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Biomarker-Based Calibration of Retrospective Exposure Predictions of Perfluorooctanoic Acid

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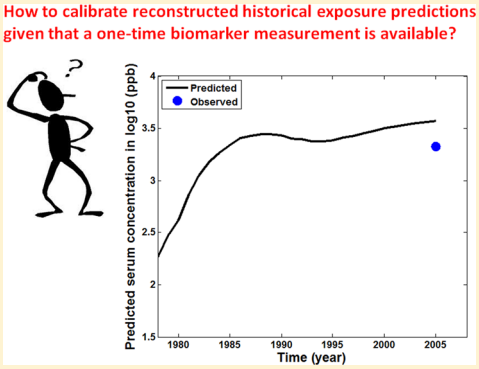
Supporting Information

ABSTRACT: Estimated historical exposures and serum concentrations of perfluorooctanoic acid (PFOA) have been extensively used in epidemiologic studies that examined associations between PFOA exposures and adverse health outcomes among residents in highly exposed areas in the Mid-Ohio Valley. Using measured serum PFOA levels in 2005−2006, we applied two calibration methods to these retrospective exposure predictions: (1) multiplicative calibration and (2) Bayesian pharmacokinetic calibration with larger adjustments to more recent exposure estimates and smaller adjustments to exposure estimates for years farther in the past. We conducted simulation studies of various hypothetical exposure scenarios and compared hypothetical true historical intake rates with estimates based on mis-specified baseline exposure and pharmacokinetic models to find the method with the least bias. The Bayesian method outperformed the multiplicative method if a change to bottled water consumption was not reported or if the half-life of PFOA was mis-specified. On the other hand, the multiplicative method outperformed the Bayesian method if actual tap water consumption rates were systematically overestimated. If tap water consumption rates gradually decreased over time because of substitution with bottled water or other liquids, neither method clearly outperformed another. Calibration of retrospective exposure estimates using recently collected biomarkers may help reduce uncertainties in environmental epidemiologic studies.



1. INTRODUCTION

Perfluorooctanoic acid (PFOA) is one of the perfluorinated compounds commonly used as a surfactant in the manufacture of fluoropolymers. PFOA is usually not detected in the products of fluoropolymers.[1] However, the occurrence of PFOA is ubiquitous, having been detected worldwide in the environmental media including air,[2] soil,[3,4] house dust,[5] drinking water,[6] and biota[7] as well as human serum.[8−11] Primary exposure routes to general populations are not well-known, but the median serum PFOA level was about 4 μg/L in most U.S. populations from 2003 to 2008.[12] PFOA exposure is a significant concern to epidemiologists, toxicologists, and regulators due to potential adverse health effects to humans. Although PFOA has been shown to have toxic effects in various systems in animal studies,[13−15] the health effects in humans are still unresolved due to a limited number of epidemiological studies (many of which are cross-sectional) and inconsistent findings.[16]

People living or working in the Mid-Ohio Valley have been exposed to PFOA through drinking water ingestion or air inhalation released from the DuPont Washington Works Facility in Parkersburg, West Virginia since the early 1950s.[6] We recently estimated historical PFOA exposures and serum concentrations for participants in the C8 Health Project, a cross-sectional study that collected residential, occupational, and medical histories and serum samples from 2005 to 2006.[10,17] We linked estimated annual average PFOA concentrations in ambient air and drinking water from Shin et al.[18] fate and transport models to each individual's residential history and exposure information (i.e., tap water consumption rates and drinking water sources). Then, a one-compartment pharmacokinetic model was applied to predict year-by-year PFOA serum concentrations for each individual.[17] Among all participants (N = 43 449), the Spearman's rank correlation coefficient for predicted versus observed serum concentrations in 2005−2006 was 0.68. Median predicted and observed serum concentrations in 2005−2006 were 13.7 and 23.5 ppb, respectively.[18] Despite limited individual information on historical drinking water consumption rates and drinking

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water sources (i.e., public water, private water, bottled water), comparison of a one-time observed concentration with the prediction in the corresponding year suggests that the predicted serum concentrations from our integrated exposure and pharmacokinetic model are reasonable for use in epidemiologic studies.

