing PFOS or PFOA, does not result in serum concentrations higher than the serum concentration associated with the RfD. The TK model developed by MDH predicts serum concentrations at various developmental stages over a person's lifetime resulting from a constant PFOA or PFOS concentration in drinking water, including the serum concentration an individual is born with as a result of maternal exposure.

In order to ensure that health-based water guidance values for PFOS and PFOA are adequately protective for all life stages, including more highly exposed infants, two RME scenarios were evaluated: 1) an infant fed exclusively with formula reconstituted with contaminated water starting at birth, followed by a lifetime of drinking contaminated water; and 2) an infant exclusively breastfed for 12 months, followed by a lifetime of drinking contaminated water. Both scenarios began life with a pre-existing body burden through placental transfer. In order to achieve an RME scenario, a mixture of central and upper percentile values for the various parameters are used, as described in Table 8 below.

MDH carefully selected model parameters, based on the best available science, external peer review comments, and departmental policy. A formal in-depth sensitivity analysis of the model, which would provide additional information regarding model performance, has not been conducted at this time. Based on the performance of the model, MDH notes that water concentration, duration of breastfeeding, and breastmilk intake rates are the most sensitive parameters.

Verner and colleagues (2016) conducted a global sensitivity analysis of the Verner model and found that duration of breastfeeding, breastmilk intake rates, and maternal serum/breastmilk partitioning were among the most sensitive parameters.

Table 8. Summary of MDH model input parameters

Model Parameter	Value(s) Used	Source	Value Type/ Description	Confidence/Uncertainty Comment
Half-life (t½)	PFOS 5.4 years (1,971 days) PFOA 2.3 Years (840 days)	Olsen et al. 2007 based on occupational workers Bartell et al. 2010 based on population exposed via drinking water	Central (mean value)	Same half-life values used by USEPA in their evaluations. Very limited data for PFOS. Several publications regarding PFOA, with average half-life ranging from 2.3 to 3.8 years. Lack of accounting for background exposures can over estimate half-life. In the absence of life-stage specific information, the same half-life was used across all life stages. This remains an area of uncertainty.
Volume of Distribution (Vd)	PFOS 0.23 L/kg PFOA 0.17 L/kg	USEPA 2016, Hans et al. 2012	Central (mean value)	Same Vd used by Loccisano et al. 2013, Verner et al. 2016, and USEPA 2016. Consistent with extracellular fluid as volume of distribution.
Vd Age Adjustment Factor (Vd AF)	0-1 day – 2.4 1 – 30 days – 2.1 1 – 3 mons – 1.7 3-6 mons – 1.6 6-12 mons – 1.5 1 – 3 yrs – 1.4 3-5 yrs – 1.1 5-10 yrs – 1.2 >10 yrs - 1.0	Friis-Hansen 1961 (also consistent with Felter et al. 2015)	Central (mean value)	Early life stages are known to have higher body water content per unit weight than adults. The adjustment factor is designed to account for this known difference between infants and adults, in the context of PFOS and PFOA kinetic determinations for Vd. This is an area of uncertainty since the precise nature of the Vd is not known. However, removal of the Vd AF appears to result in overestimation of serum concentrations when compared to empirical data.
Clearance Rate (CR)	Calculated *CR = Vd (L/kg) × (Ln2/half-life, days)* PFOS 0.00008 L/kg-d PFOA 0.00014 L/kg-d	Calculated value. Same value calculated and used by USEPA 2016	Central (based on mean half-life)	Based on half-life information. In the absence of life-stage specific information the same half-life was used across all life stages. This remains an area of uncertainty.
Maternal Serum Concentration	Calculated steady-state serum level (µg/L)	Calculated (see Equation 3)	Upper	Assumes mother is at steady-state at time of delivery based on proposed water guidance level. Maternal exposure based on 95th percentile water ingestion rate.
Newborn Serum Concentration	Calculated *Maternal serum concentration (µg/L) × Placental Transfer Factor*	MDH calculated value. Transfer Factor based on average of reported mean maternal serum	Elements of Central and Upper (based on mean transfer	Limited individual matching maternal serum to cord blood matching pair data are available. Mean, median and upper percentile ratios are within a factor of 2. See Appendix I for more information.

Model Parameter	Value(s) Used	Source	Value Type/ Description	Confidence/Uncertainty Comment
	(0.46 for PFOS and 0.87 for PFOA)	to cord blood ratios (see Appendix I)	factor × maternal serum)	
Breastmilk Concentration	Calculated *Maternal serum concentration (µg/L) × Breastmilk Transfer Factor* (0.013 for PFOS and 0.052 for PFOA)	MDH calculated value. Transfer Factor based on average of reported mean maternal serum to breastmilk concentration ratios (see Appendix I)	Elements of Central and Upper (based on mean transfer factor × maternal serum)	Limited individual serum to breastmilk data are available. Mean, median and upper percentile ratios are within a factor of 2. See Appendix I for more information.
Breastmilk Intake Rate (BIR)	Upper percentile values for exclusively breastfed infants (mL/kg-d) Birth to <1 mon – 220 1 to < 3 mon – 190 3 to < 6 mon – 150 6 to < 12 mon – 130	Table 15-1 (USEPA 2011)	Upper	Use of upper percentile intakes is MDH policy.
Breastfeeding Duration	1 year of exclusive breastfeeding	Selected by MDH to represent reasonable maximum exposure scenario.	Upper	CDC 2016 Minnesota specific data: 53.9 and 31.4% of mothers reported exclusively breastfeeding at three and six months. The percent reporting breastfeeding at twelve months dropped to 41%, the percent exclusively breastfeeding at this time point was not reported.
Water Intake Rate (WIR)	Age-specific 95th percentile values consumers only (mL/kg-d) Birth to <1 mon – 238 1 to < 3 mon - 285 3 to < 6 mon – 173 6 to < 12 mon – 129 1 to < 2yr – 75 2 to < 3 yr – 62 3 to < 6 yrs – 52 6 to < 11 yrs – 47 11 to < 16 yrs – 35	Table 3-1 (USEPA 2011)	Upper	Age-specific intakes used in model. For calculation of maternal serum concentration at time of delivery a time-weighted average water intake rate was calculated from birth to 30-35 years of age, resulting in a water intake rate of 47 mL/kg-d.

