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Drinking Water PFAS Concentrations and Exposure Factors Influencing Measured and Predicted Serum PFAS Concentrations

Report 2 of the North Kent County Exposure Assessment

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Division of Environmental Health
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Contents

Introduction

Per- and poly-fluoroalkyl substances (PFAS) are a class of thousands of organic fluorinated chemicals that are resistant to heat, water, and oil. They have been used for decades in hundreds of industrial applications and consumer products.[1] In some research studies, several types of PFAS are associated with adverse health effects in people including pregnancy-induced hypertension, liver damage, high cholesterol, thyroid disease, decreased vaccine response, decreased fertility, asthma, small decreases in birth weight, and testicular and kidney cancer.[1]

In communities with known sources of PFAS contamination, consumption of contaminated drinking water is associated with elevated serum PFAS concentrations.[2] Previous work on the determinants of PFAS exposure in the general population and in communities affected by PFAS contamination have identified demographic factors such as age,[3,4] sex,[5,6] and race[7,8] as predictors of serum PFAS concentrations. Studies have also shown that firefighters[9] and workers in fluorochemical production plants tend to have higher PFAS concentrations in their serum.[10]

Elevated concentrations of certain PFAS have been found in foods such as eggs,[11] vegetables,[12] fish,[13] and wild game[14] from contaminated sites. Several studies have documented associations between consumption of specific foods and serum PFAS concentrations.[6,15,16] Blood loss via menstrual bleeding[17] or blood donation[18,19] is associated with lower concentrations of PFAS. Among women, higher parity and longer duration of breastfeeding are associated with lower PFAS body burdens.[20,21] Among infants and children, breastfeeding[22] is also positively associated with serum PFAS concentrations.

During an environmental investigation, the Michigan Department of Environment, Great Lakes, and Energy (EGLE) found PFAS in samples of private drinking water wells in areas near former waste disposal sites in northern Kent County, Mich., in 2016. Wolverine Worldwide, Inc., a shoe manufacturer based in Rockford, Mich., had disposed of waste associated with its leather tanning and shoe manufacturing operations in multiple areas in northern Kent County.[23,24,25,26] Throughout the resultant environmental investigation, EGLE found concentrations of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) ranging from below laboratory detection limits ('non-detect') to concentrations exceeding 50,000 parts per trillion (ppt). In 2016, the U.S. Environmental Protection Agency (EPA) established a Lifetime Health Advisory (LHA) of 70 ppt[a] for two PFAS, PFOA and PFOS, individually or in combination.[27] The Michigan Department of Health and Human Services (MDHHS) published non-enforceable public health drinking water screening levels for five PFAS in February 2019: PFOA (9 ppt), PFOS (8 ppt), perfluorononanoic acid (PFNA) (9 ppt), perfluorohexane sulfonate (PFHxS) (84 ppt), and perfluorobutane sulfonic acid (PFBS) (1,000 ppt).[28] As of September 2018, 1,783 private drinking water wells in the northern Kent County area were tested for PFAS. Of these, 982 had detections of any of the PFAS for which the water was tested, and 299 had detections of total measured PFAS over 70 ppt. Comparing the results from these tests to MDHHS drinking water screening levels, 238 had detections of PFOA over 9 ppt, 157 had detections of PFOS over 8 ppt, 15 had detections of PFNA over 9 ppt, 57 had detections of PFHxS over 84 ppt, and less than 5 homes had detections of PFBS over 1,000 ppt.

[a] Throughout this report, ppt is used as an equivalent to nanogram per liter or ng/L.

During 2017 and 2018, mitigation actions were taken to help northern Kent County residents reduce their exposure to PFAS from drinking water. Starting in August 2017, MDHHS, the Kent County Health Department (KCHD), and Wolverine Worldwide, Inc.'s contractors installed point-of-use or point-of-entry filters in the homes of affected residents and provided bottled water or cisterns of water, as appropriate.

While exceedances of health-based screening levels do not mean that harm to human health has or will occur, presence of such exceedances may warrant further investigation of the extent of human exposure to these chemicals. The Agency for Toxic Substances and Disease Registry of the U.S. Centers for Disease Control and Prevention (CDC/ATSDR) developed an approach for investigating PFAS exposure called the PFAS Exposure Assessment Technical Tools (PEATT).[29] The PEATT is designed to investigate PFAS exposures resulting from contaminated municipal water. In November 2018, MDHHS and KCHD launched an investigation of PFAS exposure from private residential drinking water wells using a modified version of the PEATT protocol.

The objectives of the North Kent County Exposure Assessment (NKCEA) were to:

1. Determine the mean concentration of 30 PFAS in participants' serum.
2. Compare concentrations of PFAS in participants' serum to those among participants in the National Health and Nutrition Examination Survey (NHANES), a national survey representative of PFAS concentrations in the U.S. general population.[30]
3. Determine the mean concentration of 30 PFAS in participants' unfiltered private well water and filtered private well water (for those with drinking water filters).
4. Describe the data on individual person characteristics that could affect PFAS exposure or elimination.

In August 2020, MDHHS released the first report that described the demographics of people who participated in the exposure assessment and provided a preliminary description of the results of serum testing (addressing the first objective above).[31] The first report also compared participants' serum PFAS concentrations to those of other populations, including the U.S. population and occupationally exposed populations.

This report—the second on the NKCEA—addresses all four of the study's objectives. It describes PFAS concentrations in NKCEA participants and describes PFAS concentrations in private drinking water wells. While the first report compared PFAS concentrations measured in NKCEA participants' serum for only individuals ages 12 and older to those of the U.S. population ages 12 and older, this report also compares NKCEA participants ages 3-11 to the U.S. population ages 3-11. Using graphical and regression modeling approaches, this report also examines the relationship between private drinking water well PFAS concentrations and participant serum PFAS concentrations as well as the relationship between self-reported factors affecting PFAS exposure and elimination and serum PFAS concentrations. By addressing all four objectives, this report aims to answer key questions about the factors affecting serum PFAS concentrations in this population.

Methods

Design

A stratified[32] random sample of eligible households was invited to participate in the exposure assessment. Addresses were eligible for inclusion in the exposure assessment sampling frame if all the following criteria applied:

- They were residential properties.
- They had a private drinking water well in the EGLE North Kent study area.
- They had their private drinking water well tested for PFAS by, or at the direction of, EGLE prior to September 1, 2018.
- They had validated detectable concentrations of measured PFAS in their private drinking water well that were reported to MDHHS by EGLE.

Of the 1,783 addresses that were sampled in the EGLE North Kent study area,[26] 773 households met the eligibility criteria. This sampling frame was then divided into two strata: households whose unfiltered private drinking water well sample contained less than 70 ppt total measured PFAS (n=591) and households whose unfiltered private drinking water well sample contained greater than or equal to 70 ppt total measured PFAS (n=182). The threshold of 70 ppt total measured PFAS (i.e., the sum of all measured PFAS) was chosen to reflect the EPA LHA (70 ppt PFOA + PFOS) while taking into consideration that other PFAS were also detected in the environmental investigation area. All households in the higher exposure stratum (n=182) (100%) and a simple random sample from the low stratum households was selected for recruitment (n=235) (39.7%). The number of households selected was based on calculations using estimated parameters for the sample size needed to detect a difference in the mean serum PFOS concentrations of at least 4 µg/L between the North Kent County and NHANES samples using a two-sample t-test at α=0.05 with 80% power. Serum PFAS is measured in µg/L, which is equivalent to parts per billion (ppb).

Current residents of all ages living in the selected households at the time of recruitment were eligible for participation if they met all of the following criteria:

- Lived at the selected address on or before January 1, 2018,
- Used a private well as the source of drinking water at the home, and
- Weighed at least 16 pounds (lbs.) at the time of recruitment.

Potential participants must have lived at the selected address since on or before January 1, 2018, because filters were distributed to many households with PFAS detections starting August 2017 and were continuing to be distributed at the time recruitment for the study began. Setting a residency period requirement helped ensure that individuals participating in the exposure assessment were those who had consumed non-filtered water with PFAS detections. In consultation with the Kent County medical director, the minimum participant weight (16 lbs.) was set based on the weight needed to safely collect the minimum amount of blood for PFAS analysis (2 milliliters [mL]).

Participant Recruitment

Targeted recruitment of eligible individuals began in November 2018 and continued through the spring of 2019. Selected households were first sent an introductory letter inviting residents to call MDHHS to determine their eligibility. Households that did not respond to the introductory letter were sent a follow-up letter. Households that did not respond to the second letter were contacted by phone at least three times to elicit participation.

For households unreachable by phone, MDHHS staff attempted a home visit. If MDHHS staff contacted residents at the home, they gave them recruitment materials and encouraged them to call MDHHS to determine their eligibility. If MDHHS staff were not able to contact residents at the home, they left study materials encouraging residents to call MDHHS. Non-targeted recruitment efforts included press releases, public meetings, and MDHHS staff presence at public events in the community, such as farmers' markets.

When MDHHS staff talked with residents by phone, they took a census of the household, i.e., noted the number of residents and their ages and sexes, administered a brief eligibility questionnaire for each interested member of the household, and then scheduled one clinic appointment per interested and eligible resident. MDHHS staff also scheduled a single appointment at a participating household with an adult for a drinking water sample to be collected at their residence. Participants were then mailed a packet that included directions to the clinic, information about what to expect at their appointment, copies of informed consent forms and, if applicable, minor assent forms. MDHHS texted or emailed participants (depending on the person's communication preference) with reminders about their scheduled appointment.

Data Collection

Clinic Appointment

At the clinic appointment, MDHHS staff reviewed the informed consent documents (and minor assent forms, if applicable) with participants. Participants gave consent before data or sample collection took place. MDHHS required consent from the legal guardians of all minors eligible to participate in the study.

An exposure questionnaire was administered verbally by trained MDHHS and KCHD staff, who recorded participant answers electronically on iPads using REDCap electronic data capture tools.[33] Data was collected from all participants about their history of living in the North Kent County area, water consumption habits, diet, and demographics. Adults were asked about health conditions that may affect PFAS excretion and their occupational history, as they may have had exposure to PFAS from drinking the water at their workplace in the North Kent County area or by working directly with PFAS. Adult women were also asked about menstruation, menopause, parity, and breastfeeding. Parents or guardians with young children participating in the study were asked about each participating child's breastfeeding history, formula feeding history, and history of school and daycare attendance in the North Kent County area.

Participants weighing more than 56 pounds had 20 mL of blood drawn; participants weighing less than 56 pounds had a reduced volume drawn commensurate with their weight. Trained phlebotomists collected blood in two 10 mL red top tubes with serum separator as recommended by CDC for blood

samples collected for PFAS analyses in exposure assessments. Blood was allowed to clot for up to 60 minutes; then the tube was centrifuged at 1,000-1,300 g for 15 minutes. After centrifugation, approximately 10 mL of serum was extracted from each 20 mL of whole blood, aliquoted into 2 mL cryovials, and frozen at or below -20 ^{o}C at the KCHD clinic facility in Grand Rapids. Five (5) mL of the serum was used for PFAS testing and 5 mL was reserved for follow-up testing if a sample needed to be retested. The frozen serum specimens were packed on dry ice and transported to the MDHHS laboratory facilities in Lansing.

