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A revised and improved toxicokinetic model to simulate serum concentrations of bioaccumulative PFAS

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Abstract

Minnesota has been grappling with public health issues regarding exposure to per- and polyfluoroalkyl substances (PFAS) since 2002. For some PFAS, the traditional paradigm for developing health-based water guidance values (HBGVs) is inadequate due to their tendency to accumulate within the body and to transfer from mother to newborn via placental transfer and breastfeeding. In 2017, the Minnesota Department of Health (MDH) developed an Excel-based model to simulate daily serum PFAS concentrations over a lifetime of exposure to facilitate the derivation of HBGVs for bioaccumulative PFAS. Model results compare favorably to data on breastfed infants, who represent a susceptible and highly exposed population. Since 2017, new data have emerged that warranted a re-evaluation of key model parameters. Here, we present a revised and updated version of the 2017 model and assess the impact of the updates on the model results for perfluorooctanoate (PFOA). Updates to the model's calculations and input parameters resulted in a 57% reduction in peak modeled PFOA serum concentrations in 1-year-old infants compared to the original model. However, the significantly lower epidemiologic-based reference serum concentration of 0.93 ng/mL (compared to the laboratory animal-based value of 130 ng/mL used in 2017) resulted in a decrease in the noncancer guidance value from 35 to 0.24 ng/L. Currently available serum PFOA data indicate that at drinking water concentrations at or below ~1 ng/L, drinking water would not be a major source of PFOA exposure compared to non-water sources.

Keywords: PFAS, breastmilk, breastfeeding, infants, exposure model, toxicokinetic model, bioaccumulation

INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS) are a class of fluorinated organic compounds with numerous past and present commercial and industrial uses. Many PFAS are of concern to public health due to their ubiquity, persistence, solubility, and capacity to bioaccumulate in humans. These attributes pose a challenge to the development of health-based guidance values (HBGVs) for drinking water. Following the U.S. Environmental Protection Agency (EPA)'s 2016 issuance of lifetime Health Advisories for PFOA and PFOS[1], the Minnesota Department of Health (MDH) carried out a reassessment of its own HBGVs for these chemicals. Because PFOA and PFOS are bioaccumulative, an individual's serum concentration can exceed the concentration of the exposure medium, such as drinking water, and an individual's current serum levels are impacted by years of past exposure. Available research at the time of the reassessment demonstrated placental transfer of PFAS from mother to infant[2-5] and partitioning of PFAS into breastmilk[5-8]. These two routes of exposure suggested that infants, particularly breastfed infants, were a potentially highly exposed subpopulation. This indicated a need for a new approach to deriving guidance values that would incorporate both bioaccumulation and maternal transfer.

MDH addressed this need by developing a toxicokinetic (TK) model to simulate daily serum concentrations of PFAS beginning at birth over a lifetime of daily intake and elimination of bioaccumulative PFAS[9]. The TK model was instrumental in the development of MDH's 2018 HBGVs for perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), and perfluorohexane sulfonic acid (PFHxS)[10-12]. For each of these chemicals, the model results indicated that breastfed infants had serum PFAS levels that were markedly higher than those of formula-fed infants, as well as those of older children or adults consuming contaminated water. The model results further indicated that it took several years for breastfed infants' serum PFAS levels to decline to levels comparable to those of formula-fed infants. This is consistent with empirical measurements of bioaccumulative PFAS in breastfed infants' sera[13,14]. MDH set the HBGVs for drinking water at levels that were protective of exclusively breastfed infants. The term "exclusively breastfed" means that breastmilk, not formula, is the sole source of milk[15]; "exclusively breastfed" does not mean breastmilk is the sole source of all nourishment.

PFAS is a very active area of scientific research; this necessitates continued attention to current research and regular re-evaluations of HBGVs when new, impactful data become available. The HBGVs for PFOA and PFOS were updated in 2024[16,17]. The ensuing review process presented an opportunity and need for a revised version of the model that would more accurately reflect the intake and elimination of PFAS as it is currently understood. The toxicokinetic model developed in 2017 was therefore improved and updated to reflect current scientific knowledge and understanding. These revisions included both operational changes to the model's calculations and chemical-specific updates reflecting new research. Here, we present the revised and updated model and demonstrate its application to the development of a revised HBGV for PFOA.