Model Parameter	Value(s) Used	Source	Value Type/ Description	Confidence/Uncertainty Comment
	16 to < 18 yrs – 30 18 to < 21 yrs – 36 ≥21 yrs - 42			
Body Weight (BW)	Age specific values calculated from intake volume (mL/day) and intake rate (mL/kg-d).	Table 3-1 for water ingestion exposure and Table 15-1 for breastmilk ingestion exposure	Consistent with Central (Mean) values	

3.0 Derivation of Health-Based Water Guidance Values

Three components are used in the derivation of health-based water guidance values: 1) a measure of toxicity, (RfD); 2) relative source contribution to apportion a fraction of the RfD to water ingestion; and 3) a measure of exposure, the water/breastmilk intake rate. Selection of the RfD and RSC are briefly described in the following section. Water and breastmilk intake rates are described in Sections 2.3.1.2 and 2.1.4, respectively.

3.1 Reference Doses and Corresponding Serum Concentrations

MDH conducted an expedited and focused re-evaluation of the available toxicological information, relying in part on USEPA's 2016 health assessment documents ((USEPA, 2016a) (USEPA, 2016c)). Several key studies (e.g., candidates for forming the basis of an RfD) were identified for PFOS and PFOA.

For PFOS, the sensitive health endpoints included development, liver changes, decreases in thyroid hormone serum levels, and immune suppression. While these effects were observed in different studies they were observed at similar serum concentration levels. A two generation reproductive study was selected as the study upon which to base the final RfD. This is the same critical study used by USEPA as the basis of their RfD. The no observable adverse effect level (NOAEL) average serum concentration from this study was 6.26 mg/L. The human equivalent dose corresponding to this serum concentration can be calculated using Equation 2:

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

$$= 6.26\left(\frac{mg}{L}\right) x\ 0.000081\left(\frac{L}{kg \cdot day}\right)$$

$$= 0.00051\left(\frac{mg}{kg \cdot day}\right)$$

Uncertainty factors of 3 for potential interspecies differences in toxicodynamics, 10 for intraspecies variability within the human population, and 3 for database deficiencies regarding immunotoxicity were selected. The value of the individual uncertainty factors are multiplied, resulting in a total uncertainty adjustment of 100. [For more information on how total uncertainty is calculated see page 3 of (MDH, 2008). Application of a total uncertainty adjustment of 100 results in an RfD of 0.0000051 mg/kg-d (0.00051/100). The serum concentration corresponding to this RfD is 0.063 mg/L. In addition to developmental effects identified in the two generation study, immune, liver, and thyroid systems are also identified as additivity health endpoints.

For PFOA, the sensitive health endpoints included development, liver changes, immune suppression, and kidney effects. These effects were observed in different studies, however, they were observed at similar serum concentration levels. A developmental study was selected as the study upon which to base the final RfD. This is the same critical study used by USEPA as the basis of their RfD. The lowest dose level tested in this study resulted in health effects; therefore, a NOAEL was not available. The average serum concentration at the lowest dose tested, 38 mg/L, was identified as the LOAEL. The human equivalent dose corresponding to this serum concentration can be calculated using Equation 2:

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

$$= 38\left(\frac{mg}{L}\right) x\ 0.00014\left(\frac{L}{kg \cdot day}\right)$$

$$= 0.0053 \left(\frac{mg}{kg \cdot day}\right)$$

Uncertainty factors of 3 for potential interspecies differences in toxicodynamics, 10 for intraspecies variability within the human population, 3 for use of a LOAEL rather than a NOAEL, and 3 for database deficiencies regarding the lack of an acceptable two generation study were selected. The value of the individual uncertainty factors are multiplied, resulting in a total uncertainty adjustment of 300. Application of a total uncertainty adjustment of 300 results in an RfD of 0.000018 mg/kg-d (0.0053/300). The serum concentration corresponding to this RfD is 0.13 mg/L. In addition to developmental effects identified in the developmental study, immune, liver, and kidney systems are also identified as additivity health endpoints.