A series of epidemiologic studies have been conducted to determine a probable link between PFOA exposures and human health outcomes, based on our retrospective serum concentration estimation.[19−26] However, because the exposures were reconstructed based on limited data, parameters, and imperfect models, it is likely that there is some degree of exposure misclassification. For example, tap water consumption rates were self-reported, may not reflect historical tap water consumption rates, and are only available for part of the participants. Our estimates of historical air and water PFOA concentrations depend on fate and transport modeling with uncertain and variable annual emissions rates, meteorological conditions, and physicochemical properties. Moreover, the elimination rate for PFOA may not be accurately estimated and likely varies among our study participants over the course of their lifetime.

The one-time serum measurements collected during 2005−2006 allow for validation of the integrated exposure and pharmacokinetic model but also raise the question of whether the limited cross-sectional serum data should be used to calibrate the retrospective exposure predictions.[27−29] This study focuses on the calibration of retrospective exposure predictions using one recent biomarker measurement per person, applying two different calibration methods as a sensitivity analysis. In addition, simulation studies were conducted to compare hypothetical true historical intake rates with estimates based on mis-specified baseline exposure and pharmacokinetic models. The objectives of this study are (1) to calibrate retrospective PFOA serum concentration predictions for the participants in the C8 Health Project using two different calibration methods with single biomarker measurements and (2) to determine the individual-level calibration method with the least bias under several different scenarios using simulations.

2. MATERIALS AND METHODS

2.1. Calibration Methods. Model predictions or parameters can be calibrated in many ways. For example, multiple (linear) regression methods have been used to optimize exposure model parameters for a subsample of subjects with measured exposures, and then model-based predictions are extrapolated to larger groups of subjects with no measured exposures.[27,28,30] By way of another example, we used multiplicative calibration to choose the organic carbon partition coefficient (K_{oc}) and water-district correction factors for our fate and transport model predicted water PFOA concentrations in this study area.[18] In yet another example, Bayesian methods including Markov chain Monte Carlo (MCMC) simulation and the Kalman filter are common approaches to calibrating model parameters for predictions in environmental systems.[31−33] However, such group-level calibration models rely on multiple observations per parameter, such as multiple measurements of serum PFOA for each person or groups of people with identical exposure characteristics. In this study, there is only a single biomarker measurement per person, and no two people share the same exposure characteristics due to participant-specific exposure variables including drinking water consumption rates, drinking water sources, and non-water PFOA exposures. Further difficulties are posed by missing data—particularly the lack of self-reported drinking water consumption rates for many study participants. Approximately 50% of participants provided their best estimates of the total number of cups per day.

Instead of group-level calibration, we chose two individual-level calibration methods—multiplicative calibration and Bayesian pharmacokinetic calibration—in an attempt to improve the historical exposure reconstruction and individual-level serum estimates used in epidemiologic studies.[20,21] The first model was selected for its simplicity and identifiability with only one serum measurement per participant. The second model was designed to emphasize the temporal relationship between historical PFOA exposures and 2005−2006 serum PFOA concentrations.

2.1.1. Multiplicative Calibration. For the multiplicative calibration of PFOA serum estimates, we computed the multiplicative scaling factor, ϕ_i, for each participant i by the following equation:

$$\phi_i = \frac{C_{\mathrm{obs},i,t}}{C_{\mathrm{pred},i,t}} \tag{1}$$

where ϕ_i is the calibration coefficient for a participant i, $C_{\mathrm{obs},i,t}$ is the observed serum concentration (μg/L) for a participant i collected at the serum sampling year of t in either 2005 or 2006, and $C_{\mathrm{pred},i,t}$ is the corresponding prediction of the PFOA serum concentration (μg/L) for a participant i at the serum sampling year of t from baseline exposure and pharmacokinetic models. Since we have a one-time observed serum concentration (t = 2005 or 2006), ϕ_i is simply multiplied by prior predicted serum concentrations ($C_{\mathrm{pred},i,t}$) to make new calibrated serum concentration predictions. This approach scales the serum concentration predictions for each participant according to his or her single serum PFOA concentration measurement, while retaining the shape of time versus serum concentration curve generated from the baseline exposure and pharmacokinetic models.