MATERIALS AND METHODS

Model revisions

MDH's original TK model was developed as a Microsoft Excel spreadsheet to maximize accessibility, transparency, and customizability[9]. As a single-compartment model operating under first-order kinetics, the governing equations are relatively simple. To ensure the model included the full effects of maternal transfer, the mother was assumed to have consumed contaminated water long enough to have reached a steady-state serum PFAS level. The infant's serum PFAS concentration at birth was then calculated using a placental transfer factor applied to the maternal steady-state serum concentration. On subsequent days, the infant's serum concentration was calculated from the previous day's serum concentration and the current

day's intake, with a decay constant applied, as shown in Equation 1. This model can be configured to simulate PFAS intake from breastfeeding or from formula feeding (or, with some modifications by the user, both simultaneously.) For breastfeeding intake, daily PFAS concentrations in breastmilk were calculated from the daily maternal serum concentration using a breastmilk transfer factor. For intakes from formula feeding, the concentration of PFAS in formula was based on the PFAS drinking water concentration set by the user.

Revisions to the model consisted of (1) improvements that relate to the model's fidelity to available data, including better tracking of the movement of chemical mass during intake, elimination, childbirth, and breastfeeding; (2) updates of chemical-specific model parameter values; and (3) enhancements that improve usability.

Model improvements

MDH's original TK model[9] was modified to more accurately account for the movement of chemical mass and to better reflect real-world conditions.

Maternal loss from placental transfer

The infant serum concentration at delivery is calculated by multiplying the maternal steady-state serum concentration by a placental transfer factor. The corresponding chemical mass, calculated as the product of the infant's serum concentration at delivery, the newborn's body weight, and the volume of distribution (V_d), represents the mass of chemical in the newborn that is lost from the mother. To better account for the maternal transfer and loss of chemical during gestation, the model was modified to subtract this transferred mass from the mother's body burden on the first day of the simulation period.

Milk intake phase-in and smoothing

Following delivery, a mother's lactation rate takes time to ramp up to a stable value[18]. In recognition of this, milk consumption [Table 1] is phased in rather than abruptly started on the day of delivery. The updated model permits the user to enter percentage values to be applied on the first four days of the model's simulation period. Milk volume increases in an approximately linear trend from 36 to 96 h postpartum, and then levels off[18]. Using the data from Neville *et al.* and considering the mean plus two standard deviations to be a surrogate for the 95th percentile breastmilk intake rate, we calculated appropriate percentage values that reflected the available data[18] [Table 1].

Breastmilk intake rates were further refined by smoothing out the abrupt changes in intake that occur when applying intake rates for four time periods between birth and one year of age. As was done with other parameters, the intake rate for each interval was assigned to the midpoint of the interval, and intake rates for all other days were calculated using linear interpolation.

Mass balance

In the original model, each day's infant chemical intake was converted to a concentration using the current day's body weight and volume of distribution, while the previous day's serum concentration was carried over directly:

$$\text{Serum Conc.}\left(\frac{\text{mg}}{\text{L}}\right) = \left[\text{Prev. day Serum Conc.}\left(\frac{\text{mg}}{\text{L}}\right) + \frac{\text{Today's Intake (mg)}}{V_d\left(\frac{\text{L}}{\text{kg}}\right) \times \text{BW(kg)}}\right] \times e^{-k} \quad (1)$$

Table 1. A comparison of exposure and toxicokinetic parameters between the 2018 guidance and the present (2024) revision

Parameter	2018 guidance[9]	2024 guidance (RME scenario)	Source of 2024 value
Water intake rate (mL/kg/day) Upper percentile values	Age:Value < 1 month: 238 1 to < 3 month: 285 3 to < 6 month: 173 6 to < 12 month: 129 1 to < 2 year: 75 2 to < 3 year: 62 3 to < 6 year: 52 6 to < 11 year: 47 11 to < 16 year: 35 16 to < 18 year: 30 18 to < 21 year: 36 > 21 year: 42 Lactating woman: 55	Age:Value < 1 month: 240 1 to < 3 month: 290 3 to < 6 month: 186 6 to < 12 month: 151 1 to < 2 year: 119 2 to < 3 year: 67 3 to < 6 year: 45 6 to < 11 year: 41 11 to < 16 year: 31 16 to < 21 year: 31 21 to < 30 year: 47 31 to < 40 year: 44 40 to < 50 year: 43 50 to < 60 year: 42 Lactating woman: 47	Values for consumers only. EPA EFH, 2019 update[20]
Breastmilk intake rate (mL/kg per day)	Age:Value < 1 month: 220 1 to < 3 month: 190 3 to < 6 month: 150 6 to < 12 month: 130	Age:Value < 1 month: 220 1 to < 3 month: 190 3 to < 6 month: 150 6 to < 12 month: 130	EPA EFH, 2011[19] [no change from 2017]
Breastmilk phase-in (percentage of 0-1 month intake rate)	N/A	Day 1: 0% Day 2: 13% Day 3: 26% Day 4: 76%	Derived from Neville *et al.* (1991)[18]
Body weight (kg)	Age:Value < 1 month: 3.6 1 to < 3 month: 3.7 3 to < 6 month: 6.8 6 to < 12 month: 8.9 1 to < 2 year: 11.9 2 to < 3 year: 14.7 3 to < 6 year: 19.2 6 to < 11 year: 29.9 11 to < 16 year: 56.5 16 to < 18 year: 62.8 18 to < 21 year: 78.3 > 21 year: 73.6 Lactating woman: 65.2	Age:Value < 1 month: 3.6 1 to < 3 month: 3.8 3 to < 6 month: 7 6 to < 12 month: 8.9 1 to < 2 year: 10.5 2 to < 3 year: 13.4 3 to < 6 year: 18.6 6 to < 11 year: 30.7 11 to < 16 year: 56.8 16 to < 21 year: 71.4 21 to < 30 year: 72.5 31 to < 40 year: 74.5 40 to < 50 year: 78.5 50 to < 60 year: 80.7 Lactating woman: 65.1	Derived from consumer-only intakes in EPA EFH, 2019 update[20] Body weight was calculated by dividing intake (mL/day) by weight-normalized intake (mL/kg/day)