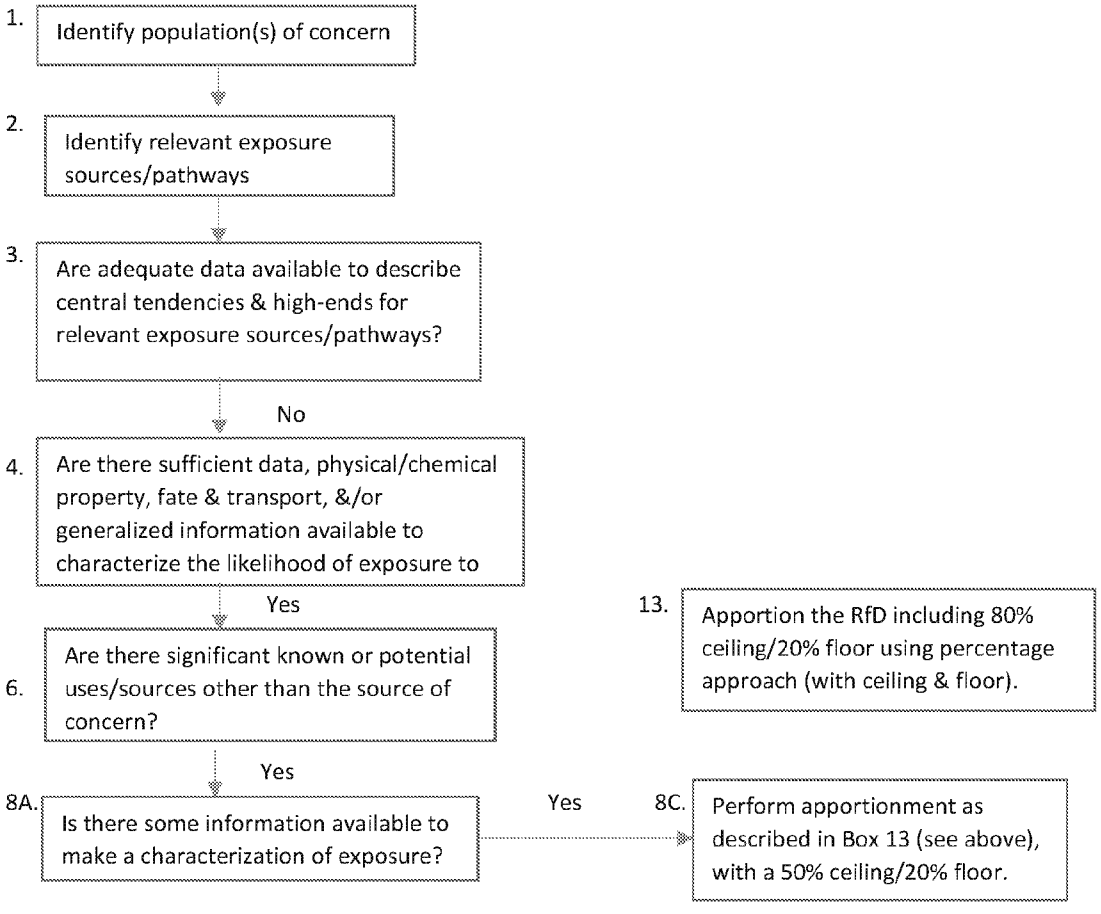
3.2 Relative Source Contribution Factor

When MDH develops guidance values for a chemical, it considers the contribution of non-water exposures to an individual's total exposure. The TK model, as originally conceived, predicts serum PFOS or PFOA concentrations arising directly and indirectly (e.g. breastmilk) from water intake only. However, exposures may also occur from other sources. These other exposures are taken into account by MDH through a Relative Source Contribution (RSC) factor, which allocates a fraction of the RfD to water exposures and the remaining portion to other sources. In the case of PFOS and PFOA, the RSC concept needed to be applied in a framework recognizing the long elimination half-lives of PFOS and PFOA, such that a person's serum concentration at any given age is not the result of only his or her current or recent exposures within the duration of concern, but also from his or her exposures (or maternal exposures) from years past.

Non-water exposure to PFOS has been examined by Egeghy and Lorber (Egeghy PP and M Lorber, 2011). These researchers used a two-pronged approach: 1) exposure media concentration data from multiple sources and 2) based on serum concentrations reported in the 2003-04 NHANES Study. For the first approach, Egeghy and Lorber selected exposure media concentration data from multiple sources in the literature to estimated daily median and 95th percentile exposure intakes for young children and adults from dust, diet, water, and air. Because of the sparseness of media-specific data, the authors characterized the resulting intake estimates as subject to considerable uncertainty. This uncertainty was greater for the upper percentile estimates than for the median values. Due to the high uncertainty in the intake estimates and use of NHANES serum data that is over a decade old, especially as the serum concentrations have been decreasing over time, MDH did not use the results of Egeghy and Lorber (2011) quantitatively for RSC apportionment. Instead, MDH used the recent NHANES biomonitoring data (2013-2014) and East Metro new resident biomonitoring data (2014), to estimate upper-end non-water exposures for PFOS and PFOA (similar to option 2 in Egeghy and Lorber, 2011, which is more reflective of current exposures.

MDH utilizes the USEPA Exposure Decision Tree process (USEPA, 2000) to identify and select the most appropriate RSC. The Decision Tree presents a series of decision points at which the quality and quantity of available exposure data are evaluated and at which the derivation of the RSC is ultimately steered toward one of several conclusions indicating an appropriate RSC. In other chemical assessments, MDH often relied upon the percentage method, which is intended to reflect relative portions of other (non-water ingestion) routes of exposure and the likelihood for changing levels within those multiple sources (MDH, 2008). The relevant portions of the Exposure Decision Tree are presented below.

Figure 12. Exposure Decision Tree.
(Adapted from USEPA 2000 - box numbers correspond to USEPA 2000 document, only relevant boxes are selected for presentation below)



The 80 percent ceiling within the Decision Tree is to ensure that the health-based goal will be low enough to provide adequate protection for individuals whose total exposure is, due to any of the exposure sources, higher than currently indicated by the available data (US EPA 2000). This also increases the margin of safety to account for possible unknown sources of exposure. Since serum concentrations are the best measure of PFOS and PFOA exposure, these values can be used in place of the RfD in the Decision Tree process.

3.2.1 Selection of RSC for PFOS

High quality national and Minnesota-specific data sources are available which establish human serum concentrations of PFOS across many individuals, although data for infants and young children are not available. Given the long half-life of PFOS, these biomonitoring results from the East Metro (new residents) and NHANES can be compared to the serum concentration of 0.063 mg/L corresponding to the PFOS RfD to provide insight into the magnitude of non-water exposures. *[Please note that this 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.]*

CDC (CDC, 2017) has been measuring PFOS in the serum of the general population since 1999. The most recent (2013-2014) biomonitoring results were: geometric mean 0.00499 mg/L and 95th percentile 0.0185 mg/L. It is

important to note that the general population (NHANES) serum levels have been decreasing over time, with a 3 to 4-fold drop since 2003-04 (the serum levels used in Egeghy and Lorber 2011). The 2013-14 data provide the most recent data regarding 'background' serum levels in the US general populations.

MDH's East Metro PFC biomonitoring project sampled a subset of people living in the East Metro region who were connected to a contaminated public water supply (Nelson, 2016). Treatment to remove perfluorochemicals (PFCs) was added to the public water system (PWS) and volunteer participants had PFOS blood levels measured at three time points: 2008, 2010, and 2014. As part of the last biomonitoring effort, new East Metro residents (N=156) were also sampled in 2014. These individuals did not have historical exposure to the contaminated water, so their serum samples can be considered representative of Minnesota non-water exposures (geometric mean 0.0072 mg/L and 95th percentile 0.021 mg/L). These levels are slightly higher than the NHANES 2013-14 values but are noticeably lower than the East Metro population that were historically exposed to contaminated water.

Data on PFOS serum levels in infants are not available; however, there are publications regarding serum levels in young children ((Schecter, 2012), (Wu, 2015), and (Harris, 2017)). These publications indicate that the geometric means and 95th percentile values in young children are similar to adult levels. Therefore, available data supports the use of upper-end percentile values from NHANES and the East Metro new resident as conservative representations of 'background' non-water ingestion routes of exposure.

To assist in identifying an appropriate RSC (apportionment to water ingestion) for PFOS MDH took the ceiling of 80% (per Decision Tree, USEPA 2000) and subtracted a conservative (95th percentile) serum value from the recent biomonitoring data from the East Metro new residents (which was slightly higher than the 2013-2014 NHANES 95th percentile value) as follows:

- 80% Ceiling = 80% of the serum concentration associated with the RfD = 0.063 mg/L × 0.8 = 0.0504 mg/L
- Subtraction of the serum level associated with non-water exposures, as reflected by the 95th percentile value based on the new East Metro residents (0.021 mg/L), from the 80% ceiling = 0.0504 mg/L – 0.021 mg/L = 0.0294 mg/L. This value of 0.0294 mg/L represents the residual or maximum serum level that can be apportioned to exposure via water ingestion, while still keeping the total serum level below the 80% ceiling.
- The residual or maximum serum level that can be apportioned to exposure via ingestion of water (0.0294 mg/L) is approximately 50% of the serum concentration at the RfD (0.063 mg/L).