Water Sampling

MDHHS sanitarians conducted water sampling at participating households. If a PFAS-reducing water filter was present at the household, drinking water samples were collected both before and after filtration. If the household had both point-of-entry and point-of-use filters, one sample would be collected after the point-of-entry filter and before the point-of-use filter, and the other collected after the point-of-use filter. A drinking water sample collected at a point where water has *not* passed through any filter is described as an "unfiltered drinking water sample." A drinking water sample collected at a point where water has passed through *any* filter is described as a "filtered drinking water sample." Quality assurance procedures included the use of field blanks, trip blanks, and the collection of duplicate samples every week or every 20 samples, whichever was more frequent. All samples were packed on ice and transported to the MDHHS laboratory for analysis.

Confirmatory resampling was conducted when field or trip blanks had detections of one or more analytes, when filtered samples had higher results than the unfiltered sample for one or more analytes, or when filtered samples were higher than MDHHS screening levels at the time. Confirmatory resampling was also done in cases where any analyte in the NKCEA unfiltered sample was more than 20% higher or lower than results for that analyte during previous drinking water sampling done as part of EGLE's environmental investigation. When the EGLE environmental investigation sample was a non-detect, confirmatory resampling was done when the NKCEA sample was more than 20% higher than either the EGLE or MDHHS reporting limit for that analyte, whichever was higher. Resampling was conducted with permission from the designated adult in the household.

Lab Analyses and Results Reporting

The MDHHS laboratory analyzed the serum specimens and water samples for PFAS using a high-pressure liquid chromatography tandem mass spectrometry (HPLC-MS/MS) method.[34] There were 24 types of PFAS measured, three of which were measured as linear isomers and branched isomers, making a total of 30 analytes reported. The full names, abbreviations, and CAS numbers of the analytes are provided in Supplemental Table 1. Throughout the report, analytes that are linear isomers are denoted by an "L-" prefix and analytes that are branched isomers are denoted by a "Br-" prefix. The instruments used were the Shimadzu Nexera X2 Series HPLC system (using a 50 mm x 2.1 mm, 3 µm Supelco Ascentis® C8 RP column as an analytical column and a second as a guard/delay column placed before the autosampler) interfaced to a Shimadzu LCMS-8060 triple quadrupole mass spectrometer with thermally assisted electrospray ionization (ESI) source run in the negative ion mode.

Results were evaluated by MDHHS laboratory chemists and MDHHS toxicologists for quality. After this review, MDHHS sent a letter to each participant with their serum PFAS results. The letters included the geometric mean and 95th percentile for their age group from the most recent cycle of NHANES for each analyte for which data were available.

MDHHS laboratory scientists and toxicologists also reviewed results from filtered and unfiltered water samples collected during the study. Quality controls for consistency were done against water samples collected during the earlier EGLE environmental investigation. MDHHS sent each household a letter with the concentrations of the 30 reported analytes in their filtered and unfiltered drinking water well samples as applicable. The letters included a table comparing the households results to the MDHHS screening levels for PFOA, PFOS, PFHxS, PFNA, PFBS used at the time, and to the U.S. EPA LHA for summed PFOA and PFOS. Total PFAS was also reported but no comparison value was available.

Data Analysis

For all analyses, consistent with NHANES methods,[7] values for serum PFAS concentrations below the laboratory limit of quantification (LOQ) were substituted by the LOQ divided by the square root of two. The LOQ was determined by calculating the standard deviation at each standard concentration following repeated measurements of the low concentration standards in methanol. The standard deviations were then plotted against concentration, with the y-intercept of the least squares fit of this line equaling signal at 0 concentration (S_0) and the concentration at 10 times S_0 equaling the LOQ. LOQs for each analyte are listed in Supplemental Table 1.

For PFOS, PFOA, and PFHxS, for which both linear and branched isomers were measured, results were also reported as the sum of linear and branched values as reported by the laboratory. If the value for either measure was below the LOQ, it was substituted by the LOQ of that analyte and divided by the square root of two. If both isomers were reported as less than the LOQ, then two imputed values were summed.[7]

Descriptive Analyses - Serum

Descriptive statistics for serum concentrations of PFAS were calculated for analytes that were detected among at least 60% of participants, consistent with NHANES methods.[35]

Sampling weights (w) were determined by Equation 1.

$$\textit{Equation 1: } w_j = N_j / n_j$$

In Equation 1 N_j is the number of households in each stratum *j*, and n_j is the number of households with at least one participant in stratum *j*.

For calculation of percentiles and 95% confidence limits, two-stage survey weighted bootstrapping was used. Primary sampling units (PSUs), in this case households, were selected proportionally to their probability of inclusion in the study, followed by random selection of a single respondent for each PSU. From each bootstrap sample, the desired percentiles were calculated, and the bootstrap distribution was summarized to estimate each percentile and its 95% confidence limits. Bootstrapping was done with the “boot” function in the R package “boot” using R version 4.0.4.

Calculations of geometric means (the *n*th root, usually the positive *n*th root, of a product of *n* factors) and 95% confidence intervals from the sample of households were performed using SAS© PROC SURVEYMEANS in Base SAS 9.4 with survey weights applied. The household was the primary sampling unit (PSU); hence the unit of analysis for the purpose of estimating a population mean is the household.

For all analytes where NHANES comparison results are available, the percent of individuals exceeding the NHANES 95th percentile was calculated using a weighted logistic regression using SAS© PROC GLIMMIX.

Descriptive Analyses - Water

Descriptive statistics for the drinking water concentrations of the PFAS were calculated at the household level (i.e., in households with more than one person, the drinking water samples were not counted more than once when calculating the detection frequency, median, or geometric mean). When calculating geometric means, results below the reporting limit were replaced by the reporting limit divided by the square root of two.

Participants were asked about their drinking water history, including their current source (e.g., source is private drinking water well, bottled water, or municipal water) and filter use. For past sources, up to three changes to their source or filter use were asked of each participant. For determining what participants' major historic water source was, the first out of three reported past sources were used. If people reported that that source was their unfiltered private well, we considered the PFAS concentration of the water they consumed to be the PFAS concentration measures in our study. Since some participants reported already using filters or used a water source other than their private well (i.e., bottled water or municipal water), we considered the PFAS concentration of the water they consumed as non-detect.

If a participant provided data on the number of cups consumed per day, the water intake rate for this participant was determined by Equation 2. Participant responses showed that reported drinking water rates within participants did not change much over time. The most recent reported number of cups consumed per day was used.

$$\textit{Equation 2: water intake rate } (mL/day) = \textit{number of cups drank per day} \times 8oz/cup \times 29.57mL/oz.$$

For adult participants who did not indicate the number of cups consumed per day (n < 5) or responded with extreme outliers (>17 cups per day; n = 15), the water intake rate was estimated by one of two methods. If the participant's body weight was measured at the clinic appointment, the water intake rate is estimated by Equation 3 where 16 mL/kg/day drinking water ingestion rate is obtained from EPA's 2019 exposure handbook (Table 3-1, Consumers Only, ≥21 years, mean value). [36]

$$\textit{Equation 3: water intake rate } (mL/day) = 16\, mL/kg/day \times \textit{body weight } (kg)$$

If the participant's body weight was not measured at the clinic appointment, the water intake rate (mL/day) was obtained directly from EPA's 2019 exposure handbook (Table 3-1, Consumers Only, ≥21, mean value)[36].

For minor participants, there was complete data for water intake, so estimation was not needed. The values for ingestion rate and water intake used were specifically for adults.

If a participant did not indicate the water source or filter status, we assumed they drank the unfiltered private well water at the household from which they were recruited.

All participants were divided into three groups based on their water intake rate, water source, and filter status: 1) used a filter or did not drink private well water (n=78), 2) drank <6 cups of private well water per day without using a filter (n=213), and 3) drank ≥ 6 cups of private well water per day without using a filter (n=122). The water source used was the source participants reported drinking from immediately prior to the discovery of PFAS in the investigation area (2017 to 2018).

We chose 6 cups as the cutoff because 6 cups is close to the 75th percentile of daily water ingestion used in EPA's 2019 exposure handbook[36] (Table 3-17, all ages) and is the median daily water intake rate of participants in this study.

The daily intake of each PFAS from drinking water for every participant is calculated using Equation 4.

Equation 4: $PFAS\ daily\ intake\ =\ PFAS\ water\ concentration\ \times\ water\ intake\ rate$

In Equation 4, PFAS water concentration is any of the following:

1) The PFAS concentration measured in the unfiltered sample if the participant indicated drinking from a private residential well and not using a filter during that time.

2) The PFAS concentration measured in the filtered sample if the participant indicated drinking from a private residential well and was using a filter during that time.

3) The analysis batch reporting limit of the specific PFAS divided by the square root of two, either if the participant indicated their water source was not a private residential well (i.e., municipal water or bottled water) or if any of the concentration from 1 or 2 above is a non-detect or below the reporting limit.

For participants who indicated their drinking water source was a filtered private residential well, but at whose home no filter was found during sampling, the PFAS concentrations measured in the unfiltered sample were used as the PFAS water concentration to calculate the daily intake.

Comparisons to NHANES

Comparisons were made to the latest available data from NHANES for each PFAS. For comparison with NHANES estimates, analyses were limited to participants who met all eligibility criteria, provided a blood specimen, and were in an age range for which summary statistics from NHANES are also available (ages 3-11 and ages 12 and up). Geometric means for the NKCEA study and NHANES were compared by examining confidence intervals. To compare serum PFAS concentrations in the study population to serum PFAS concentrations in the U.S. population, intercept-only weighted multilevel logistic regressions were used to calculate the proportion of participants with serum PFAS concentrations above the 50th, 75th, 90th, and 95th percentiles of the NHANES for the age group 3-11 years and 12 years and older, respectively. Analyses were done using Base SAS 9.4.

Steady State Pharmacokinetic Modeling of Serum PFAS from Water Concentrations

To estimate serum PFAS concentrations that can result for a given water concentration, a single compartment steady state pharmacokinetic equation was used. Estimating serum PFAS concentrations helps with interpretation of the measured results and can help determine if drinking water was the main source of exposure or if other routes also contributed significantly. For results where the grouping is based on water concentration, the upper and lower expected serum concentrations from the PFAS water concentrations in each group were calculated using Equation 5 below. The parameters for half-life, volume of distribution, and intake rate in Equation 5 are taken from the Michigan Science Advisory Workgroup report.[37]

Equation 5: Expected serum concentration = $$\frac{Water\ concentration \times water\ intake\ rate}{log(2) \times volume\ of\ distribution\ / half-life) / exp(log(2)/half-life)}$$

If daily intake was plotted, Equation 5 was modified by substituting the calculated daily intake value for "Water concentrations × water intake rate."

Graphs were created using R version 4.0.4 and RStudio Version 1.4.

Statistical Models

Statistical models were built to assess whether factors thought *a priori* to be determinants of PFAS exposure were significantly associated with serum PFAS concentrations. The statistical models regressed log-transformed serum PFAS concentrations on exposure variables for each of the 12 PFAS detected in at least 60% of serum from all participants and in at least 20% of all unfiltered household drinking water samples. Separate models were built for each PFAS and for certain demographic subgroups (all participants, adults, adult women, and minors).