2.1.2. Bayesian Pharmacokinetic Calibration. We also conducted Bayesian optimization of each individual's PFOA intake rate over time. Because a serum half-life of PFOA in humans is about 2−4 years[11,34,35] and some participants' water consumption behaviors were likely changed after they became aware of local water contamination in the early 2000s, PFOA serum measurements during 2005−2006 would mostly reflect exposures experienced 5 years prior to the time of measurement, with recent exposure dominating. Therefore, rather than adjusting the entire history of exposure estimates by some constant fraction (i.e., the multiplicative calibration), our Bayesian method uses time-dependent weights that rely on a pharmacokinetic model, resulting in larger adjustments to more recent exposure estimates and smaller adjustments to more historic exposure estimates. Figure S1 in the Supporting Information shows how the Bayesian calibration method differs from the multiplicative calibration method.

For the Bayesian calibration of the annual PFOA exposure estimates, we used the annual intake from the exposure model as the prior mean and the measured 2005−2006 serum concentration as the updating datum (i.e., likelihood). The model for the likelihood function is a discrete-time single compartment pharmacokinetic model, previously used for PFOA and other contaminants.[17,36,37] We assumed that

likelihood (i.e., serum concentration at the sampling time t, C_t, given a random vector of intake dose) follows a normal distribution:

$$C_t|I \sim N(\sum_{j=1}^{m} w_j I_j, \sigma_\varepsilon^2) \sim N(W'I, \sigma_\varepsilon^2) \quad (2)$$

where C_t is the observed serum concentration at the sampling year t (2005 or 2006), I is the m-length vector of PFOA intake estimates I_j for year j (μg/year) of m years of life from the exposure model, W is the m-length vector of weights w_j (year/L) reflecting the relative contribution of PFOA intake in year j to the measured serum concentration in year t, σ^2_ε is the error variance, and $W'I$ is a vector product of the weight and intake dose. The weights (w_j) derived from the one-compartment pharmacokinetic model are determined by the following function:

$$w_j = \left(\frac{1 - e^{-k}}{k \cdot V}\right) e^{-k(t-j)} \quad (3)$$

where k is the elimination rate constant (about 0.20 year^{-1}) corresponding to a half-life of 3.5 years[11] and V is the age- and gender-specific volume of distribution in liters. Assuming that V is constant over time, the time-dependent distribution of weights from eq 3 is shown in Supporting Information Figure S2. We incorporated prior information on PFOA intake estimates from the exposure model through a multivariate normal prior:

$$I \sim N_m(\mu, \Sigma) \quad (4)$$

where μ is the m-length vector of year-by-year PFOA intake estimates from the baseline exposure model, and $\sum$ is the $m \times m$ covariance matrix describing the prior uncertainty regarding the intake estimates (see below for specification of this matrix).

The posterior distribution of the intake vector (I) given the observed serum concentration (C_t), which is determined from the prior and likelihood, also follows a multivariate normal distribution with the m-length vector of intake, M, and the $m \times m$ covariance matrix, S:

$$I|C_t \sim N_m(M, S) \quad (5)$$

where $M = S'(\sum^{-1}\mu + W \times C_t \times \sigma_\varepsilon^{-2})$ and $S = (\sum^{-1} + W \times W' \times \sigma_\varepsilon^{-2})^{-1}$.