Based on this information and the USEPA Decision Tree (e.g., box 8C), MDH selected an RSC of 50% for PFOS water ingestion. It should be noted that the results of this analysis do not support raising the apportionment of water ingestion sources to 80 percent.

3.2.2 Selection of RSC for PFOA

High quality biomonitoring data are also available for PFOA and a similar approach to apportionment of the RSC as described for PFOS was also undertaken for PFOA. Biomonitoring results from the East Metro (new residents) and NHANES were used in comparison to the serum concentration corresponding to the PFOA RfD of 0.13 mg/L to provide insight into the magnitude of non-water exposures. *[Please note that this 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.]*

CDC (CDC, 2017) has been measuring PFOA in the serum of the general population since 1999. The most recent (2013-2014) biomonitoring results were: geometric mean 0.00194 mg/L and 95th percentile 0.00557 mg/L. It is important to note that the general population (NHANES) serum levels have been decreasing over time, with a 2 to 3-fold drop since 2003-04 (the serum levels used in Egeghy and Lorber 2011). The 2013-14 data provide the most recent data regarding 'background' serum levels in the US general populations. New East Metro residents (N=156) were also sampled for PFOA in 2014: geometric mean 0.0018 mg/L and 95th percentile 0.005 mg/L. These levels are similar but slightly lower than the NHANES 2013-14 values.

Data on PFOA serum levels in infants are not available; however, there are publications regarding serum levels in young children ((Schecter, 2012), (Wu, 2015), and (Harris, 2017)). These publications indicate that the geometric means and 95th percentile values in young children are similar to adult levels. Therefore, available data support the use of upper-end percentile values from NHANES and the East Metro new resident as conservative representations of 'background' non-water ingestion routes of exposure.

To assist in identifying an appropriate RSC (apportionment to water ingestion) for PFOA, MDH took the ceiling of 80% (per Decision Tree, USEPA 2000) and subtracted a conservative (95^{th} percentile) serum value from the recent biomonitoring data from 2013-2014 NHANES (which was slightly higher than the new East Metro residents 95^{th} percentile value) as follows:

- 80% Ceiling = 80% of the serum concentration associated with the RfD = 0.130 mg/L × 0.8 = 0.104 mg/L
- Subtraction of the serum level associated with non-water exposures, as reflected by the 95^{th} percentile value based on 2013-2014 NHANES data (0.00557 mg/L), from the 80% ceiling = 0.104 mg/L – 0.00557 mg/L = 0.0984 mg/L. This value of 0.0984 mg/L represents the residual or maximum serum level that can be apportioned to exposure via water ingestion, while still keeping the total serum level below the 80% ceiling.
- The residual or maximum serum level that can be apportioned to exposure via ingestion of water (0.0984 mg/L) is approximately 75% of the serum concentration at the RfD (0.13 mg/L).

This calculation suggests an RSC of greater than 50% but less than 80%. However, given the limited information regarding background exposure in the population of concern (i.e., infants) and the process outlined in the USEPA Decision Tree (e.g., box 8C), MDH selected an RSC of 50% for PFOA water ingestion.

3.3 Reasonable Maximum Exposure Scenarios

As mentioned above, two exposure scenarios were examined: 1) an infant exclusively fed formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breastfed for 12 months, followed by drinking contaminated water through life. Both of these scenarios are presented graphically in Figures 10 and 11, respectively, in Section 2.3.

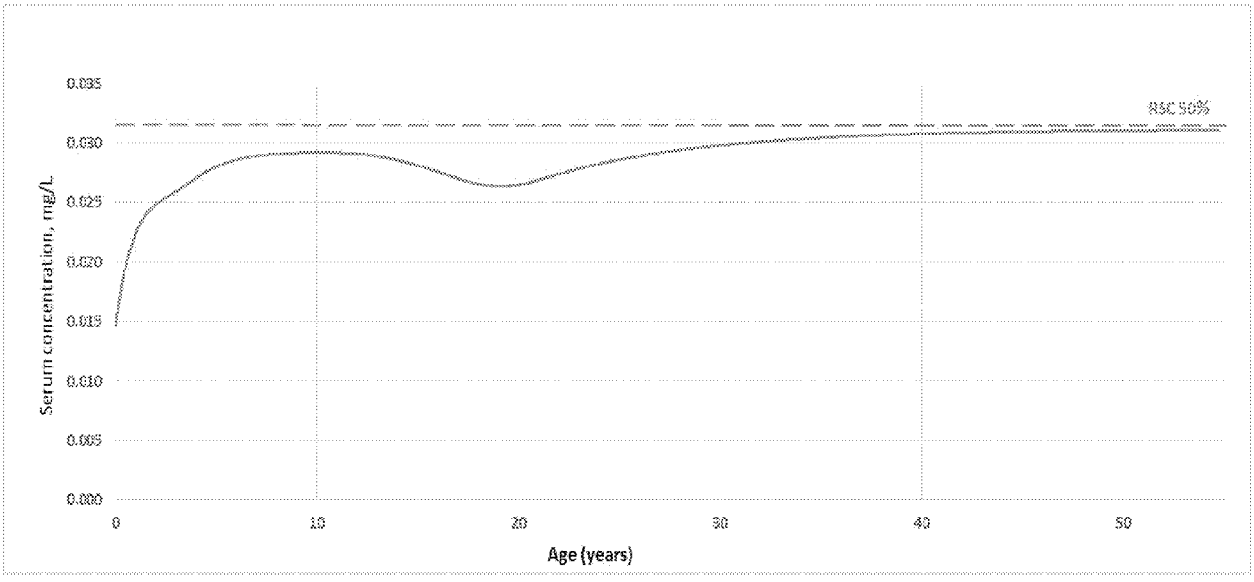
An iterative process was used to identify the water concentration that resulted in maintaining a serum concentration at or below 50% (RSC) of the serum concentration associated with the RfD. The chemical-specific and exposure parameter inputs used are provided above in Table 8.

3.3.1 Scenario #1 – Exclusively formula-fed infant

3.3.1.1 PFOS

The water concentration that maintained a PFOS serum concentration at or below an RSC of 50% (i.e., 0.063 × 0.5 = 0.0315 mg/L) throughout life was 0.060 µg/L.