Candidate variables that were considered for inclusion in statistical models are listed in Table S2. Prior to multivariable analysis, exploratory analyses were performed to assess the qualitative and quantitative properties of the data. Univariate analyses were performed on all variables that were candidates for inclusion in the models, including both exposure and outcome variables. This was done to explore patterns and trends in the data as well as to assess (in the case of categorical and binomial variables) whether sufficient sample size for analysis existed in each category. Adjustments to category sizes were made as required, and potential exposure variables of interest were excluded if the number of responses was insufficient for analysis (this was the case with the question about the consumption of milk from animals raised within the study area). Bivariate analysis of each exposure variable of interest with each PFAS was then performed to assess the relationships prior to multivariable analysis. That is, bivariate analysis was used to check model assumptions (e.g., normally distributed residuals, homoscedasticity, etc.), initial model convergence, and, qualitatively, for unexpected relationships that might prompt further investigation. Each model was run both as a bivariate analysis and with adjustment for daily intake of PFAS in drinking water. Log transformation of non-normal variables (natural (base e) logarithm) was done as needed. Final models were built using *a priori* knowledge based on existing literature on factors affecting serum PFAS concentrations rather than pre-determined significance levels from bivariate analysis. Directed Acyclic Graphs (DAGs) were used to determine the

minimal sufficient adjustment set of potentially confounding factors from all potential covariates, thus resulting in the most parsimonious model for testing the hypotheses of interest.

DAGs were constructed using DAGitty 3.0.[34] The minimal sufficient adjustment set as identified in the DAGs was adjusted for in each of the regression analyses (Table S3). Linear mixed effects models (multi-level models)[38] with household-level random intercepts were used to compute estimates for the associations between exposures of interest and individual-level serum PFAS concentrations as a continuous, log-transformed outcome. All models used weights (calculated as described above in "Descriptive Analyses – Serum").

For models of the association between estimated daily intake of PFAS from contaminated drinking water and serum PFAS concentrations, both the predictor (estimated daily intake) and the outcome (serum PFAS concentration) were log-transformed prior to analysis, as both were lognormally distributed for all PFAS. Results are reported as the percent change in serum PFAS concentrations associated with a 1% change in estimated daily intake.

For models of the consumption of food (i.e., game meat, fish, vegetables, eggs) with serum PFAS concentrations, original survey response options were categorized into a three-level categorical variable due to low numbers of participants indicating some response options. Food consumption data was categorized as never consuming the food, consuming the food a few times per year or less, and consuming the food once per month or more. Log-transformed serum PFAS concentration was regressed on each of these three-level food variables and results are shown as the percent change in serum PFAS concentration (calculated as $(\exp(\beta) - 1) \times 100$) associated with a one-level increase in food consumption, where β is the regression coefficient for the variable of interest.

For analysis, health condition variables for self-report of kidney disease, anemia, or diabetes were coded as either ever been diagnosed or never have been diagnosed. The variables for total years lived in the home, total number of births (adult women only), total months spent breastfeeding children (adult women only), total months being breastfed (minors only), number of blood or plasma donations per year (adults only), and age were treated as simple continuous variables. Again, log-transformed serum PFAS concentration was regressed on each of these variables and results are shown as the percent change in serum PFAS concentration (calculated as $(\exp(\beta) - 1) \times 100$) associated with a one-unit increase in the independent variable.

Due to low counts of participants identifying as certain races, for regression analyses that adjusted for race, responses were condensed into non-white single race (Black, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, or other), race not specified, two or more races, and white.

For all models, significance was determined at $\alpha=0.05$. Non-overlapping 95% confidence intervals indicate significant differences at $\alpha=0.05$. Model assumptions and fit were checked before finalization.

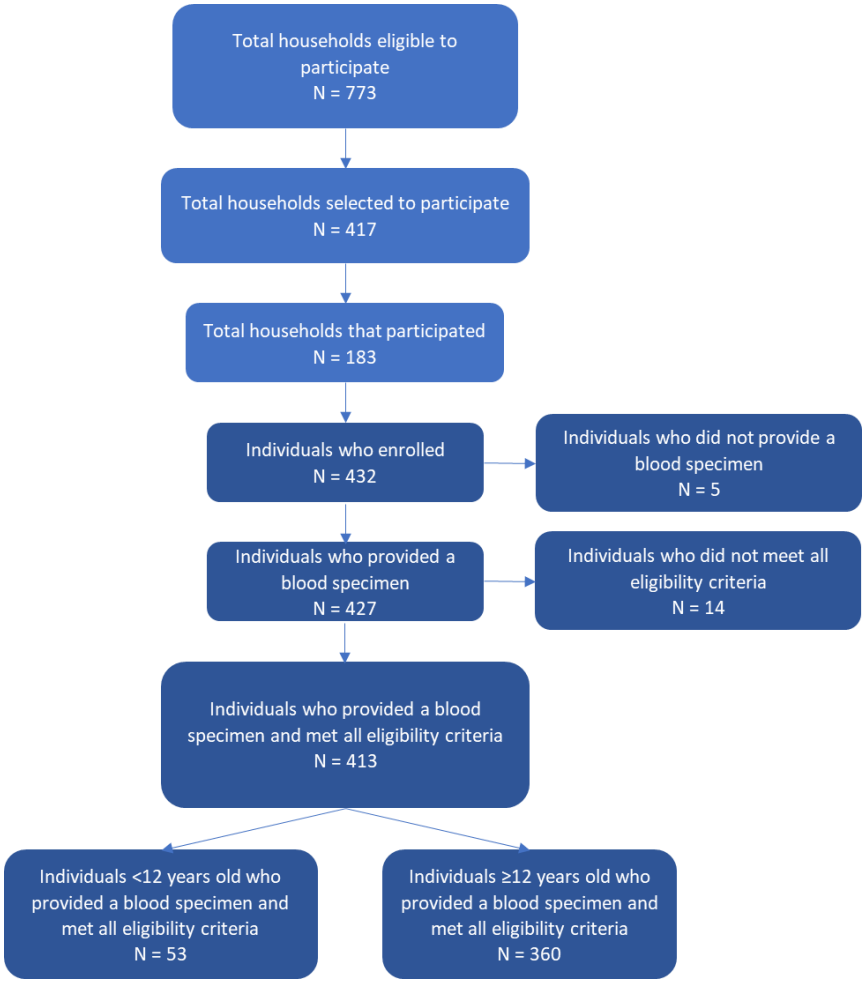
All study activities were approved by the MDHHS Institutional Review Board (201807-06-EA).

Results

Enrollment

A total of 773 households were eligible; among these, 417 were selected, as described in the Methods section. By the end of data collection, 183 households had enrolled: 95 from high-stratum households and 88 from low-stratum households (Figure 1). Among these households, 432 individuals enrolled: 250 from high-stratum households and 182 from low-stratum households. Of these individuals, 413 provided a blood specimen and met all eligibility requirements. The remaining 19 were excluded from analyses because they were not current residents of an eligible household (n=14), or they did not provide a blood specimen (n=5).

Figure 1: Enrollment of participants in the exposure assessment.



Participant Characteristics

More females than males participated in the exposure assessment and most participants were white and non-Hispanic. Most adult participants attended at least four years of college and reported an income above $75,000 (Table 1).

Table 1: Sex, race, and ethnicity of exposure assessment participants (N=413) and annual household income and education levels of adult exposure assessment participants (n=331).

Participant Characteristics	Count (%)
Sex on original birth certificate	
Male	195 (47.2)
Female	218 (52.8)
Race	
White	390 (94.4)
Other races, including multiple races	21 (5.1)
Don't know or no answer	2 (0.5)
Ethnicity	
Hispanic/Latino	5 (1.2)
Non-Hispanic	405 (98.1)
Don't know or no answer	3 (0.7)
Annual household income*	
<$25,000	17 (5.1)
$25,000-$34,999	8 (2.4)
$35,000-$49,999	23 (6.9)
$50,000-$74,999	44 (13.3)
$75,000-$99,999	52 (15.7)
≥$100,000	141 (42.6)
Don't know or no answer	45 (13.6)
Education*	
High school or less	61 (18.4)
Some college or technical school	97 (29.3)
Four years or more of college	110 (33.2)
Graduate or professional degree	58 (17.5)
Don't know or no answer	5 (1.5)

*Questions on annual household income and education were only asked of adults aged 18 years or older (n=331).

Serum PFAS Concentrations

Twelve of the 30 analytes were detected in over 90% of participants. All PFAS in the target analysis list were detected in the serum of at least one participant (Table 2).

Table 2: PFAS detection frequency, range, and estimated selected percentiles (weighted) of serum PFAS concentrations in the NKCEA study population (N=413).

Analyte	Participant detection frequency (%)	Range (µg/L)	50th percentile (weighted) (µg/L)	75th percentile (weighted) (µg/L)	90th percentile (weighted) (µg/L)	95th percentile (weighted) (µg/L)
PFOA	99.8	ND - 433	1.85	3.07	7.95	19.6
L-PFOA	100.0	0.05 - 433	1.84	2.97	7.91	19.3
Br-PFOA	52.5	ND - 40.8	0.01	0.04	0.10	0.24
PFOS	99.3	ND - 3,170	6.11	9.96	18.2	25.3
L-PFOS	98.6	ND - 589	2.60	4.91	9.02	14.7
Br-PFOS	99.5	ND - 2,580	3.09	5.31	10.1	14.8
PFNA	99.5	ND - 3.05	0.44	0.72	1.02	1.39
PFHxS	99.3	ND - 884	2.03	4.15	9.62	28.3
L-PFHxS	99.8	ND - 884	2.01	4.09	9.07	27.2
Br-PFHxS	73.1	ND - 12.7	0.04	0.11	0.37	0.89
PFBS	27.6	ND - 0.61	^	0.02	0.04	0.05
PFTeA	12.4	ND - 0.20	^	^	0.02	0.04
PFTriA	51.8	ND - 0.27	0.01	0.03	0.06	0.09
PFDoA	69.0	ND - 0.31	0.01	0.03	0.04	0.07
PFUnA	92.3	ND - 0.48	0.07	0.11	0.16	0.22
PFDA	98.3	ND - 1.93	0.14	0.23	0.38	0.51
PFHpA	86.0	ND - 1.80	0.04	0.08	0.13	0.17
PFHxA	17.9	ND - 0.07	^	^	0.03	0.03
PFPeA	42.6	ND - 0.24	^	0.03	0.04	0.05
PFBA	85.2	ND - 9.97	0.04	0.06	0.11	0.15
PFDS	29.3	ND - 0.54	^	0.02	0.05	0.08
PFNS	13.3	ND - 2.16	^	^	0.02	0.05
PFHpS	95.9	ND - 337	0.27	0.52	1.04	3.09
PFPeS	87.4	ND - 19.6	0.05	0.13	0.65	1.48
PFOSA	43.6	ND - 0.14	^	0.01	0.02	0.03
FTS 8:2	31.7	ND - 0.40	^	0.02	0.04	0.06
FTS 6:2	1.2	ND - 4.37	^	^	^	^
FTS 4:2	4.4	ND - 0.07	^	^	^	0.01
EtFOSAA	30.8	ND - 0.61	^	0.02	0.04	0.06
MeFOSAA	93.5	ND - 5.45	0.10	0.21	0.39	0.76

ND = The analyte was not detected.

^ = The estimate is below the limit of quantitation (LOQ).

Comparison of NKCEA Participants to a Nationally Representative Sample

The proportion of participants ages 12 and older exceeded the expected proportions reported by NHANES for the general population for the 95th, 75th, 50th, and 25th percentiles for multiple PFAS.