The posterior mean vector, M, expresses the calibrated annual intake estimates for the participant and is used as the expected value for the Bayesian calibration. The posterior covariance matrix, S, expresses the uncertainty of the intake estimates for each year and is only used as part of calculating M. We derived the closed-form solutions of posterior mean vector (M) and covariance matrix (S) rather than using statistical software for Bayesian analysis such as WinBUGS because it took too long (initial WinBUGS runs with the model described in this article required 7 min per participant with 1000 iterations). The closed-form solutions with a multivariate normal prior distribution are derived in the Supporting Information. The weight (W) is larger as it is closer to the serum sampling year. Thus, M is weighted more toward the observed serum concentration. We also rely on a prior estimate of σ_ε^2, assumed here to be the square of 10% of C_t based on quality of assurance data on the intralab coefficient of variation for PFOA,[10] and $\sum$, assumed here to be a matrix with all variances (diagonals) equal to the square of 400% of μ, reflecting a large degree of uncertainty regarding our exposure model. We also choose off-diagonals of the prior covariance to stipulate autocorrelation of uncertainties across years, with a correlation of $0.75^{|i-j|}$ between years i and j (e.g., the correlation between 1999 and 2000 = 0.75 and that between 1999 and 2001 = 0.75^2 = 0.56). This is subjective error, reflecting a large degree of uncertainty regarding our exposure model estimates and a strong belief that if we mis-estimated the exposure to a participant in any one year, then we likely mis-estimated in the same direction for nearby years. The sensitivity of two parameters (σ_ε^2 and $\sum$) on model predictions is shown in Figure S3. In some cases, M includes one or more negative values; we substituted zeros for these values in order to ensure that all annual intake estimates were non-negative. The fraction of negative values of M varies with time and is shown in Figure S4.

2.2. Simulation Studies. We conducted simulation studies to examine how each calibration method performs under particular hypothetical "true" exposure scenarios versus our exposure model. First, we selected one typical participant who had a drinking water source from a highly contaminated water district at the time of serum sample (e.g., a 50 year old male) and generated serum concentrations for this participant using predicted intake rates from the baseline exposure model. We call these intake rates the "guess" intake vector. Second, we defined the "true" intake vector for any of the four hypothesized exposure scenarios (see below), assuming that different scenarios may have led to exposure mis-specification in our guess intake vector. Third, we generated serum concentrations according to that true intake vector, using our pharmacokinetic model. Fourth, we generated multiple simulated serum concentrations (n = 1000) by multiplying the actual measured concentration of the selected participant in 2005−2006 by normal random errors with mean of 1 and standard deviation of 0.1. Last, we applied different calibration methods (i.e., multiplicative calibration and Bayesian calibration) to the guess intake vector and derived predicted 2005−2006 serum concentrations based on that vector using our pharmacokinetic model.

For the multiplicative calibration, we first computed the calibration coefficient (ϕ) by dividing the mean of multiple simulated serum concentrations from the fourth step by the corresponding predicted serum concentration from the guess intake vector. Then, we multiplied the calibration coefficient by the guess intake vector. For the Bayesian calibration, we used closed-form solutions of an intake vector described in the model description to calibrate the intake vector. For example, we used the guess intake vector as a prior mean vector, μ. For covariance matrix, $\sum$, we used a correlation coefficient of 0.75 between variables and the square of 400% of μ. Then, we compared their performance based on the amount of relative bias between true intake and the mean of calibrated intake across 1000 simulations from each method.

$$\text{bias} = |\text{calibrated intake} - \text{true intake}|/\text{true intake} \quad (6)$$

Because drinking water was the primary source of PFOA exposure for most of the residents in the Mid-Ohio Valley, its related parameters (e.g., drinking water source, tap water consumption rate) are the primary determinants of historical exposures. Compared to infants or children or teenagers, older participants more than 20 years of age are not likely to have significant changes in physiologic parameters (e.g., body weight) before the time of serum samples, and compared to