Figure 13. Exclusively formula-fed infant PFOS serum concentrations over a lifetime, based on 95th percentile water intake rates, an RSC of 50%, and a water concentration of 0.060 µg/L.

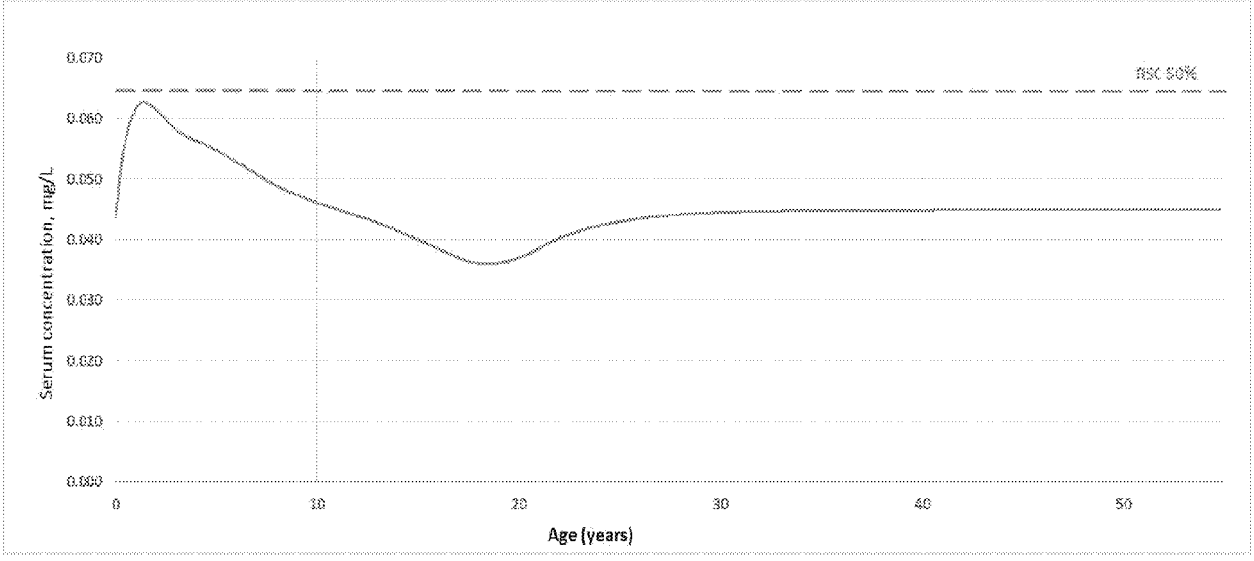


Because of the long half-life, the PFOS serum concentration curve is very flat and even a small incremental increase in the water concentration (0.061 µg/L) raised the predicted PFOS serum concentration above the 50 percent threshold for nearly 9 years.

3.3.1.2 PFOA

The water concentration that maintained a PFOA serum concentration for exclusively formula-fed infants at or below an RSC of 50% (i.e., 0.13 × 0.5 = 0.065 mg/L) throughout life was 0.15 µg/L.

Figure 14. Exclusively formula-fed infant PFOA serum concentrations over a lifetime, based on 95th percentile water intake rates, an RSC of 50%, and a water concentration of 0.15 µg/L.



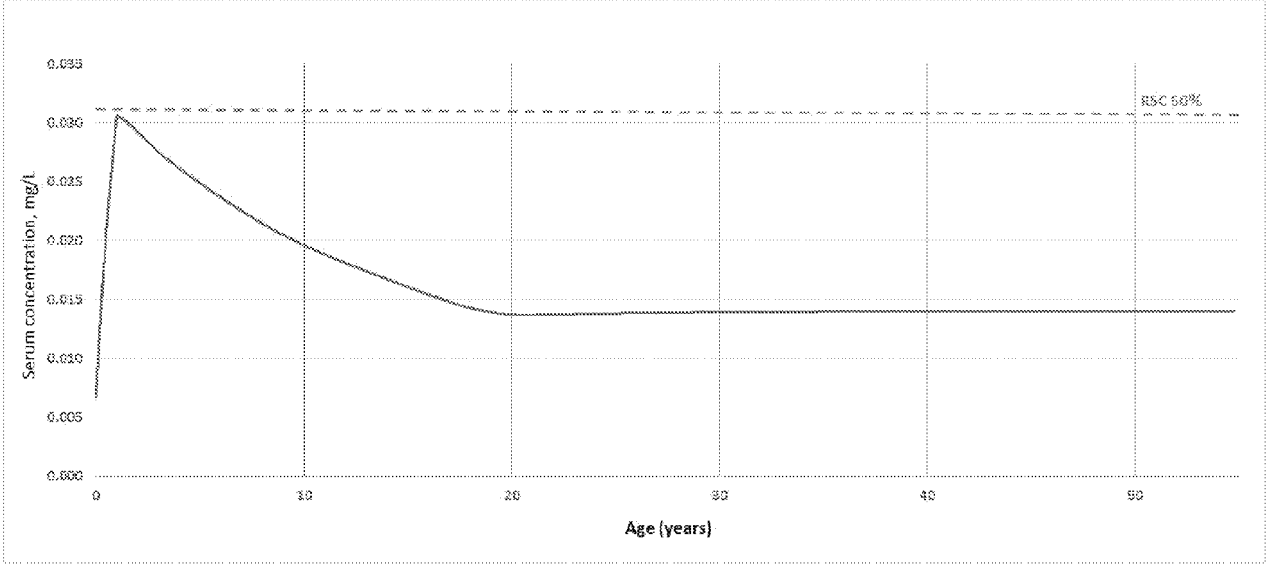
Serum concentrations were sensitive to changes in water concentrations. An increase in the water concentration to 0.16 µg/L raised the serum concentration above the 50 percent threshold for more than one year.

3.3.2 Scenario #2 – Exclusively breastfed infant

3.3.2.1 PFOS

As stated in Section 3.3.1.1, a water concentration of 0.060 µg/L is protective throughout life for individuals who are exclusively formula-fed as infants. However, this water concentration based on formula-fed infants is not sufficiently protective for infants who are exclusively breastfed for a year when considering the chronic bioaccumulative maternal exposure with subsequent transfer in breastmilk. At a water concentration of 0.060 µg/L, predicted PFOS serum levels for exclusively breastfed infants exceed the serum concentration at the RfD for more than one year and exceed the 50% RSC threshold for nearly 19 years. In order to maintain PFOS serum concentrations at or below the 50% RSC serum concentration (i.e., 0.0315 mg/L) the water concentration had to be lowered to 0.027 µg/L.