Body weight (kg) (breastfed infant)	Age:Value < 1 month: 4.3 1 to 3 month: 5.2 3 to 6 month: 6.7 6 to 12 month: 7.7	Age:Value < 1 month: 4.3 1 to 3 month: 5.2 3 to 6 month: 6.7 6 to 12 month: 7.7	Derived from intakes in EPA EFH, 2011[19]. [no change from 2017] Body weight was calculated by dividing breastmilk intake (mL/day) by weight-normalized intake (mL/kg/day)
Half-life ($t_{½}$) (days)	**840**	**902**	Central tendency value from Li *et al.* (2022)[21]
Placental (infant:maternal) transfer	**0.87**	**0.83**	Central tendency value; mean of 25 studies [Supplementary Table 1]
Breastmilk (milk:maternal) transfer	**0.052**	**0.068**	95% Upper Confidence Limit on the mean of 7 studies [Supplementary Table 2]. Mean value was 0.046
Volume of Distribution (V_d)	**0.17**	**0.36**	Calculated from clearance rate and half-life; see text
V_d adjustment factors	Age:Value 0 to 1 day: 2.4 1 to 30 days: 2.1 1 to < 3 month: 1.7 3 to < 6 month: 1.6 6 to < 12 month: 1.5 1 to < 3 year: 1.4 3 to < 5 year: 1.1 5 to < 10 year: 1.2 > 10 year: 1.0	N/A	V_d adjustment factors were not used in the 2024 evaluation; see text

Chemical-specific values are indicated in bold. RME: Reasonable Maximum Exposure; EPA: Environmental Protection Agency; EFH: Exposure Factors Handbook; N/A: not applicable.

where BW is body weight (kg), V_d is the volume of distribution (L/kg), and k is a rate constant equal to the natural log of 2 divided by the elimination half-life ($t_{½}$) in days. The previous day's serum concentration was carried over to the next day, resulting in a slight discrepancy when the previous day's concentration was applied to the current day's body weight. To assure mass balance, the calculation was changed to apply the current day's body weight to the previous day's chemical mass, rather than the previous day's concentration. During infancy, the daily change in body weight is enough for this difference to have more than a negligible effect on the serum concentration curve. The following revised equation accounts for the additional amount of dilution of the chemical due to a daily change in body weight:

$$\text{Serum Conc.}\left(\frac{\text{mg}}{\text{L}}\right) = \left[\frac{\text{Previous day's mass (mg)} + \text{Today's Intake(mg)}}{\text{V}_\text{d}\left(\frac{\text{L}}{\text{kg}}\right) \times \text{BW(kg)}}\right] \times e^{-k} \quad (2)$$

Body weight transition

In the original (2017) model, body weights were calculated from data published in the EPA Exposure Factors Handbook[19,20] by dividing the fluid intake rate (mL/day) by the weight-normalized intake rate (mL/kg/day). Separate body weights were calculated for formula-fed and breastfed infants from birth to 1 year

of age[9] [Table 1]. In the breastfed scenario, the infant transitions from breastfeeding to drinking water at 1 year of age, and the model transitioned from the body weights based on nursing infants to those calculated from water intake, resulting in an abrupt body weight increase of 0.8 kg (9%) in the breastfed infant scenario at 1 year of age. To address this, in the 2024 model, the gradual upward trend of breastfed infant body weights at 1 year of age was extended linearly for six months, at which point it matched the water intake-based body weight value for the 1- to 2-year-old age group (10.5 kg).