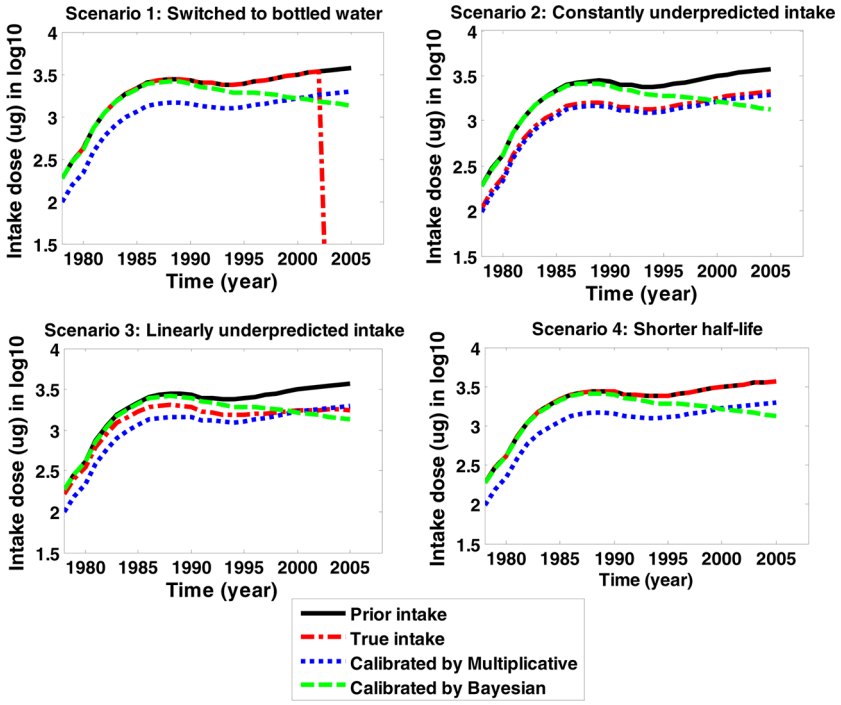

Figure 1. Intake doses (μg/year) by different scenarios for the participant in highly contaminated water districts in log10 scale. True intakes are shown as red dotted lines, guess intakes as black dotted lines, mean calibrated intakes by multiplicative calibration as blue dotted lines, and mean calibrated intakes by Bayesian closed-form calibration as green dotted lines. Each scenario is described in detail in the method. In scenario 1, intake dose after 2000 was assumed to be 1 μg/year.

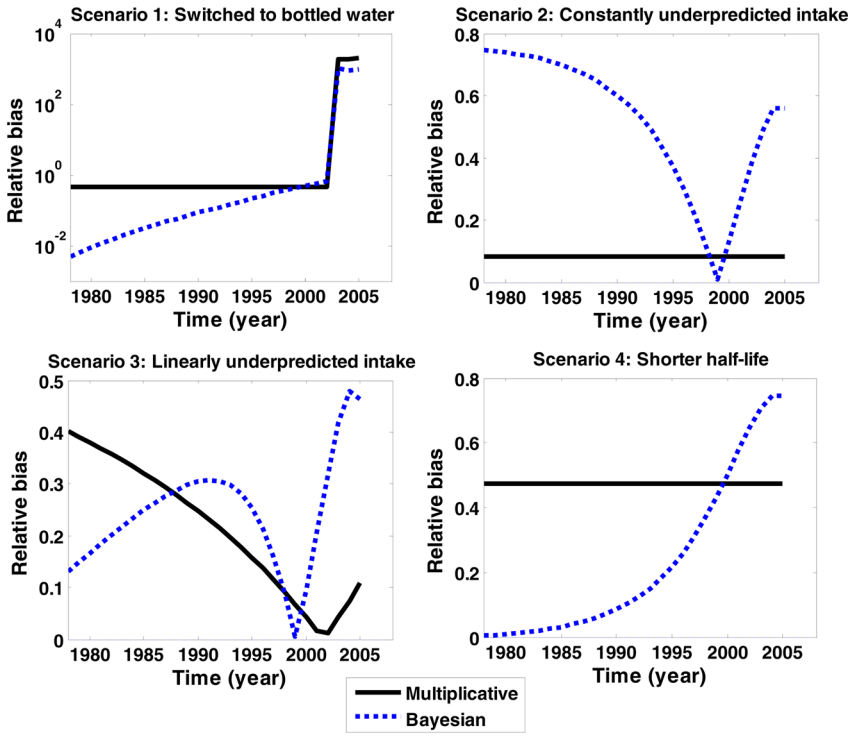

Figure 2. Relative bias by different scenarios for the participant in highly contaminated water districts. Biases from multiplicative calibration are shown as black solid lines and those from Bayesian calibration are shown as blue dotted lines. Each scenario is described in detail in the method.