For participants investigation ages 12 and older:

- For the 95th percentile, it is expected that if the NKCEA participants were similar to the general U.S. population, 5% of participants would have serum values for each PFAS above the 95th percentile value available for comparison from NHANES. For PFOA, L-PFOA, PFOS, L-PFOS, Br-PFOS, PFHxS, and PFHpS more than 5% of the NKCEA participants had serum concentrations that exceeded these analytes' 95th percentile values (Table 3). For PFUnA and PFDA, less than 5% of the NKCEA participants had serum concentrations that exceeded these analytes' 95th percentile values.
- For the 90th percentile, it is expected that if the NKCEA participants were similar to the general U.S. population, 10% of people would have serum values for each PFAS above the 90th percentile value available for comparison from NHANES. For PFOA, L-PFOA, PFOS, L-PFOS, Br-PFOS, PFHxS, PFHpA, and PFHpS more than 10% of the NKCEA participants had serum concentrations that exceeded these analytes' 90th percentile values (Table 3). For PFUnA, less than 10% of the NKCEA participants had serum concentrations that exceeded these analytes' 90th percentile values.
- For the 75th percentile, it is expected that if the NKCEA participants were similar to the general U.S. population, 25% of people would have serum values for each PFAS above the 75th percentile value available for comparison from NHANES. For PFOA, L-PFOA, PFOS, L-PFOS, Br-PFOS, PFHxS, PFHpS, and MeFOSAA more than 25% of NKCEA participants had serum concentrations that exceeded these analytes' 75th percentile values (Table 3). For PFUnA and PFDA, less than 25% of the NKCEA participants had serum concentrations that exceeded these analytes' 75th percentile values.
- For the 50th percentile, it is expected that if the NKCEA participants were similar to the general U.S. population, 50% of people would have serum values for each PFAS above the 50th percentile value available for comparison from NHANES. For PFOA, L-PFOA, PFOS, L-PFOS, Br-PFOS, PFHxS, PFHpS, and MeFOSAA more than 50% of NKCEA participants had serum concentrations that exceeded these analytes' 50th percentile values (Table 3). For PFUnA and PFDA, less than 50% of the NKCEA participants had serum concentrations that exceeded these analytes' 50th percentile values.
- The geometric means for participants ages 12 and above were significantly higher than NHANES geometric means for PFOA, L-PFOA, PFOS, Br-PFOS, and PFHxS (Table 3). The NHANES geometric mean was significantly higher than the NKCEA participant geometric mean for two PFAS, PFUnA and PFDA.

For other PFAS, either no comparison could be made or the NKCEA result was comparable to that from NHANES.

Table 3: PFAS detection frequency, estimated percent above select NHANES percentiles (weighted), and estimated geometric means (weighted) and confidence intervals of NKCEA participants aged 12 and older compared to geometric means of NHANES participants aged 12 and older (n = 360).

Analyte	Participant detection frequency (%)	Percent of participants above NHANES 50th percentile (weighted) (%)	Percent of participants above NHANES 75th percentile (weighted) (%)	Percent of participants above NHANES 90th percentile (weighted) (%)	Percent of participants above NHANES 95th percentile (weighted) (%)	NKCEA geometric mean and 95% confidence interval (weighted) (µg/L)	*NHANES geometric mean and 95% confidence interval (µg/L)
ᵛPFOA	100.0	62.5	43.4	25.2	18.6	**2.07 (1.80-2.39)**	1.42 (1.33-1.52)
L-PFOA	100.0	65.0	43.8	25.6	18.3	**2.04 (1.76-2.35)**	1.32 (1.23-1.42)
Br-PFOA	49.7	^NA	^NA	^NA	4.8	NC	NC
ᵛPFOS	99.4	65.8	40.8	22.1	16.6	**6.14 (5.18-7.28)**	4.25 (3.90-4.62)
L-PFOS	99.2	48.3	25.7	12.6	9.0	2.82 (2.36-3.36)	2.94 (2.70-3.21)
§Br-PFOS	99.7	85.4	66.0	44.9	34.9	**3.04 (2.53-3.63)**	1.22 (1.10-1.35)
PFNA	99.7	58.0	28.1	10.9	5.4	0.44 (0.38-0.50)	0.41 (0.36-0.46)
ᵛPFHxS	99.2	76.6	55.1	36.8	29.6	**2.30 (1.92-2.75)**	1.08 (1.00-1.18)
L-PFHxS	99.7	‡NA	‡NA	‡NA	‡NA	2.22 (1.84-2.66)	‡NA
§Br-PFHxS	70.3	‡NA	‡NA	‡NA	‡NA	0.04 (0.03-0.05)	‡NA
PFBS	23.6	^NA	^NA	^NA	^NA	NC	NC
PFTeA	11.9	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFTriA	53.6	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFDoA	68.6	^NA	^NA	^NA	^NA	0.01 (0.01-0.02)	NC
PFUnA	93.3	32.3	6.9	1.9	0.9	0.06 (0.05-0.07)	**0.13 (0.12-0.14)**
PFDA	98.3	32.0	16.1	9.7	3.5	0.14 (0.12-0.16)	**0.19 (0.18-0.21)**
PFHpA	84.2	^NA	^NA	13.8	1.2	0.04 (0.03-0.04)	NC
PFHxA	17.5	^NA	^NA	^NA	^NA	NC	NC
PFPeA	43.6	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFBA	85.3	‡NA	‡NA	‡NA	‡NA	0.03 (0.03-0.04)	‡NA
PFDS	30.0	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFNS	13.6	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFHpS	95.8	63.3	48.9	37.0	20.5	0.26 (0.21-0.32)	0.22 (0.18-0.26)
PFPeS	86.4	‡NA	‡NA	‡NA	‡NA	0.06 (0.05-0.07)	‡NA

Analyte	Participant detection frequency (%)	Percent of participants above NHANES 50th percentile (weighted) (%)	Percent of participants above NHANES 75th percentile (weighted) (%)	Percent of participants above NHANES 90th percentile (weighted) (%)	Percent of participants above NHANES 95th percentile (weighted) (%)	NKCEA geometric mean and 95% confidence interval (weighted) (µg/L)	*NHANES geometric mean and 95% confidence interval (µg/L)
PFOSA	42.8	^NA	^NA	^NA	^NA	NC	NC
FTS 8:2	31.7	‡NA	‡NA	‡NA	‡NA	NC	‡NA
FTS 6:2	0.6	‡NA	‡NA	‡NA	‡NA	NC	‡NA
FTS 4:2	4.2	‡NA	‡NA	‡NA	‡NA	NC	‡NA
EtFOSAA	30.8	^NA	^NA	^NA	1.5	NC	NC
MeFOSAA	93.1	51.9	28.4	10.0	6.6	0.10 (0.09-0.12)	0.13 (0.12-0.15)

* Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. National Report on Human Exposure to Environmental Chemicals. Updated March 2022. https://www.cdc.gov/exposurereport/. Accessed July 6, 2023.

Bold typeface values indicate significantly higher results compared to the other group.

NC = Not calculated because the analyte was not detected for more than 60% of participants.

NA = Not available from NHANES.

‡ Not available from NHANES because the analyte was not measured in NHANES for this age group.

^ Not available because the NHANES 95th percentile was below the NHANES limit of detection.

§ MDHHS Bureau of Labs is evaluating the comparability of sums of linear and branched isomers between the NHANES laboratory method and the MDHHS laboratory method and has determined that the branched isomer calibration methods used for the NKCEA specimen analysis resulted in branched PFOS results biased high relative to NHANES branched PFOS results and linear PFOS results biased low relative to NHANES linear PFOS results.

[v] MDHHS Bureau of Labs is evaluating the comparability of sums of linear and branched isomers between the NHANES laboratory method and the MDHHS laboratory method and has determined that the branched isomer calibration methods used for the NKCEA specimen analysis resulted in branched PFOS results biased high relative to NHANES branched PFOS results and linear PFOS results biased low relative to NHANES linear PFOS results.

The proportion of participants ages 3 through 11 exceeded the expected proportions reported by NHANES for the general population for the 95th, 75th, 50th, and 25th percentiles for multiple PFAS.

For those aged 3 through 11:

- For the 95th percentile, it is expected that if the NKCEA participants were similar to the general U.S. population, 5% of people would have serum values for each PFAS above the 95th percentile value available for comparison from NHANES. For PFOA, L-PFOA, Br-PFOA, PFOS, Br-PFOS, PFHxS, and PFHpA more than 5% of the NKCEA participants had serum concentrations that exceeded these analytes' 95th percentile values (Table 4). For PFNA, PFUnA, PFDA, MeFOSAA, L-PFOS less than 5% of the NKCEA participants had serum concentrations that exceeded these analytes' 95th percentile values.
- For the 90th percentile, it is expected that if the NKCEA participants were similar to the general U.S. population, 10% of people would have serum values for each PFAS above the 90th percentile value available for comparison from NHANES. More than 10% of the NKCEA participants had serum concentrations of PFOA, L-PFOA, Br-PFOA, Br-PFOS, PFHxS, and PFHpA that exceeded these analytes' 90th percentile values (Table 4). For PFNA, PFUnA, PFDA, MeFOSAA, L-PFOS less than 10% of the NKCEA participants had serum concentrations that exceeded these analytes' 90th percentile values.
- For the 75th percentile, it is expected that if the NKCEA participants were similar to the general U.S. population, 25% of people would have serum values for each PFAS above the 75th percentile value available for comparison from NHANES. For PFOA, L-PFOA, Br-PFOS, PFHxS, and PFHpA more than 25% of NKCEA participants had serum concentrations that exceeded these analytes' 75th percentile values (Table 4). For PFNA, PFUnA, MeFOSAA, L-PFOS less than 25% of the NKCEA participants had serum concentrations that exceeded these analytes' 75th percentile values.
- For the 50th percentile, it is expected that if the NKCEA participants were similar to the general U.S. population, 50% of people would have serum values for each PFAS above the 50th percentile value available for comparison from NHANES. For PFOA, L-PFOA, Br-PFOS, and PFHxS more than 50% of the NKCEA participants had serum concentrations that exceeded these analytes' 50th percentile values (Table 4). For PFNA, L-PFOS, and MeFOSAA, less than 50% of the NKCEA participants had serum concentrations that exceeded these analytes' 50th percentile values.
- The geometric means for participants ages 3-11 were significantly higher than NHANES geometric means for PFOA, Br-PFOS, and PFHxS. The NHANES geometric mean was significantly higher than the NKCEA participants' geometric mean for PFNA (Table 4).

For other PFAS, either no comparison could be made or the NKCEA result was comparable to that from NHANES.

Table 4: PFAS detection frequency, estimated percent above NHANES percentiles (weighted), and estimated geometric means (weighted) and confidence intervals of NKCEA participants ages 3-11 compared to geometric means and confidence intervals of NHANES participants (n=49).