Parameter updates

Changes to model parameters are summarized in Table 1. Updated values included water intake rates and chemical-specific toxicokinetic parameters (e.g., half-life, placental transfer, breastmilk transfer). MDH utilizes a Reasonable Maximum Exposure (RME) scenario in the development of HBGVs, which consists of selecting a mix of upper percentile values (e.g., fluid intake rate) and central tendency values (e.g., half-life). This is consistent with our program mission to develop drinking water guidance values that are protective of sensitive and/or highly exposed population groups. For more information, see the original model publication[9].

Water intake rates

Water intake rates were updated to reflect the most recent revision of the EPA Exposure Factors Handbook[20], which provided revised intake values for all ages, including intake rates specific to formula-fed infants and lactating women, and some changes to the age groupings for individuals over 16 years of age [Table 1]. The 95th percentile intake rates were used to ensure that the resulting guidance values would be protective of individuals with high water intake. Breastmilk intakes, unchanged from the previous version of the model, were sourced from the most current breastmilk consumption data from the EPA Exposure Factors Handbook[19]. Using these data, body weights for each age group and population were calculated by dividing intake (mL/day) by weight-normalized intake (mL/kg/day).

A literature search for published studies regarding PFOA serum half-life, placental transfer, and breastmilk transfer was conducted, incorporating publications up to July 31, 2023. This cutoff date was necessary for MDH to develop revised guidance values in the second half of 2023 for public release in early 2024. A search for studies between August 2023 and January 2024 found no additional studies that would affect the selected parameter values. Empirical data published since the development of the original 2017 model were incorporated into the calculation and selection of central tendency chemical-specific parameter values.

Human half-life

A mean PFOA serum elimination half-life value of 902 days (2.47 years) from Li *et al.* was selected as a central tendency value for humans[21]. This value is based on serial blood samples collected over the course of 4 years in a community in Ronneby, Sweden (n = 114, age range 4 to 84 years) that was exposed to contaminated drinking water.

Placental transfer

Studies of placental transfer published since 2017 were incorporated into calculating a central tendency value for the ratio of cord to maternal serum concentrations. An overall mean of 0.83 was calculated from 25 studies, with mean values in individual studies ranging from 0.32[22] to 1.44[23]. This value is similar to central tendency values of 0.82 and 0.79 reported in review papers by Appel *et al.*[24] and Pizzurro *et al.*[25]. For more information, refer to Supplementary Table 1.

Breastmilk transfer

Study data for calculating the breastmilk transfer factor are limited and few additional studies containing both maternal serum and corresponding breastmilk concentrations have been published since 2017. This is a key parameter for estimating exposure in breastfed infants and remains a critical data gap. The overall mean of mean values from seven studies, 0.046, was calculated and initially used in validation testing [Supplementary Table 2]. However, the use of this overall mean value (0.046) was found to consistently underestimate measured serum concentrations. To address this, two other options were considered during model validation: (1) a mean of the four studies in which maternal serum and milk samples were collected within a similar timeframe of each other (0.056); and (2) a one-tailed 95 percent upper confidence limit (95UCL) on the mean of the seven studies (0.068). For more information, see the validation section below.

Volume of distribution

MDH's original (2017) model used a volume of distribution (V_d) of 0.17 L/kg from US EPA[26], based on Thompson *et al.*, and a half-life of 2.3 years[27]. This value was consistent with the volume of extracellular water in the body. To account for higher water content in the body during early life stages, MDH applied extracellular water V_d adjustment factors (V_dAFs) from birth to 10 years of age[28]. A more recent evaluation suggests that this V_d is too small. In its Public Health Goal for PFOA, California EPA (2024) calculated a clearance rate (CR) for PFOA of 0.00028 L/kg/day based on a regression analysis of reported serum levels and estimated exposures in communities with contaminated drinking water[29]. This regression-based approach is consistent with that of Johanson *et al.*[30]. Assuming steady-state conditions, the CR and V_d are related (Equation 3):

$$CR\left(\frac{L}{kg\ day}\right) = V_d\left(\frac{L}{kg}\right) \times \frac{\ln(2)}{\frac{t_1}{2}(day)} \quad (3)$$

Applying the 2024 California EPA CR[29] and the mean half-life of 902 days from Li *et al.*, Equation 3 yields a V_d of 0.36 L/kg[21]. This value exceeds the volume of extracellular water in the body, suggesting that extracellular water V_dAFs were no longer appropriate. Removal of the adjustment factors was also supported by validation testing in which the inclusion of the V_dAFs resulted in an underestimation of infant serum concentrations. The functionality of V_dAFs remains in the model, but MDH sets the values to 1 when applying the model to PFOA.

Model enhancements

The model revision also included some enhancements that improve usability. The model spreadsheet now includes a matrix of cells that plot a threshold line on the main chart of model results. This threshold line allows the comparison of model results to any value of interest, such as a reference serum concentration with a Relative Source Contribution (RSC) value applied. The main chart has also been updated with a title string linked to a table cell, allowing easier editing of the chart title. Additional charts have also been added to the model spreadsheet, showing the values of key model parameters to assist users in verifying and visualizing any modifications.