female participants who delivered a baby before the sampling time, male participants do not have excretion events such as delivery and breastfeeding. Thus, we selected an older male participant who is likely to have consumed contaminated drinking water from a single water district over the course of his lifetime so that we could evaluate two calibration methods only for mis-specified information related to drinking water ingestion and the half-life. Therefore, we created four hypothetical exposure scenarios for the simulation studies, all

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based on a 50 year old male whose serum concentrations were overpredicted compared to the measured serum concentration:

1. The participant consumed drinking water from highly contaminated public wells throughout most of his life but switched to bottled water in 2000 without our knowledge (i.e., self-reported as a public water consumer). Although participants in the 2005−2006 C8 Health Project were asked whether they consumed primarily public or private water, bottled water consumption appears to have been under-reported[17] possibly due to changes in behavior after local media began reporting on PFOA contamination of public water supplies.

2. The participant's actual ("true") tap water consumption rate was smaller than the rate we used in our model by some constant fraction for his entire life (e.g., 50% smaller over his entire life). Tap water consumption rates were not assessed in the original C8 Health Project, but self-reported values are available for some participants (about 50%) who were recontacted in 2010−2011. When self-reported values were lacking in our original exposure study, we used a default water consumption rate of 1.40 L (U.S. EPA 2009).

3. The participant's actual tap water consumption rate decreased linearly during his life because of substitution with bottled water or other liquids (e.g., 5% decrement every year). Self-reported tap water consumption rates were only available in 2010−2011 but might have been different in previous years and may have been gradually reduced over time as bottled water and other beverages became more popular.

4. The true serum half-life value of PFOA (e.g., 2.3 years) was shorter than that we assumed in our exposure model (3.5 years). Although a half-life of 3.5 years was observed in a retired occupational cohort,[11] a recent study reported a 2.3 year half-life among adult residents of various ages during the first year after an exposure intervention.[34]

3. RESULTS AND DISCUSSION

3.1. Performance of Calibration Methods from Simulation Studies. Simulation studies are routinely used to assess the performance of statistical methods. Here we compare the performance of two calibration methods, the multiplicative and the Bayesian, based on the bias between calibrated intake and true intake. A hypothetical true intake vector, prior ("guess") intake vector, and mean calibrated intake vector from both the multiplicative and the Bayesian calibration methods are shown in Figure 1 for each of the four hypothetical scenarios. For all scenarios, the only difference in the simulations is how the true intake vector was defined.

Figure 2 shows relative bias by different scenarios. For the first scenario when a participant did not report that they switched their drinking water source from a public water district to bottled water, the bias in intake estimation from the Bayesian calibration was almost always smaller than that from the multiplicative calibration, except for a few years near 2003. For the second scenario in which the tap water intake rate was actually smaller than the standard intake rate by some constant fraction, the bias from the multiplicative calibration was almost always smaller than that from the Bayesian calibration. For the third scenario in which the actual tap water consumption rate was decreased linearly over lifetime, neither method outperformed another throughout the entire period. For the last scenario when the actual half-life of PFOA was shorter than that we used in the pharmacokinetic model, the Bayesian calibration performed better than the multiplicative calibration for years further from the measurement time and worse for years closer to the measurement time.

These results suggest that if our intake (guess intake) predictions from baseline exposure and pharmacokinetic models are inaccurate due solely to the under-reported bottled water use rate or a mis-specified (overestimated) half-life value, the Bayesian calibrated serum estimates would outperform the multiplicative calibrated serum estimates. On the other hand, if actual tap water consumption rates for each individual were lower than the standard rates by some constant, the calibrated predictions by the multiplicative calibration should be used in the epidemiologic studies.

3.2. Example Applications in Epidemiologic Analyses. Two calibration methods presented here were previously applied in an epidemiologic analysis of 11 pregnancy and 6 birth outcomes associated with PFOA exposures.[20,21] The calibrated predictions strengthened the association (about 30% increases) with two of the pregnancy and birth outcomes: preterm birth <32 weeks (N = 40) and term low birth weight (N = 99). The Bayesian calibrated predictions resulted in increased risk of preterm birth <32 weeks compared to the uncalibrated predictions; the adjusted odds ratio (AOR) with continuous exposure indices was increased from 1.29 to 1.67 (95% confidence interval: 1.03, 2.70). The multiplicative calibrated predictions resulted in increased risk of term low birth weight compared to the uncalibrated predictions; the AOR with continuous exposure indices increased from 1.04 to 1.33 (95% confidence interval: 1.04, 1.69). Associations between predicted serum PFOA concentrations and most pregnancy and birth outcomes were not statistically significant, regardless of calibration methods.