Analyte	Participant detection frequency (%)	Percent of participants above NHANES 50th percentile (weighted) (%)	Percent of participants above NHANES 75th percentile (weighted) (%)	Percent of participants above NHANES 90th percentile (weighted) (%)	Percent of participants above NHANES 95th percentile (weighted) (%)	NKCEA geometric mean and 95% confidence interval (weighted) (µg/L)	*NHANES geometric mean and 95% confidence interval (µg/L)
PFOA [v]	98.0	51.5	32.5	25.1	23.9	**2.90 (2.99-4.21)**	1.92 (1.75-2.12)
L-PFOA	98.0	57.0	33.7	25.1	23.9	2.84 (1.96-4.13)	1.81 (1.64-2.01)
Br-PFOA [§]	69.4	^NA	^NA	^NA	18.4	0.03 (0.02-0.06)	NC
PFOS[v]	100.0	46.6	25.2	9.8	6.1	3.94 (3.15-4.94)	3.88 (3.53-4.27)
L-PFOS	95.9	25.2	16.0	6.7	2.5	1.53 (1.01-2.32)	2.51 (2.30-2.74)
Br-PFOS [§]	98.0	79.8	44.8	27.6	16.6	**2.10 (1.67-2.64)**	1.23 (1.09-1.40)
PFNA	98.0	11.0	1.2	0.0	0.0	0.30 (0.19-0.46)	**0.80 (0.68-0.93)**
PFHxS[v]	100.0	78.5	51.5	42.3	34.3	**2.22 (1.51-3.26)**	0.84 (0.76-0.94)
L-PFHxS	100.0	‡NA	‡NA	‡NA	‡NA	2.12 (1.44-3.12)	‡NA
Br-PFHxS[§]	91.8	‡NA	‡NA	‡NA	‡NA	0.08 (0.05-0.12)	‡NA
PFBS	53.1	^NA	^NA	^NA	^NA	NC	NC
PFTeA	14.3	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFTriA	36.7	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFDoA	69.7	^NA	^NA	^NA	^NA	0.01 (0.01-0.02)	NC
PFUnA	83.7	^NA	12.9	0.0	0.0	0.04 (0.03-0.06)	NC
PFDA	98.0	^NA	25.8	4.3	0.0	0.11 (0.08-0.16)	NC
PFHpA	98.0	^NA	^NA	^NA	^NA	0.08 (0.06-0.11)	NC
PFHxA	20.4	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFPeA	36.7	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFBA	83.7	‡NA	‡NA	‡NA	‡NA	0.04(0.03-0.06)	‡NA
PFDS	24.5	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFNS	10.2	‡NA	‡NA	‡NA	‡NA	NC	‡NA
PFHpS	95.9	‡NA	‡NA	‡NA	‡NA	0.18 (0.11-0.28)	‡NA
PFPeS	93.9	‡NA	‡NA	‡NA	‡NA	0.11 (0.07-0.18)	‡NA
PFOSA	46.9	^NA	^NA	^NA	^NA	NC	NC

Analyte	Participant detection frequency (%)	Percent of participants above NHANES 50th percentile (weighted) (%)	Percent of participants above NHANES 75th percentile (weighted) (%)	Percent of participants above NHANES 90th percentile (weighted) (%)	Percent of participants above NHANES 95th percentile (weighted) (%)	NKCEA geometric mean and 95% confidence interval (weighted) (µg/L)	*NHANES geometric mean and 95% confidence interval (µg/L)
FTS 8:2	28.6	‡NA	‡NA	‡NA	‡NA	NC	‡NA
FTS 6:2	6.1	‡NA	‡NA	‡NA	‡NA	NC	‡NA
FTS 4:2	6.1	‡NA	‡NA	‡NA	‡NA	NC	‡NA
EtFOSAA	28.6	^NA	^NA	^NA	^NA	NC	NC
MeFOSAA	95.9	39.3	13.5	5.5	1.2	0.10 (0.07-0.15)	NC

* Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. National Report on Human Exposure to Environmental Chemicals. Updated March 2022. https://www.cdc.gov/exposurereport/. Accessed July 6, 2023.

Bold typeface values indicate significantly higher results.

NC = Not calculated because the analyte was not detected for more than 60% of participants.

NA = Not available from NHANES.

‡ Not available from NHANES because the analyte was not measured in NHANES for this age group.

^ Not available because the NHANES 95th percentile was below the NHANES limit of detection.

§ MDHHS Bureau of Labs is evaluating the comparability of sums of linear and branched isomers between the NHANES laboratory method and the MDHHS laboratory method and has determined that the branched isomer calibration methods used for the NKCEA specimen analysis resulted in branched PFOS results biased high relative to NHANES branched PFOS results.

[v] MDHHS Bureau of Labs is evaluating the comparability of sums of linear and branched isomers between the NHANES laboratory method and the MDHHS laboratory method and has determined that the branched isomer calibration methods used for the NKCEA specimen analysis resulted in branched PFOS results biased high relative to NHANES branched PFOS results.

Water PFAS Concentrations

Descriptive Statistics of Water Concentrations

From the questionnaire, 258 out of 413 (62.47%) participants indicated their current drinking water source at the time of their participation was bottled water and seven participants (1.69%) indicated their source was municipal water. The remaining 148 participants (35.84%) indicated they were still using their private well as their main drinking water source; of this group, 111 participants indicated that their water was filtered.

On the drinking water history portion of the questionnaire, 360 participants indicated their prior drinking water source was a private well; 16 indicated their main source was bottled water; five indicated their main source was municipal water; and 32 did not indicate a prior drinking water source. Of the 360 participants who indicated drinking from private wells, 57 participants indicated they used a filter and 301 participants indicated not using a filter.

Unfiltered Drinking Water Sample Descriptive Statistics

In total, 183 unfiltered drinking water samples were collected. This is one sample for every participating household (Figure 2). Twenty-nine of the 30 measured PFAS were detected in at least one water sample. PFTeA was not detected in any water samples. (Table 5). The median was reported as below the reporting limit if the PFAS was detected in less than 50% of samples. PFOA, L-PFOA, Br-PFOS, PFHpA, PFHxA, PFPeA, PFBA, PFHxS, L-PFHxS, PFPeS, and PFBS were frequently detected (detection rates >50%) in unfiltered drinking water samples. The geometric means for PFOA and PFOS in unfiltered drinking water were both above the comparison values MDHHS set for public health assessment.[b] Maximum detected concentrations exceeded comparison values for five out of the seven PFAS for which comparison values are available.

[b] The MDHHS comparison values for seven PFAS are: PFNA: 6 ppt; PFOA: 8 ppt; PFHxA: 400,000 ppt; PFOS: 8 ppt; PFHxS: 51 ppt; PFBS: 420 ppt.

Table 5: Unfiltered drinking water sample PFAS concentration summary statistics (n=183).

Analyte	Unfiltered drinking water detection frequency (%)	Median concentration (ng/L)	Geometric Mean (ng/L)	Maximum concentration (ng/L)	MDHHS comparison values (ng/L)
PFOA	54	5	14.97	13,184	8
L-PFOA	64	4	10.07	10,710	NA
Br-PFOA	46	<RL	5.15	2,474	NA
PFOS	41	<RL	10.35	46,048	8
L-PFOS	33	<RL	4.08	15,038	NA
Br-PFOS	51	2	6.3	31,011	NA
PFTeA	0	NC	NC	< RL	NA
PFTriA	2	<RL	3.13	11	NA
PFDoA	2	<RL	1.69	4	NA
PFUnA	10	<RL	1.59	13	NA
PFDA	6	<RL	1.49	9	NA
PFNA	13	<RL	1.72	35	6
PFHpA	59	3	6.52	2,564	NA
PFHxA	58	3	5.73	1,374	400,000
PFPeA	63	4	5.18	462	NA
PFBA	54	3	4.10	819	NA
PFDS	3	<RL	1.58	4	NA
PFNS	2	<RL	1.46	13	NA
PFHpS	36	<RL	3.28	3,564	NA
PFHxS	54	6	11.62	8,691	51
L-PFHxS	73	4	8.22	7,103	NA
Br-PFHxS	48	<RL	4.10	1,588	NA
PFPeS	62	4	7.32	3,545	NA
PFBS	90	11	13.26	1,996	420
PFOSA	6	<RL	4.23	24	NA
8:2 FTS	3	<RL	1.62	8	NA
6:2 FTS	3	<RL	1.47	7	NA
4:2 FTS	2	<RL	1.54	9	NA
EtFOSAA	1	<RL	1.87	3	NA
MeFOSAA	2	<RL	1.56	15	NA

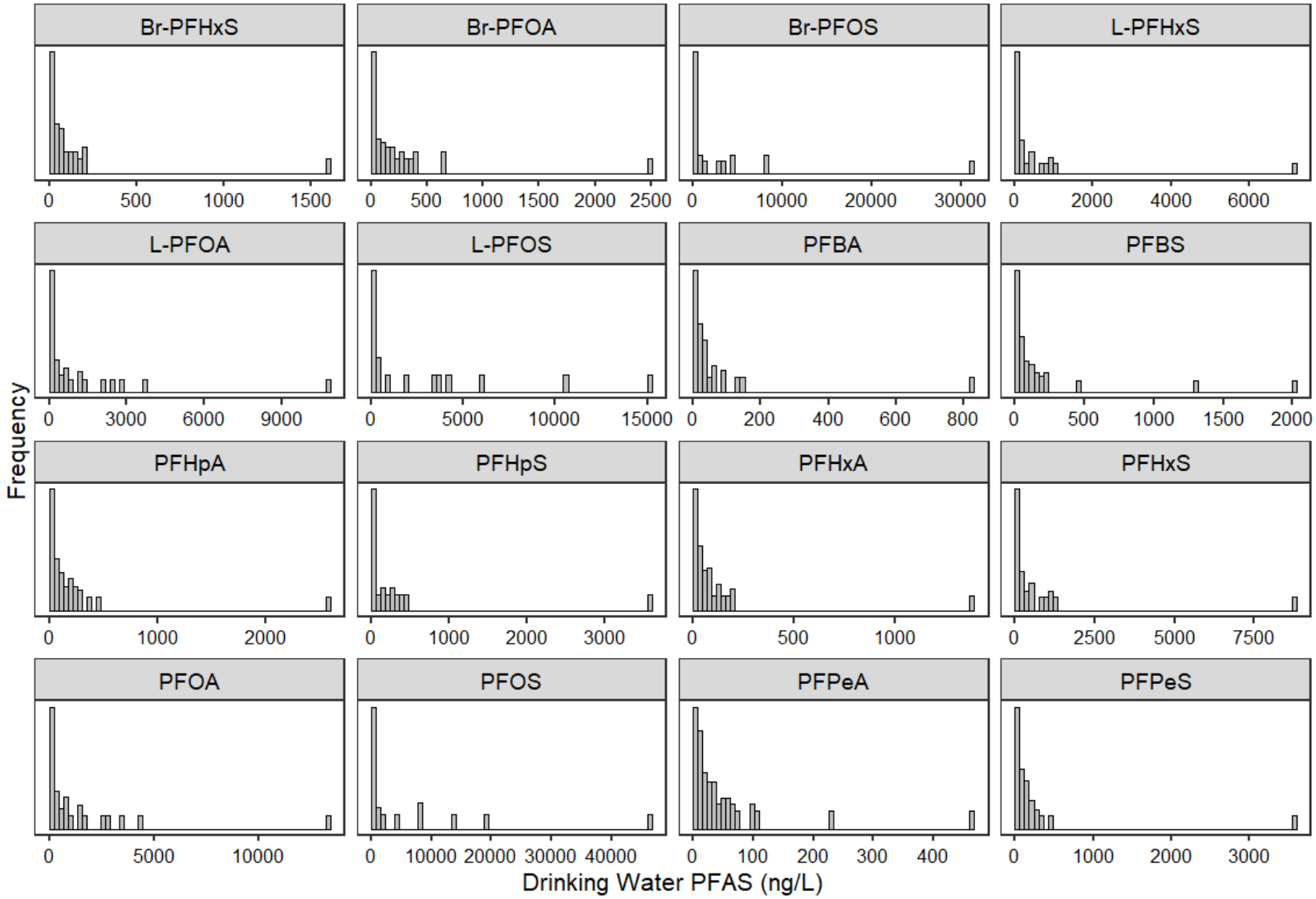
<RL = The measurement is below MDHHS laboratory reporting limit.