Figure 15. Exclusively breastfed infant PFOS serum concentrations over a lifetime, based on Upper/95th percentile breastmilk/water intake rates, an RSC of 50%, and a water concentration of 0.027 µg/L.



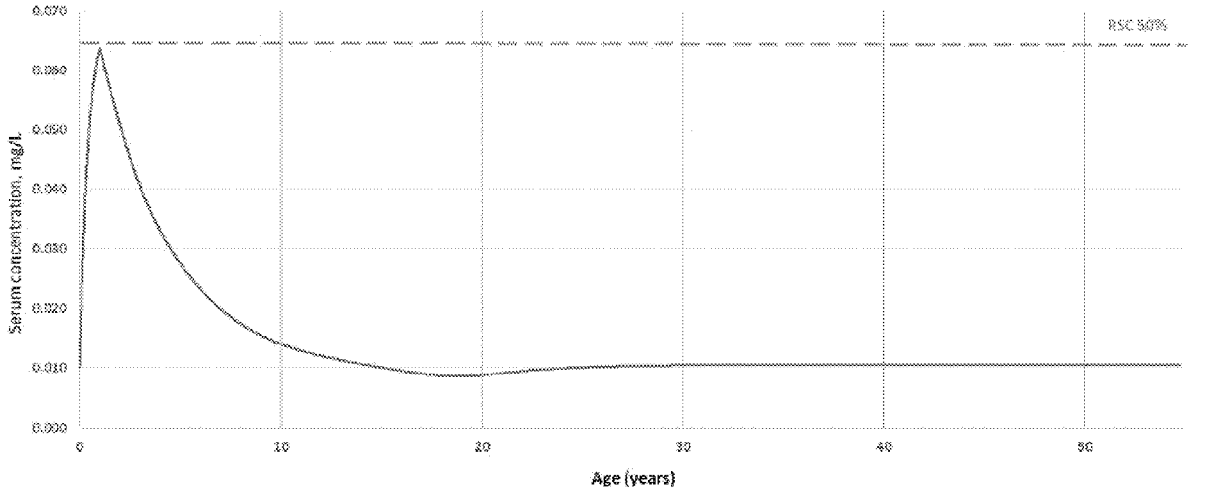
Even a small incremental increase in the water concentration (i.e., 0.028 µg/L) raised the serum concentration above 50% RSC threshold for more than three months during early life. Therefore, the health-based water guidance for PFOS was set at 0.027 µg/L to be protective of developmental concerns and to prevent exceedance of the 50% threshold that could occur as a result of exposure over a subchronic period of time.

3.3.2.2 PFOA

As stated in Section 3.3.1.2, a water concentration of 0.15 µg/L is protective throughout life for individuals who are exclusively formula-fed as infants. However, this water concentration based on formula-fed infants is not sufficiently protective for infants who are exclusively breastfed for a year when considering the chronic bioaccumulative maternal exposure with subsequent transfer in breastmilk. At a water concentration of 0.15 µg/L, predicted PFOA serum levels for exclusively breastfed infants exceed the serum concentration at the RfD for more than 4 years and exceed the 50% RSC threshold for more than 9 years.

In order to maintain PFOA serum concentrations at or below the 50% RSC serum concentration (i.e., 0.065 mg/L), the water concentration had to be lowered to 0.035 µg/L.

Figure 16. Exclusively breastfed infant PFOA serum concentrations over a lifetime, based on Upper/95th percentile breastmilk/water intake rates and an RSC of 50%, and a water concentration of 0.035 µg/L.



Even a small incremental increase in the water concentration (0.036 µg/L) raised the serum concentration above the 50 percent threshold for approximately one month during early life. Therefore, the health-based water guidance for PFOA was set at 0.035 µg/L to be protective of developmental concerns.

3.4 Conclusions/Summary

Due to the bioaccumulative nature of PFOS and PFOA, chronic exposure to mothers and the subsequent transfer to infants through breastfeeding resulted in the highest exposures and lowest acceptable water concentrations under the scenarios evaluated by MDH. To ensure protection of all segments of the population, the final MDH health-based values for PFOS and PFOA were set at 0.027 and 0.035 µg/L, respectively.

Breastfeeding is important for the short and long term health of both a mother and infant. MDH used an RME scenario to generate the health-based values for PFOS and PFOA. An RME scenario depicts a realistic but maximum exposure situation to ensure that even the most heavily exposed individuals within the population will be protected. The majority of the population experience lower exposures than the RME. MDH recommends that women currently breastfeeding, and pregnant women who plan to breastfeed, continue to do so. Exclusive breastfeeding is recommended by doctors and other health professionals. It is unlikely that potential health concerns exceed the known benefits of breastfeeding. Application of the final health-based values will ultimately result in lower body burdens and breastmilk concentrations of PFOS and PFOA so that infants can receive the optimal benefits from breastfeeding.

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APPENDIX I — Summary of placental and breastmilk transfer study data.

Placental Transfer

Several studies measured maternal and cord serum levels of PFOS and PFOA near the time of delivery, thereby permitting an estimation of placental transfer and initial body burden in the newborn infant.

PFOS Maternal Serum and Cord Blood Concentration Summary

Study Description	PFOS Maternal Serum Concentration (µg/L)			PFOS Cord Blood Concentration (µg/L)			**PFOS Cord Blood to Maternal Ratio**		
	Mean	Median	95th or Max	Mean	Median	95th or Max	**Mean**	**Median**	**95th or Max**
Tittlemier et al. 2004 – pooled samples	36.9			16.7			0.45		
Fei et al. 2007 – maternal samples taken in second trimester	29.9			11			0.37		
Midasch et al. 2007	12.1			7.2			0.60*		
Monroy et al. 2008	16.19	14.54		7.19	6.08		0.44	0.42	
Fromme et al. 2010	3.5	3.2	6.1	1.1	1.0	2.2	0.31	0.31	0.36
Liu et al. 2011	3.184	2.922	13.188	1.686	1.470	6.674	0.53	0.50	0.50
Kim et al. 2011	5.6		9.4	2.0		3.6	0.36		0.38
Cariou et al. 2015	3.67	3.065	24.5	1.28	1.115	8.04	0.35	0.36	0.33
						**Minimum	**0.31**	**0.31**	**0.33**
						**Maximum	**0.60**	**0.50**	**0.51**
						**Average	**0.43**	**0.40**	**0.39**
						**Geometric Mean	**0.42**	**0.39**	**0.39**

*Individual maternal:cord blood ratios ranged from 0.41 to 0.80

**Excluding Tittlemier et al. (pooled samples) and Fei et al. (maternal serum measured in second trimester). In all other studies maternal samples were taken at or within first week after delivery.