3.3. Implications and Limitations. We calibrated retrospective exposure predictions using two different calibration methods. Since only one serum measurement was available per person, the accuracy of different calibration methods could not be determined directly but could influence the results of epidemiologic studies. Instead, simulation studies such as that presented here can be used to determine which method results in less bias under any particular true exposure pattern and mechanism of mis-specification. We investigated four realistic exposure mis-specification scenarios for this simulation study and found that performance of one calibration method may systemically outperform another depending on the type of exposure mis-specification.

It is likely that the Bayesian method systematically outperformed the multiplicative method for the cases in which a change to bottled water use was not reported (scenario 1) or a half-life value was mis-specified (scenario 4) because the Bayesian method calibrates differently in *different years*, with the 2005−2006 serum dominating the retrospective serum estimates in closer years but the exposure model estimate dominating the retrospective serum estimates in more distant years. In contrast, multiplicative calibration should be more effective when exposure factors are systematically overestimated *across all years*, such as consistent overestimation of the tap water ingestion rate (scenario 2). Consideration of the most likely sources of exposure model mis-specification in conjunction with our simulation results may also help researchers determine the most appropriate method of calibration in any particular settings.

We also note that Bayesian results may be sensitive to the choice of prior variance and serum measurement standard deviation, and that our choice for the prior variance was

subjective. A smaller prior variance would place more weight on the annual exposure estimates from the fate and transport model and less weight on the exposure estimate implied by the 2005−2006 measured serum. Future planned work will investigate the impacts of alternative choices for the prior variance, including changes to the variance over time and different correlation structure.

We only calibrated individual-level exposure predictions although a group-level calibration is another multiplicative calibration method that has been applied in occupational epidemiology.[28] For example, we could group people by water districts, gender, and/or age group and find calibration parameters to minimize the error for each group rather than each participant. In addition, group-level parameters can be estimated by applying different half-lives for different ages. However, the group-level calibration could introduce some errors by ignoring or underestimating true differences in exposure between subjects.

One of the limitations of this study was the use of a single serum measurement per person in calibrating historical exposure predictions. Limited cross-sectional serum data with measurement errors are a source of uncertainty in model calibration not assessed here (we examined bias only, averaging over many repeated applications of the same method). Nevertheless, investigators may benefit from using both types of calibration in exposure reconstruction and epidemiologic studies, as a form of sensitivity analysis. Calibration of historical exposure predictions could be improved if multiple biomonitoring data were obtained in the same participant over a period of time. Moreover, uncertainties regarding drinking water concentrations may not be adequately captured by our prior distribution. Future work may include systematic evaluation of the impacts of fate and transport and exposure parameter uncertainties on the year-by-year PFOA exposures, though this will be a challenging exercise due to extensive computational requirements of the environmental models.[18] Local vegetable consumption is another exposure source of PFOA in the study area,[8,17,38] but this was not included in the model because participant-specific exposure information for vegetable consumption is not available. In addition, historical tap water consumption rates and drinking water sources are not available for all participants. Thus, future studies in addressing environmental health issues from similar settings should collect participant-specific critical exposure information for important exposure routes to reduce the uncertainties in exposure predictions arising from the exclusion of influential exposure routes.

■ ASSOCIATED CONTENT

Supporting Information

Example calibrated intakes by two calibration methods and the time-dependent distribution of weights used in Bayesian calibration is available in the Supporting Information. Sensitivity of error variance of serum measurements and covariance matrix of prior intake estimates on calibrated intakes by the Bayesian method as well as the fraction of negative values of intake estimates are available in the Supporting Information. Derivation of Bayesian closed-form solutions with a normal prior distribution is also described in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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