NC = Not calculated because the analyte was never detected.

ng/L = nanograms per liter or parts per trillion

NA = Not applicable, no MDHHS comparison value was available at the writing of this report.

Figure 2: Frequency histogram of the detected concentrations for the 16 PFAS with detection rates above 20% in unfiltered private drinking water well samples (gray bars).



Filtered Drinking Water Sample Descriptive Statistics

In total, 195 filtered drinking water samples were collected from the 183 households. The total exceeded 183 because some households had two filters. Filtered drinking water samples generally had lower PFAS concentrations in terms of both detection rates and maximum concentrations with some exceptions. PFUnA, 8:2 FTS, 4:2 FTS, MeFOSAA, EtFOSAA, and PFDS had slightly higher maximum values (typically 1 ppt or up to 10 ppt in case of MeFOSAA) in filtered water (Table 6). The max values of PFUnA, 8:2 FTS, 4:2 FTS, MeFOSAA are all from one household. MeFOSAA also had a 1% higher detection rate in filtered water. Except for one water sample collected between a point-of-entry and point-of-use filter, filtered drinking water samples did not exceed any MDHHS comparison values.[c]

Table 6: Detection frequency and maximum value of PFAS measured in filtered drinking water samples (n = 195).

Analyte	Detection frequency (%)	Maximum (ppt)
PFOA	1	5
L-PFOA	3	5
Br-PFOA	1	2
PFOS	3	31[#]
L-PFOS	4	12
Br-PFOS	4	22
PFTeA	0	< RL
PFTriA	0	< RL
PFDoA	1	4
PFUnA	6	30
PFDA	2	9
PFNA	2	4
PFHpA	3	4
PFHxA	1	8
PFPeA	7	52
PFBA	11	269
PFDS	2	5
PFNS	1	4
PFHpS	2	4
PFHxS	2	19
L-PFHxS	2	8
Br-PFHxS	1	13
PFPeS	2	6

[#] With the exception of PFOS: PFOS comparison values were exceeded in three out of the 195 samples. At two households where the exceedance occurred, there were both point-of-entry and point-of-use filters. Only the samples taken between the two filters exceeded the comparison value for PFOS. The corresponding sample taken after the point-of-use filter (from which residents presumably directly draw drinking water) did not have PFOS detected. At the third household, the detection seems to have been a sample bottle labeling issue because the corresponding unfiltered sample does not have detectable PFAS. MDHHS attempted to collect a confirmation sample from this household but was not able to get permission from the residents.

Analyte	Detection frequency (%)	Maximum (ppt)
PFBS	3	18
PFOSA	1	4
8:2 FTS	1	35
6:2 FTS	1	3
4:2 FTS	1	11
EtFOSAA	1	4
MeFOSAA	3	29

Medians and geometric means are not reported due to low detection rates of analytes in filtered drinking water samples.
<RL = The estimate is below the MDHHS laboratory reporting limit
ppt = parts per trillion or ng/L
[#] see footnote c

Water-Serum Relationship

This exposure assessment aimed to determine the relationship between serum PFAS concentrations and drinking water PFAS concentrations, as well as the factors that influence that relationship. In this part of the analysis, PFAS concentrations from the unfiltered drinking water samples were used as the drinking water PFAS concentrations and compared to measured serum PFAS concentrations.

PFAS Drinking Water Concentrations and Serum PFAS

When comparing the serum PFAS concentrations of NKCEA participants with the PFAS concentrations in the household drinking water, there was a consistent increase in the average (geometric mean) serum PFAS concentration associated with increasing PFAS concentration in their unfiltered drinking water for most PFAS that could be analyzed; this includes PFOA, PFOS, PFHxS, PFHpS, and PFPeS (A, B, C). For PFHpA and PFBA, there was only a very slight change or no consistent change, respectively, in the average serum concentration with increasing PFAS concentration in the drinking water.

For three PFAS (PFOA, PFOS, and PFHxS), it is possible to predict the serum PFAS concentrations from drinking water with PFAS at each concentration group for a lifetime of exposure using pharmacokinetic modeling. Comparing the measured average (geometric mean) and variance (5^{th} to 95^{th} percentile) against the predicted intervals of serum concentrations in participants with 10 to 100 ng/L or greater than 100 ng/L of each respective PFAS, there was a high degree of overlap between the actual and predicted serum PFAS concentrations. When looking at the participant groups with no detected PFAS drinking water concentrations or ND to 10 ng/L and comparing the actual vs. predicted serum values, most serum PFAS concentrations from NKCEA participants were much higher than what can be explained by the amount of PFAS in their drinking water alone (underpredicted).

There was significant variability within the groups. There were some participants with serum values under the predicted range but also a few that were over (A, B, C). Underprediction indicates that measured serum PFAS is higher than expected and overprediction indicates that measured serum PFAS is lower than expected. The reasons for this are explored later in the report—but in short, this indicates other factors besides the water PFAS concentration are important in determining serum PFAS concentration.

Daily PFAS Intake via Drinking Water and Serum PFAS

The concentration of some PFAS in drinking water only partially explained the increased serum PFAS concentrations currently observed in NKCEA participants (A, B, C). To understand the influence of drinking more or less water on the relationship between PFAS in the water and serum; the participants were grouped by their self-reported filter and bottled water usage before the PFAS contamination was discovered and then based on their self-reported daily water intake (more than or equal to [>=] 6 or less than [<] 6 cups of water) if a filter was not used (Figure 4 A, B, C). For many of the PFAS tested, within each category of drinking water concentrations, those who were already using a filter or mainly drinking bottled water before contamination was discovered had the lowest average serum PFAS concentrations regardless of the PFAS concentration of their unfiltered water. Those who consumed more unfiltered water per day had higher average serum PFAS concentrations.

Since both the amount of water consumed and the drinking water PFAS concentration appears important for some PFAS, the combination of both parameters in the form of the daily PFAS intake in nanograms per day (ng/day) was compared to the serum PFAS concentrations found in that group of participants. In the highest quartile of daily intake, less variation around the geometric mean was observed compared to when drinking water concentration alone was compared to the serum PFAS concentration (Figure 5 A, B, C). For PFOA, PFOS, and PFHxS, there was also no overprediction in the estimated compared to measured serum PFAS concentrations in the highest quartile. At the lower three quartiles, measured serum PFAS concentrations are greater than the predicted serum PFAS concentrations, which is similar to the underprediction seen with use of only water PFAS concentrations.

Residence Duration and Serum PFAS Concentrations

Another component of exposure that can explain some of the variability observed is how long people were drinking the water. Participants were grouped based on how long they were living in the home where their water was sampled (“residence duration”) (Figure 6 A, B, C). Residence duration was broken down into three groups which roughly represent short, average, and long duration of living in a home. When comparing across the three residence duration groups within each daily intake group, there is not a clear and consistent pattern. However, within each residence duration group, a greater daily intake of PFAS in drinking water appeared to be associated with greater serum PFAS concentrations. Taken together, this shows that duration of exposure was not as important for increased serum PFAS concentrations in NKCEA participants, rather it was the amount of PFAS consumed via drinking water which was the largest determinant of serum PFAS concentrations. This is especially true if people had been living in the home for more than eight years.

Figure 3A: Geometric mean (center dot) and 5th to 95th percentile (top and bottom of line) of serum PFAS concentrations compared to PFAS concentrations in household private drinking water well.

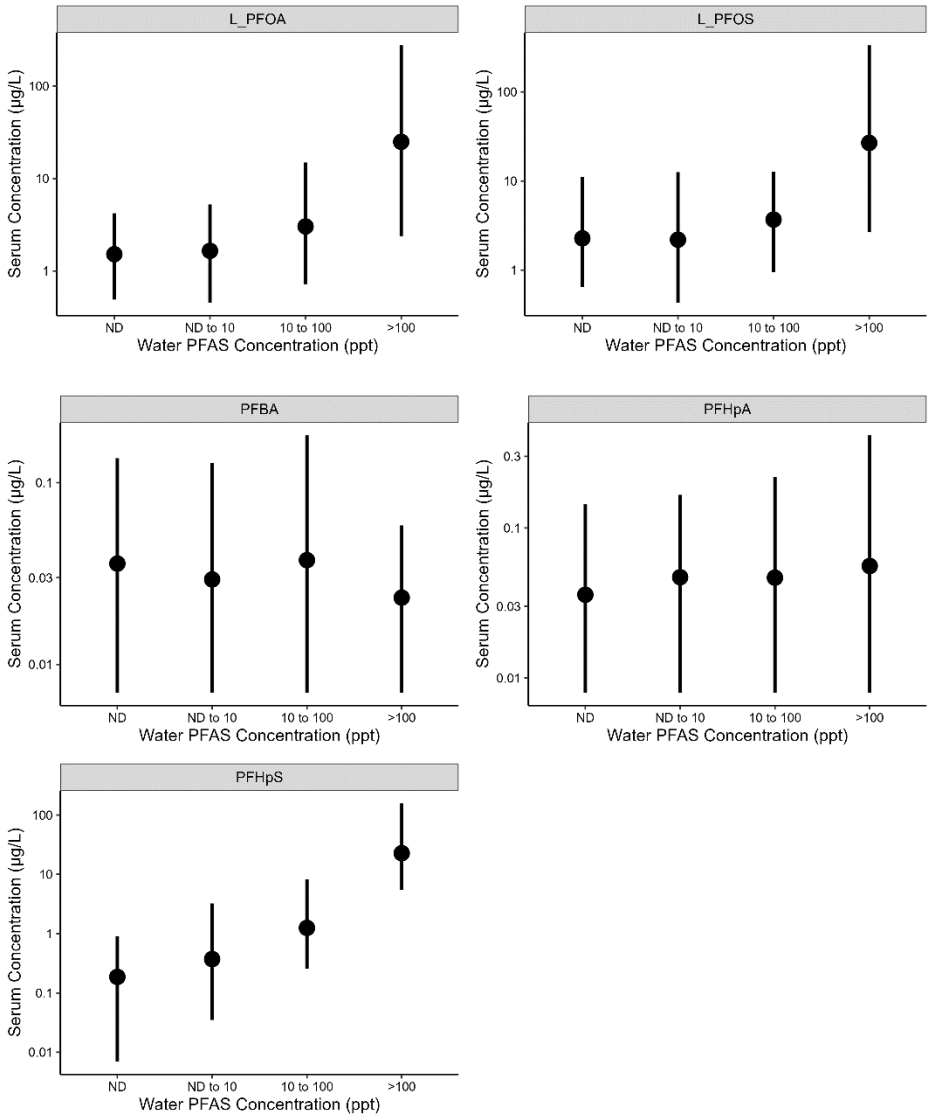


Figure 3B: Geometric mean (center dot) and 5th to 95th percentile (top and bottom of line) of serum PFAS concentrations compared to PFAS concentrations in the households private drinking water well.