RESULTS AND DISCUSSION

Model validation/evaluation

Using the revised model and updated exposure factors and toxicokinetic parameters, we compared modeled serum concentrations to empirical data in mothers and their breastfed infants to ensure that predicted serum levels were consistent and that the overall approach was protective of these sensitive groups. The

initial validation used mean values of 902 days, 0.83 and 0.046 for half-life, placental transfer and breastmilk transfer, respectively. Upper percentile values were used for breastmilk intake. As in the 2017 review of PFOA[9], we compared model outputs to measured data from a cohort of exposed mothers and infants in Germany by Fromme *et al.*[6]. In this study, 37 of the 50 subjects consumed only breastmilk, 6 predominantly consumed breastmilk, 6 partially consumed breastmilk, and 1 consumed no breastmilk. The model results and measured data from Fromme *et al.* were compared via a population-based approach and an individual-based approach.

Population-based approach

Mean or 95th percentile maternal PFOA serum concentrations at delivery[6] were entered into the appropriate cell of the model. Modeled infant and maternal serum concentrations at 6 months of age were then compared to their respective measured values [Table 2].

The use of mean values for all three chemical-specific parameters resulted in an underestimate of infant serum levels. The breastmilk transfer factor has been identified as having a significant impact on predicted infant serum levels[31]. The available dataset for breastmilk transfer is quite limited and the timing of collecting serum and a corresponding breastmilk sample was variable. To address the uncertainty in the mean value, we considered alternatives to the overall mean breastmilk transfer factor of 0.046 (mean of seven studies). One alternative was to calculate a mean value using only four of the seven studies - those in which maternal serum and milk samples were taken within a similar timeframe. The transfer factor using only those four studies is 0.056. The model results indicate a closer match to infant serum at 6 months, and a less close match to maternal serum at 6 months, compared to the seven-study mean value [Table 2].

Another alternative was to calculate a 95% upper confidence limit (95UCL) on the mean of the seven available studies. The 95UCL on the mean represents an upper limit, with 95% certainty, on the "true" mean value. For more information, refer to the Supplementary Materials. The 95UCL on the mean was calculated to be 0.068. For the population-based approach, infant serum concentrations calculated using this value were a closer match to the measured data compared to the other two alternatives, while maternal serum concentrations were slightly lower than those modeled using the seven- or four-study mean transfer factors [Table 2].

Individual approach

Serum levels for 14 infants at 6 months of age were digitized from Fromme *et al.*[6] using the online WebPlotDigitizer tool[32]. For each individual infant, the serum PFOA concentration at birth was entered into the appropriate cell in the model, and the modeled infant serum concentration after 6 months of breastfeeding was compared to the measured data. The mean of the modeled infant serum PFOA concentrations using the three different breastmilk transfer factors (seven-study mean, four-study mean, and 95UCL on the mean) was 65%, 75%, and 87% of the mean of the measured values, respectively.

Additional validation of the model was conducted using data from Verner *et al.*, which provided a ratio of infant serum PFOA level at 6 months to the mother's serum PFOA level at delivery[31]; and Thomsen *et al.*, who reported a maternal serum depuration rate for PFOA of 7.7% per month, or a decrease of 46.1% over 180 days[33]. All three breastmilk transfer values yielded a ratio that was lower than the data from Verner *et al.*[31]; the 95UCL on the mean provided the closest result (3.6 *vs.* 4). The 95UCL approach also yielded the closest match to the data from Thomsen et al. (48% *vs.* 46.1%)[33] [Table 3].

Table 2. Modeled *vs.* measured serum PFOA concentrations using various breastmilk transfer factors (seven-study mean, four-study mean, and 95UCL on the mean of seven studies)

Maternal serum level @ Delivery (model input)	Model prediction *vs.* measured maternal serum @6 months			Model prediction *vs.* measured infant serum @6 months		
	Mean (7 studies) (0.046)	Mean (4 studies) (0.056)	95UCL (7 studies) (0.068)	Mean (7 studies) (0.046)	Mean (4 studies) (0.056)	95UCL (7 studies) (0.068)
Mean	83%	77%	70%	78%	90%	104%
95th percentile	82%	76%	69%	73%	84%	96%

PFOA: Perfluorooctanoate.