PFOA Maternal Serum and Cord Blood Concentration Summary

Study Description	PFOA Maternal Serum Concentration (µg/L)			PFOA Cord Blood Concentration (µg/L)			PFOA Cord Blood to Maternal Ratio		
	Mean	Median	95th or Max	Mean	Median	95th or Max	Mean	Median	95th or Max
Tittlemier et al. 2004 – pooled samples	2.2			3.4			1.55		
Fei et al. 2007 – maternal samples taken in second trimester	4.5			3.7			0.82		
Midasch et al. 2007	2.75			3.41			1.24*		
Monroy et al. 2008	2.24	1.81		1.94	1.58		0.87	0.87	
Fromme et al. 2010	2.3	1.9	5.2	1.7	1.4	3.7	0.74	0.74	0.71
Liu et al. 2011	1.655	1.264	5.879	1.5	1.115	6.442	0.91	0.88	1.1
Kim et al. 2011	1.6		3.2	1.1		2.7	0.69		0.84
Cariou et al. 2015	1.22	1.045	7.31	0.919	0.860	7.06	0.75	0.82	0.97
						**Minimum	**0.69**	**0.74**	**0.73**
						**Maximum	**1.24**	**0.88**	**1.10**
						**Average	**0.87**	**0.83**	**0.91**
						**Geometric Mean	**0.85**	**0.83**	**0.90**

* individual maternal:cord blood ratios ranged from 0.92 to 1.95

**Excluding Tittlemier et al. (pooled samples) and Fei et al. (maternal serum measured in second trimester). In all other studies maternal samples were taken at or within first week after delivery.

The reported mean ratios of cord to maternal concentrations ranged from 0.31 (Fromme, 2010) to 0.60 (Midasch, 2007) for PFOS and from 0.69 (Kim, 2011) to 1.24 (Midasch, 2007) for PFOA. The average of the reported mean ratios from these studies were 0.42 and 0.87 for PFOS and PFOA, respectively. These average values were used by MDH in evaluating the simple TK model.

Breastmilk Transfer

Several studies measured maternal serum concentrations and breastmilk, thereby permitting an estimate of partitioning from maternal serum into breastmilk and prediction of breastmilk concentrations.

PFOS Maternal Serum and Breastmilk Concentration Summary

Study Description	PFOS Maternal Serum Concentration (µg/L)			PFOS Breastmilk Concentration (µg/L)			PFOS Breastmilk to Maternal Ratio		
	Mean	Median	95th or Max	Mean	Median	95th or Max	Mean	Median	95th or Max
Karrman et al. 2007	20.7	18.7	48.0	0.201	0.166	0.47	0.010	0.009	0.01
Fromme et al. 2010	3.2	2.9	6.3		0.04	0.08		0.014	0.013
Liu et al. 2011	3.184	2.922	13.188	0.056	0.042	0.198	0.018	0.014	0.015
Kim et al. 2011	5.6		9.4	0.061		0.13	0.011		0.014
Cariou et al. 2015	3.67	3.065	24.5	0.04	<LOQ	0.376	0.011		0.015
						Minimum	**0.010**	**0.009**	**0.01**
						Maximum	**0.018**	**0.014**	**0.015**
						Average	**0.013**	**0.012**	**0.013**
						Geometric Mean	**0.012**	**0.012**	**0.013**

PFOA Maternal Serum and Breastmilk Concentration Summary

Study Description	PFOA Maternal Serum Concentration (µg/L)			PFOA Breastmilk Concentration (µg/L)			PFOA Breastmilk to Maternal Ratio		
	Mean	Median	95th or Max	Mean	Median	95th or Max	Mean	Median	95th or Max
Fromme et al. 2010	1.7	1.5	3.9	Only 2% detection rate		0.25			0.064
Liu et al. 2011	1.655	1.264	5.879	0.181	0.121	1.44	0.109	0.096	0.245
Kim et al. 2011	1.6		3.2	0.041		0.077	0.026		0.024
Cariou et al. 2015	1.22	1.045	7.31	0.041	<LOQ	0.308	0.034		0.042
						Minimum	**0.026**	**0.096**	**0.024**
						Maximum	**0.109**	**0.096**	**0.245**
						Average	**0.052**		**0.094**
						Geometric Mean	**0.043**		**0.063**

The reported mean ratios of breastmilk to maternal serum concentration range from 0.01 (Karrman, 2007) to 0.018 (Liu, 2011) for PFOS and from 0.026 (Kim, 2011) to 0.109 (Liu, 2011) for PFOA. The average of the reported mean ratios from these studies were 0.013 and 0.052 for PFOS and PFOA, respectively. These average values were used by MDH in evaluating the simple TK model.

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APPENDIX II – Peer Reviewer Biographical Information

Dr. Jeffrey Fisher –

Dr. Jeffrey Fisher is a research toxicologist with the U.S. Food and Drug Administration, National Center for Toxicological Research. He was formerly a Professor in the Department of Environmental Health Science, College of Public Health at the University of Georgia (UGA). He joined the University of Georgia in 2000 and served as Department Head of the Department of Environmental Health Sciences from 2000 to 2006 and Director of the Interdisciplinary Toxicology Program at UGA from 2006-2010. He spent 25 years at the Toxicology Laboratory, Wright Patterson AFB, where he was Principal Investigator and Senior Scientist in the Toxics Hazards Division and Technical Advisor for the Operational Toxicology Branch.