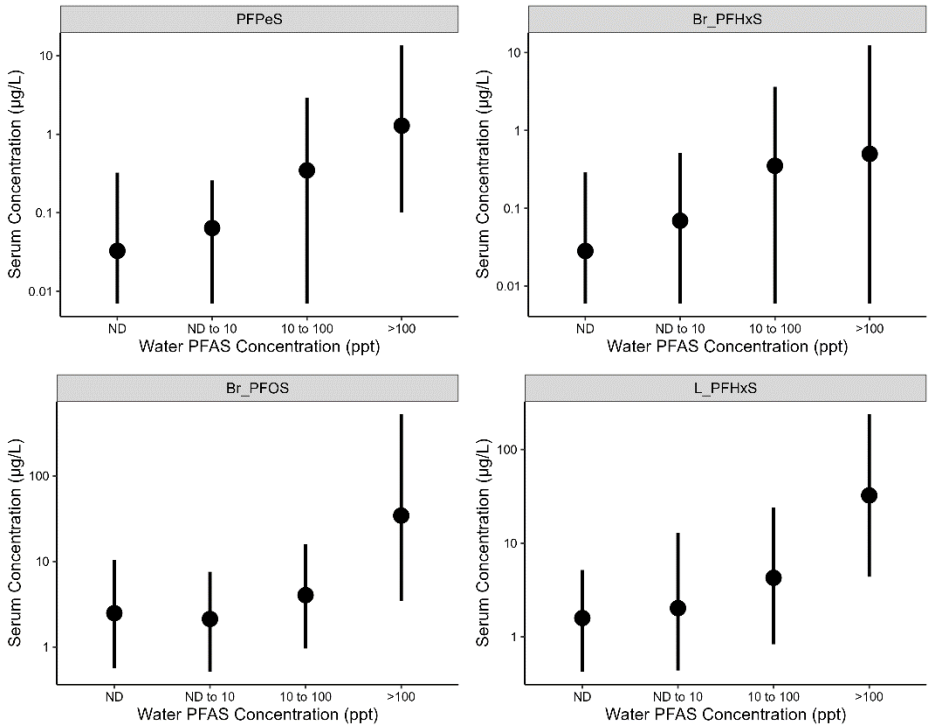


Figure 3C: Geometric mean (center dot) and 5th to 95th percentile (top and bottom of line) of serum PFAS concentrations compared to PFAS concentrations in the households private drinking water well. Gray shaded bars for PFOS, PFOA, and PFHxS are the predicted ranges of steady state serum concentrations from drinking water exposure within the respective groups. These are calculated using equation 5.

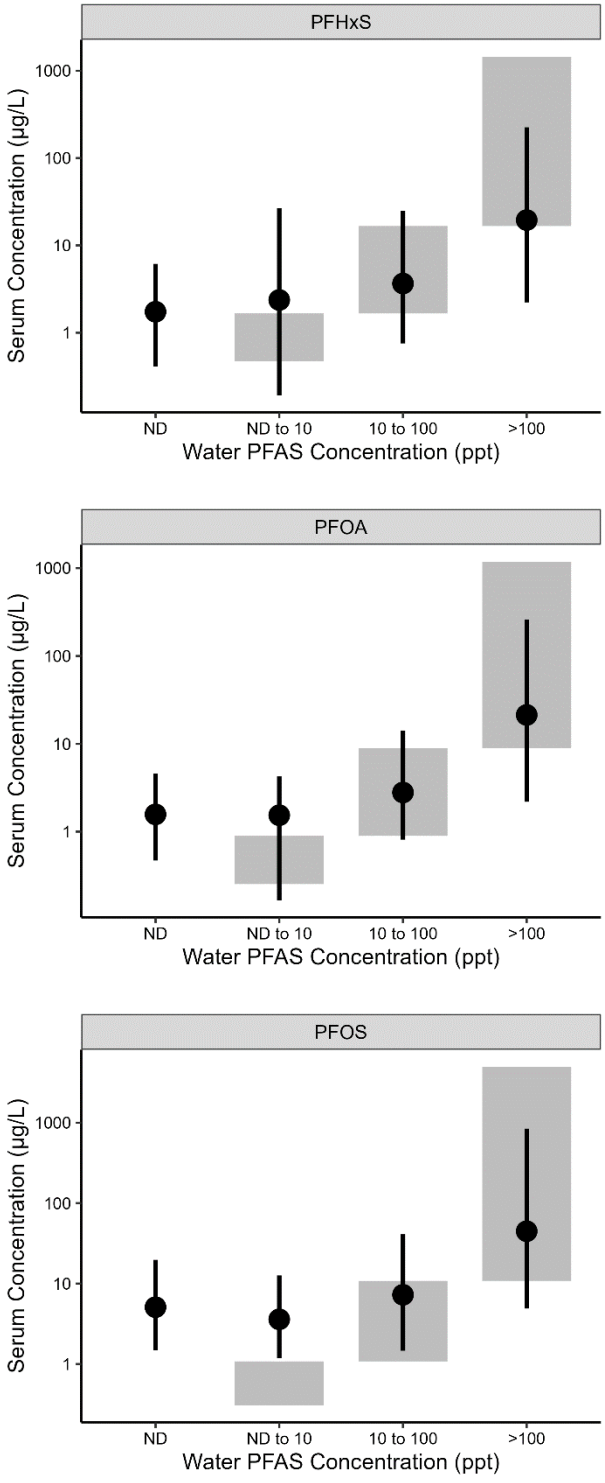


Figure 4A: Serum PFAS concentrations compared to water PFAS concentrations grouped by filter use and self-reported drinking water amount (cups per day).

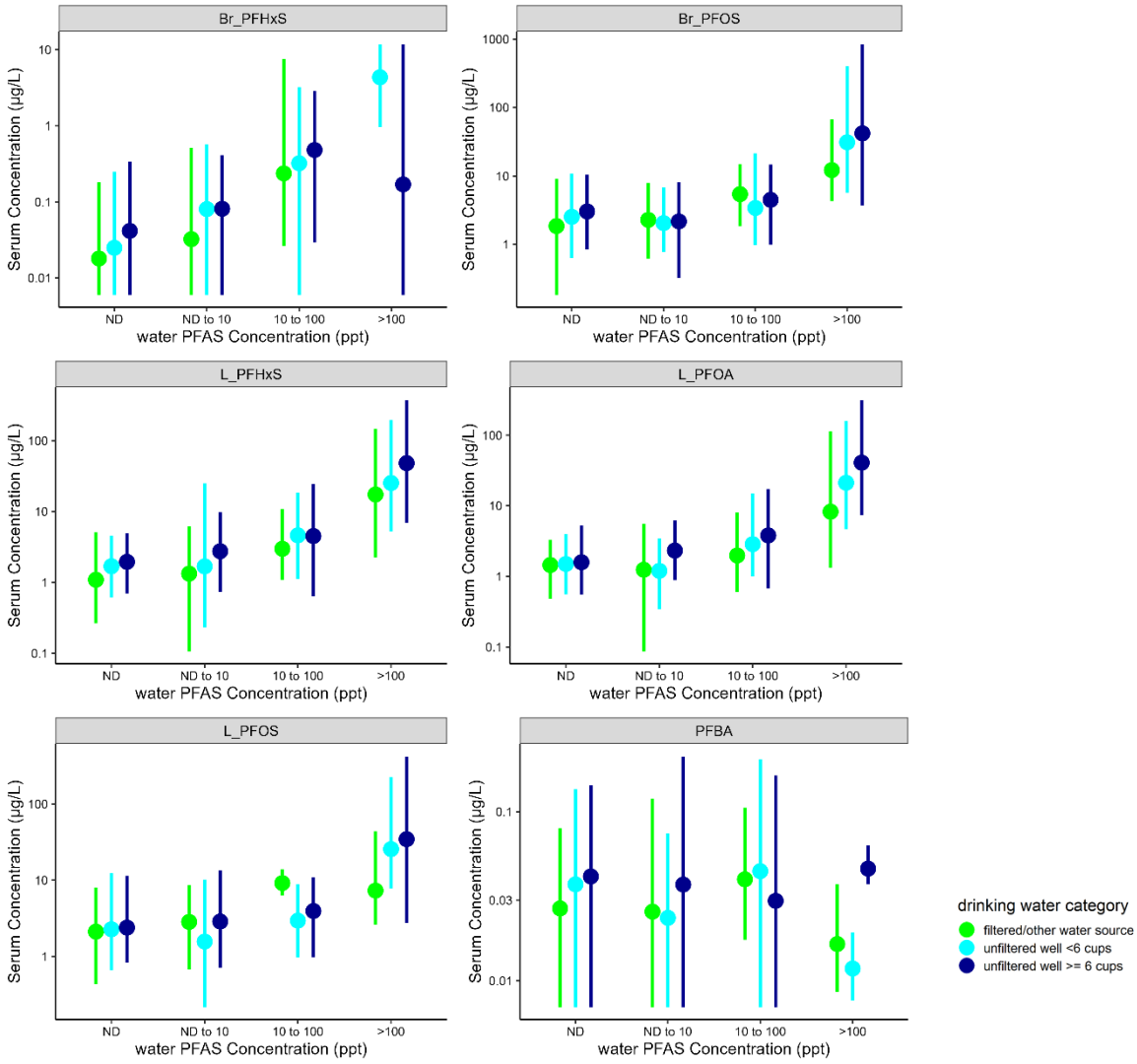


Figure 4B: Serum PFAS concentrations compared to water PFAS concentrations grouped by filter use and self-reported drinking water amount (cups per day).

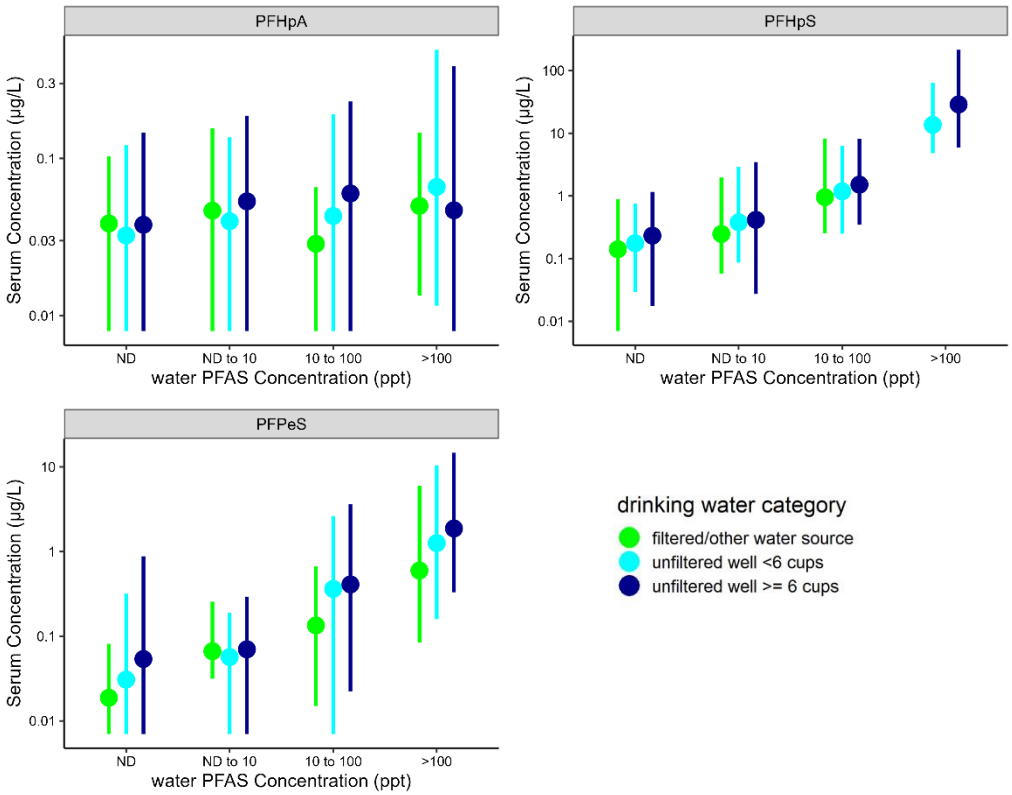


Figure 4C: Serum PFAS concentrations compared to water PFAS concentrations grouped by filter use and self-reported drinking water amount (cups per day). Grey bars for PFOS, PFOA, and PFHxS are the predicted ranges of steady state serum concentrations from drinking water exposure within the respective groups. These are calculated using equation 5.