Table 3. Comparison of (1) modeled and measured ratios of infant serum at 6 months to maternal serum at delivery; (2) modeled and measured decrease in maternal serum levels after six months of breastfeeding

Value used for breastmilk transfer	(1) Ratio of Infant Serum @6 months to maternal serum at delivery Median value from Verner *et al.* (2016)[31] is 4	(2) Percent decrease in maternal serum levels from delivery to 6 months of breastfeeding Value from Thomsen *et al.* (2010)[33] is 46.1% based on linear regression (n = 9)
Seven-study mean (0.046)	2.6	39%
Four-study mean (0.056)	3.1	43%
95UCL on mean (0.068)	3.6	48%

The breastmilk transfer factor has a significant impact on predicted infant serum levels[31]. The 95UCL on the mean was chosen as an appropriate central tendency value because it incorporated all available published studies, addressed uncertainty by utilizing an Upper Confidence Limit, and provided the overall best fit to empirical data, especially for infants, who are an especially vulnerable subpopulation for exposure to PFOA.

Derivation of Noncancer PFOA guidance

As in our earlier assessment of PFOA[9], serum concentration was identified as the best dose metric for assessing the health effects of PFOA. The reference serum concentration developed by MDH in the 2017 assessment, 130 ng/mL (equivalent to µg/L), was based on laboratory animal studies. In 2024, MDH relied upon epidemiology studies to determine a reference serum concentration of 0.93 ng/mL, based on a point of departure (POD) of 2.8 ng/mL (California EPA, 2024)[29] associated with decreased haemophilus influenzae Type B antibodies in infants (Abraham, 2020)[34] and an uncertainty factor of 3 for database uncertainty. The reference serum concentration of 0.93 ng/mL was used to derive a noncancer HBGV.

MDH's model simulates serum concentrations resulting from the ingestion of contaminated drinking water. To ensure that exposures from all sources do not result in serum concentrations that exceed the reference serum concentration for noncancer effects, an RSC factor was incorporated into the water guidance value calculation. MDH uses the EPA Exposure Decision Tree[35], which recommends a 20% floor and an 80% ceiling, as a guide to determining RSC values. In the case of PFOA, serum concentration was used as the exposure metric when determining the RSC value. Biomonitoring results from the most recent National Center for Environmental Health (NCEH) report[36] were used to represent non-water exposures for older children and adults. Both the geometric mean (1.42 ng/mL) and the 95th percentile (3.77 ng/mL) PFOA serum concentration from the NCEH report exceed the reference serum concentration of 0.93 ng/mL, indicating that a broad swath of the population have experienced exposure at levels at or above the reference

serum concentration. Infants and young children were not included in the CDC National Report, but the available data on placental transfer indicate that newborn infants would have PFOA body burdens similar to those of their mothers following months of breastfeeding. Studies of exclusively breastfed infants[6,13] found serum PFOA levels approximately 3-fold higher than their mothers. The available data therefore suggest that an RSC value equal to the floor value of 20% is appropriate for all life stages.

The revised model was used to determine a noncancer HBGV for PFOA using a maximum allowable serum concentration of 0.19 ng/mL, i.e., the reference serum concentration multiplied by the RSC (0.93 ng/mL × 0.2). As was done in MDH's 2017 review[9], the model was applied to two scenarios: (1) an infant consuming formula prepared with contaminated water, and consuming contaminated water for a lifetime; and (2) an infant breastfed for 12 months, followed by a lifetime of consuming contaminated water. Both of these model applications were RME scenarios using a mixture of central tendency and upper percentile model parameters. Under scenario 1, a drinking water concentration of 1 ng/L (0.001 μg/L) maintained a serum PFOA concentration below the target level of 0.19 ng/mL throughout the simulated lifetime [Figure 1]. Under scenario 2, a drinking water concentration of 0.24 ng/L (0.00024 μg/L), approximately four times lower than scenario 1, was required to maintain a serum PFOA concentration below 0.19 ng/mL throughout the simulated lifetime [Figure 2]. Thus, the noncancer HBGV for PFOA was set at 0.24 ng/L to ensure adequate protection of the most highly exposed population, breastfed infants.

For both model scenarios, the combined effect of model updates and chemical-specific parameter updates resulted in lower modeled serum PFOA concentrations compared to the 2017 model results using the same drinking water concentration (dashed blue lines in Figures 1 and 2). However, the significantly lower epidemiologic-based reference serum concentration of 0.93 ng/mL (compared to the laboratory animal-based value of 130 ng/mL used in 2017) was the major factor in lowering the noncancer HBGV from 35 to 0.24 ng/L.

MDH also develops separate HBGVs based on cancer risk when relevant data are available[37]. In addition to the noncancer guidance value, MDH also developed a cancer HBGV of 0.0079 ng/L for PFOA[16]. The TK model was not used to derive the cancer HBGV, which is based on an incremental lifetime cancer risk level of 1 in 100,000.