Dr. Fisher's research interests are in the development and application of pharmacokinetic and biologically based mathematical models to ascertain health risks from environmental, food-borne and occupational chemical exposures. Recently, with FDA, he has become involved in the use of PBPK models for drugs and pediatrics. Dr. Fisher's chemical toxicology modeling experience includes working with chlorinated and non-chlorinated solvents, fuels, pesticides, perchlorate, PFOA, and bisphenol A. He has developed PBPK models for use in cancer risk assessment, estimating lactational transfer of solvents, understanding in utero and neonatal dosimetry, quantifying metabolism of solvent mixtures and developing biologically motivated models for the hypothalamic-pituitary-thyroid axis in rodents and humans. Dr. Fisher has 30 years of experience in physiological modeling and has trained several graduate students and postdoctoral fellows on the concepts and application of physiological models. He was a Visiting Scientist at the Chemical Industry Institute of Toxicology in 1996 and at the NIOSH Taft Laboratory in 1999. During this time, he also served as Adjunct Professor in the Department of Pharmacology and Toxicology at Wright State University. Dr. Fisher has published over 160 papers on pharmacokinetics and PBPK modeling in laboratory animals and humans. He has served on several national panels and advisory boards for the DoD, ATSDR, USEPA and non-profit organizations. He was a U.S. delegate for the North Atlantic Treaty Organization. Dr. Fisher served on the International Life Sciences Institute Steering Committee, which evaluated chloroform and dichloroacetic acid using EPA-proposed Carcinogen Risk Guidelines. He is Past President of the Biological Modeling Specialty Section of the Society of Toxicology, reviewer for several toxicology journals, and was Co-Principal Investigator on a National Institutes of Health (NIH)-supported workshop on Mathematical Modeling at the University of Georgia in the fall of 2003. He was a member of the National Academy of Sciences subcommittee on Acute Exposure Guideline Levels (AEGLs) from 2004-2010 and Science Advisory Board for the US EPA (2007-2010). He is an ad hoc member of the SABs for dioxin and perchlorate. He is a fellow of the Academy of Toxicological Sciences and an associate editor for Toxicological Sciences. Dr. Fisher has a B.S. degree in biology from the University of Nebraska at Kearney, a M.S. degree in biology from Wright State University, and a Ph.D. in Zoology/Toxicology from Miami University.

Dr. Gary Ginsberg –

Dr. Gary Ginsberg has been a toxicologist at the Connecticut Department of Public Health, where he is the lead toxicologist on site risk assessments for remedial programs and evaluation of contaminants in consumer products, the built environment, food products, and a variety of other media and exposure sources. He has published extensively on children's health related issues. Dr. Ginsberg is adjunct faculty at the Yale School of Public Health and is assistant professor of community medicine at the University of Connecticut Health Center campus. He has served on a number of U.S. Environmental Protection Agency advisory committees and National Academy of Science panels. Dr. Ginsberg received his PhD from UConn in 1986.

Dr. Judy LaKind –

Judy LaKind, Ph.D. is President of LaKind Associates, LLC, and Adjunct Associate Professor, Department of Epidemiology and Public Health, University of Maryland School of Medicine. She is a health and environmental scientist with expertise in exposure science, assessment of human health risks, biomonitoring, scientific and technical analysis for regulatory support, and state-of-the-science reviews. Dr. LaKind has spoken and published extensively on exposure- and risk-related issues, including children's exposures to environmental chemicals, the implications of uncertainty in the risk assessment process, weighing potential risks and benefits related to chemical use, environmental chemicals in human milk, and time-dependence and distributional analysis of exposure. Dr. LaKind has taught graduate level courses at The Johns Hopkins University and the University of Maryland in risk assessment and aquatic chemistry. She serves on the editorial boards of the Journal of Toxicology and Environmental Health and Environment International and is past Associate Editor for the Journal of Exposure Science and Environmental Epidemiology. Dr. LaKind is President-Elect for the International Society of Exposure Science and has served on numerous advisory committees including the Maryland's Children's Environmental Health and Protection Advisory Council.

Mr. Mike Poulsen –

Mike Poulsen has a degree in chemistry from Stanford University and a master's degree in technology and policy from the Massachusetts Institute of Technology. Mike has been a toxicologist for seventeen years in the Cleanup Program of the Oregon Department of Environmental Quality. Prior to joining DEQ, he was an environmental consultant for fifteen years and a scientific research analyst for two years.

Mr. Poulsen provided risk assessment support for the Portland Harbor federal Superfund project. The risk assessment for the site showed that exposure to PCBs in fish results in the greatest potential cancer risk to humans. To fully evaluate non-carcinogenic effects, Mike worked for five years with EPA Region 10 toxicologists and the Oregon public health toxicologist to develop an approach for evaluating PCB risks to infants from breastfeeding. The team modified equations for a single compartment, first-order kinetic model used by EPA. The team then worked with ATSDR scientists and other researchers to compare the model with 3- and 8-compartment PBPK models. PCB-153 milk concentrations and doses to infants were calculated by the three models using data from Inuit women and their infants.

Given the closeness of the results, the simpler EPA model was selected for inclusion in Oregon DEQ risk assessment guidance. DEQ simplified the evaluation of the breastfeeding pathway in risk assessments by using the EPA model to develop a table of infant risk adjustment factors (IRAFs) that can be used to calculate potential risk to infants based on the calculated risk to the mothers from exposure to PCBs and other bioaccumulating chemicals. (Appendix D in
http://www.deq.state.or.us/lq/pubs/docs/cu/HumanHealthRiskAssessmentGuidance.pdf)

Dr. Marc-André Verner –

Marc-André Verner works as an Assistant Professor at the Department of Occupational and Environmental Health, School of Public Health, Université de Montréal (Canada). He is also a member of the Université de Montréal Public Health Research Institute (IRSPUM). Marc's research projects focus mostly on physiologically based pharmacokinetic (PBPK) modeling and quantitative structure-property relationships (QSPR) to evaluate developmental exposure to environmental chemicals in the womb and postnatally through breastfeeding. He earned his Ph.D. in Biology from the Université du Québec à Montréal (Canada). During his Ph.D., Marc developed PBPK models of persistent organic pollutants to refine exposure assessment in epidemiologic studies of breast cancer and developmental neurotoxicity. After completing his Ph.D., he continued working on PBPK

modeling during his postdoctoral training at the Karolinska Institutet in Sweden. He then moved to Boston (USA) to do a second postdoctoral training in environmental epidemiology at the Harvard Medical School/Brigham and Women's Hospital. His background in both toxicology and environmental epidemiology led him to pioneer the use of PBPK modeling in epidemiologic studies, an approach that allowed reconstructing complete exposure profiles and investigating the effects of chemicals during different windows of vulnerability. Over the years, Marc has authored and co-authored approximately 25 peer-reviewed papers and received numerous awards for his innovative work in environmental health.

Dr. Rachel Worley –

Rachel Rogers Worley is an Environmental Health Scientist at ATSDR in the Division of Community Health Investigations, Science Support Branch. Rachel has her BS in Chemistry from the University of Georgia (2006), an MA in Environmental Studies/Reproductive Toxicology from Brown University (2008), and a PhD in Toxicology from the University of Georgia (2016). Her formal training is in computational toxicology and she acts as a PFAS subject matter expert at ATSDR.