Impact of model revisions

The 57% reduction in modeled peak serum concentrations between the 2017 and 2024 model runs is the net effect of all model improvements and parameter updates [Tables 4 and 5]. The relative impacts of these changes were compared by running the RME breastfed infant scenario using the original and revised models with an identical set of chemical parameters and a drinking water concentration set to the noncancer HBGV of 0.24 ng/L. The non-chemical-specific model improvements [mass balance (including maternal loss to the infant on Day 1), body weight updates, milk intakes, and water intakes] were then added individually to the model [Table 4]. The improvements in the conservation of mass were by far the most influential changes, with the other non-chemical-specific changes having a negligible effect on the peak serum concentration.

The relative effects of the chemical-specific model parameters in the revised model were compared by implementing the PFOA parameter changes individually, using the set of 2017 parameters for PFOA as a baseline [Table 5]. Changes to the V_d parameter had the largest effect on the peak serum concentration, followed by the milk:maternal serum ratio and the $t_{½}$.

Table 4. Changes in modeled peak serum concentration for breastfed infants attributable to non-chemical-related model updates and improvements

Model update	Peak serum concentration* relative to baseline (ng/mL)
2017 Model (baseline)	0.438 (n/a)
Mass-based calculation	0.342 (-22%)
Mass-based and maternal loss to newborn	0.313 (-28%)
Milk Intake smoothing and phase-in	0.439 (+0.38%)
Milk Intake smoothing alone	0.441 (+0.62%)
Milk Intake phase-in alone	0.437 (-0.24%)
Body weight and water intake rate updates (including BW transition for breastfed infants at 1 year old)	0.438 (+0.056%)
All "non-chemical-specific" updates combined	0.318 (-27%)

*Using a drinking water concentration of 0.24 ng/L.

Table 5. Changes in modeled peak serum concentration for breastfed infants attributable to chemical parameter changes

Model parameter update	Peak serum concentration* relative to baseline, ng/mL
Revised model with 2017 chemical parameters (baseline)	0.318 [Table 4]
Half-life	0.344 (+8%)
V_d and V_dAF	0.148 (-54%)
Infant:maternal serum ratio	0.318 (-0.10%)
Milk:maternal serum ratio	0.353 (+11%)
All updates combined	0.187 (-41%)**

*Using a drinking water concentration of 0.24 ng/L; **-41% is the reduction attributable to changes in chemical parameter values. The overall change relative to the 2017 baseline value of 0.438 ng/mL using the 2017 model [Table 4] is -57%.

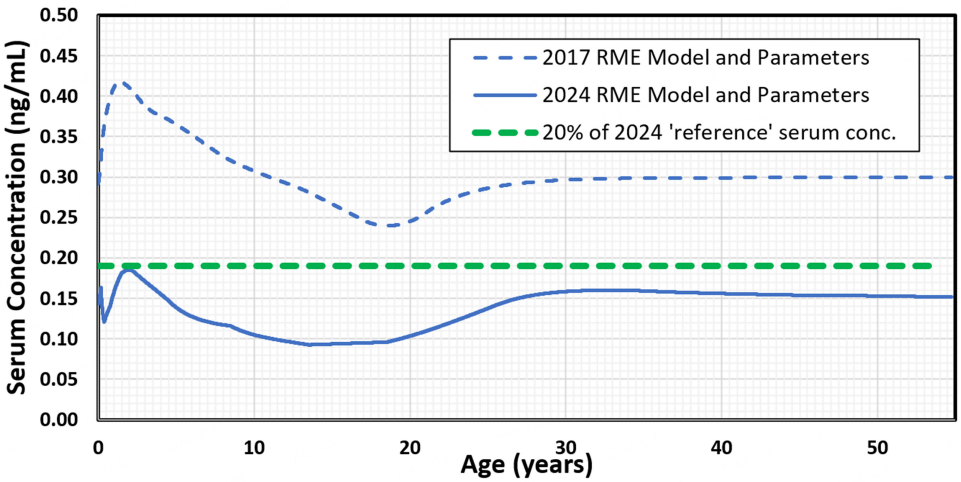

Figure 1. Comparison of original (2017) and revised (2024) model outputs for formula-fed infants at a drinking water PFOA concentration of 1 ng/L. RME: Reasonable Maximum Exposure; PFOA: perfluorooctanoate.

CONCLUSIONS

The original MDH toxicokinetic model was a simple but demonstrably fit-for-purpose approach to HBGV development for bioaccumulative PFAS[9]. The revised model uses the same principles as the original while improving the model's fidelity to real-world conditions, most notably by improving the way the model accounts for chemical mass. It also makes use of updated chemical-specific parameters, several of which

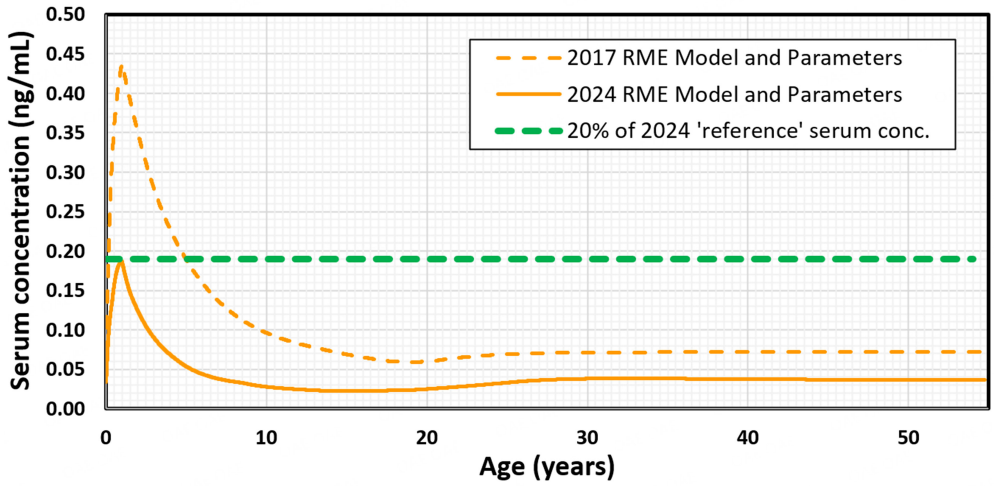

Figure 2. Comparison of original (2017) and revised (2024) model outputs for breastfed infants at a drinking water PFOA concentration of 0.24 ng/L. RME: Reasonable Maximum Exposure; PFOA: perfluorooctanoate.

significantly influenced the final noncancer HBGV. This underscores the importance of having up-to-date values for these parameters, especially those related to infant exposures.

As was the case in the previous evaluation of PFOA, the breastfed infant is the key exposed population for deriving the water guidance value. Validation of the model against the limited empirical dataset showed generally good agreement using the selected parameters. However, several notable gaps in our understanding remain. The results of seven studies, four of which were more than ten years old, were used in selecting a value for the breast milk:maternal serum ratio, but additional research would reduce uncertainty about this key parameter. The potential for the half-life and clearance rate of PFOA to vary during infancy, childhood, adolescence, and adulthood has not been well studied and could not be considered in this evaluation. Another data gap is the potential presence of PFOA in powdered infant formula, an exposure not considered in the present evaluation. Few studies are available on this subject[38,39], and MDH recently conducted an analysis of the presence of certain PFAS in infant formula; a publication is in process[40]. At present, MDH continues to promote breastfeeding as a healthy practice for infants and their mothers, stressing the known benefits of breastfeeding to infant health and development. At the same time, MDH recommends that women who plan to become pregnant follow guidelines to reduce exposure[41]. For women who plan to have children, reduction of exposure to bioaccumulative PFAS must occur long before pregnancy. The possibility exists for highly exposed individuals to refrain from breastfeeding in favor of formula feeding with non-contaminated water, or even to pump and dispose of breastmilk for a period after delivery; but the appropriateness of these measures is best left to the mother and her medical care provider.

MDH has recently completed a wide-ranging sampling effort measuring PFAS in nearly every community water system in the state. Results of the monitoring, including hazard indices for the combined effect of the six PFAS with MDH HBGVs, are presented in a publicly available mapping tool[42]. The noncancer HBGV (0.24 ng/L) for PFOA is equal to or below the common laboratory reporting limits used in this study; therefore, any reported detection of PFOA is a potential concern, and it is recommended that actions be taken to provide drinking water with PFAS levels that are as low as possible[42]. Additional data from water systems around the U.S. collected under the Unregulated Contaminant Monitoring Rule 5 (UCMR5) are forthcoming[43], and may provide additional information to characterize risk.

The general trend of HBGVs for PFOA, PFOS, and other PFAS also raises the question of the relative importance of exposures derived from water and those derived from other sources (e.g., consumer products, diet, *etc.*) A recent analysis considered this question using NHANES serum concentrations as an indicator of non-water PFOA exposure[44]. The analysis found that at a water concentration of 1 ng/L, water contributed 4% and 9.7% of total PFOA exposure for mean and 95th percentile water intake rates, respectively. Drinking water concentrations of PFOA below 0.1 ng/L showed negligible contribution to total PFOA exposure. This suggests that reductions in PFOA below 1 ng/L will have limited impact on serum levels in the general population in the absence of a coordinated effort to reduce non-water exposures to PFOA (and by extension, other bioaccumulative PFAS and their precursors) from food, consumer products, and other sources.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the conception and design of the revised model and model parameters: Greene CW, Bogdan AR, Goeden HM

Availability of data and materials

The revised toxicokinetic model is available as an Excel file; to obtain a copy, contact the authors.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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