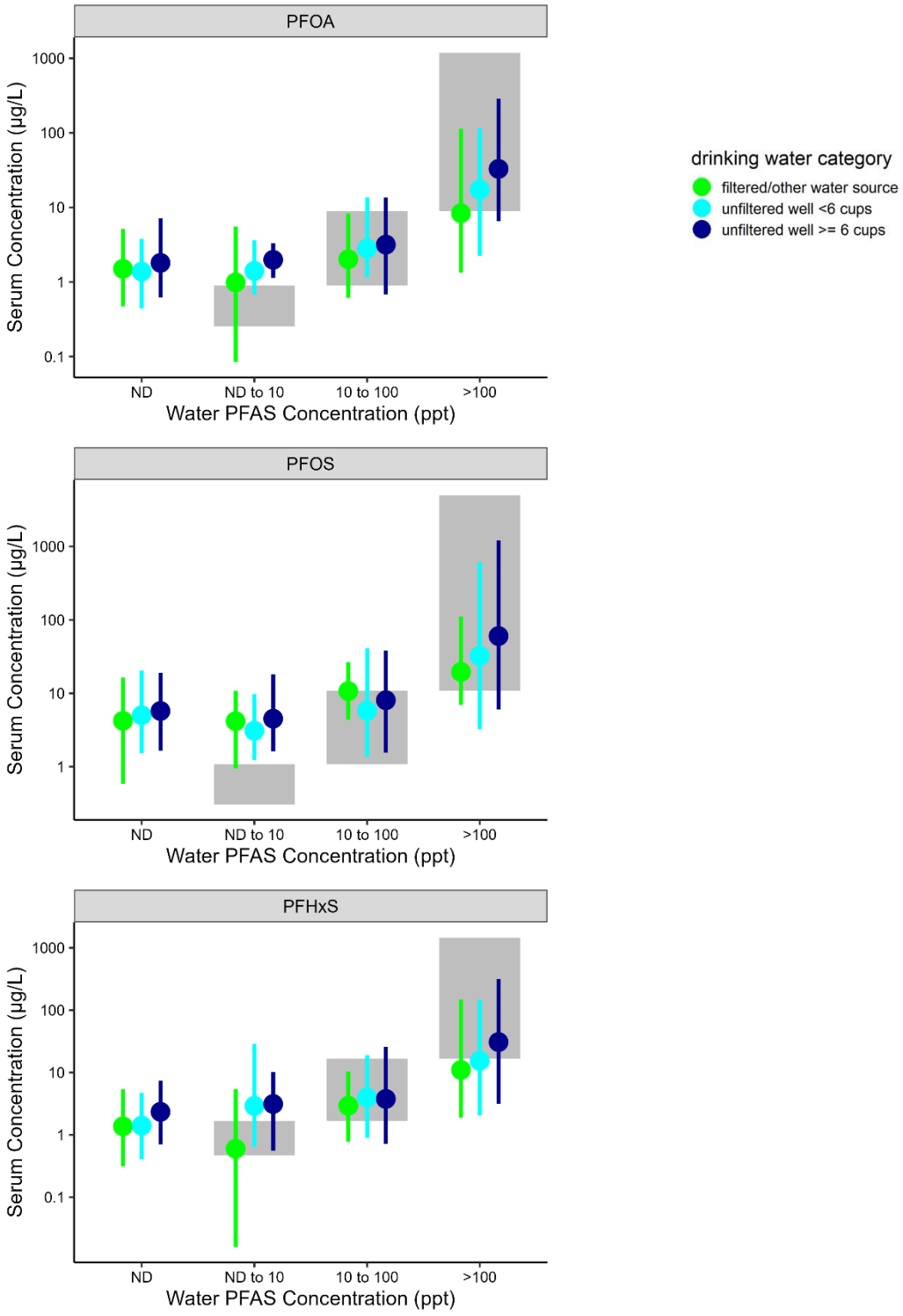


Figure 5A: Serum PFAS concentrations compared to daily intake of PFAS from drinking water.

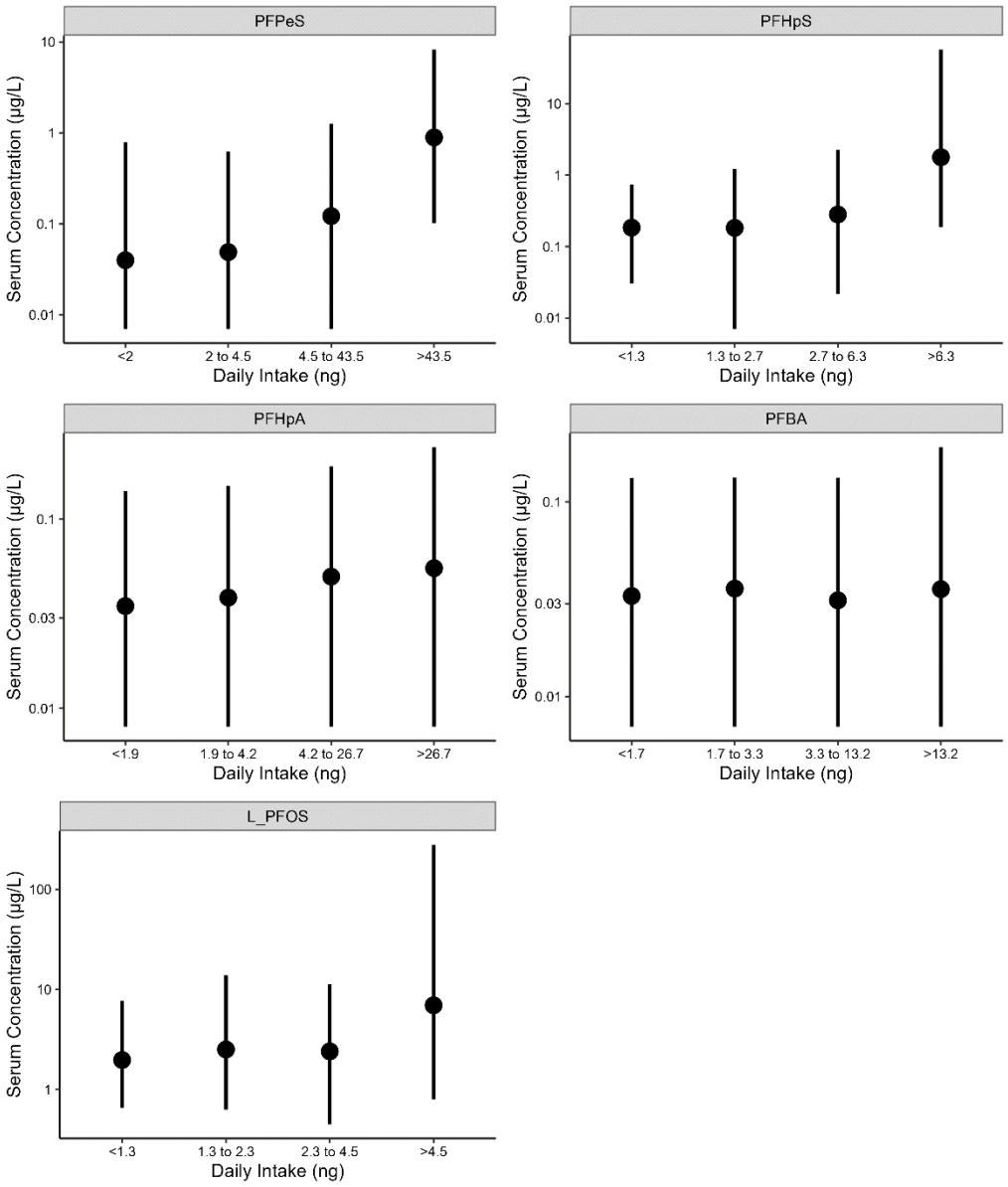


Figure 5B: Serum PFAS concentrations compared to daily intake of PFAS from drinking water.

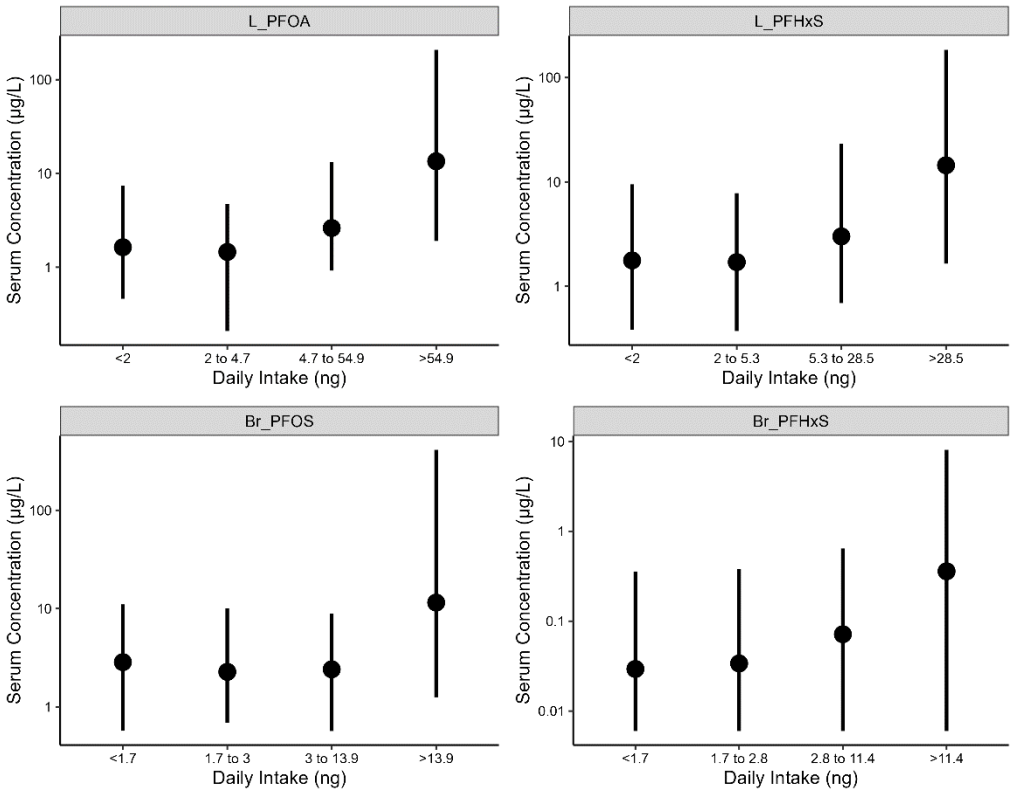


Figure 5C: Serum PFAS concentrations compared to daily intake of PFAS from drinking water. Grey bars for PFOS, PFOA, and PFHxS are the predicted ranges of steady state serum concentrations from daily intake water exposure within the respective groups. These are calculated using the modified equation 5.

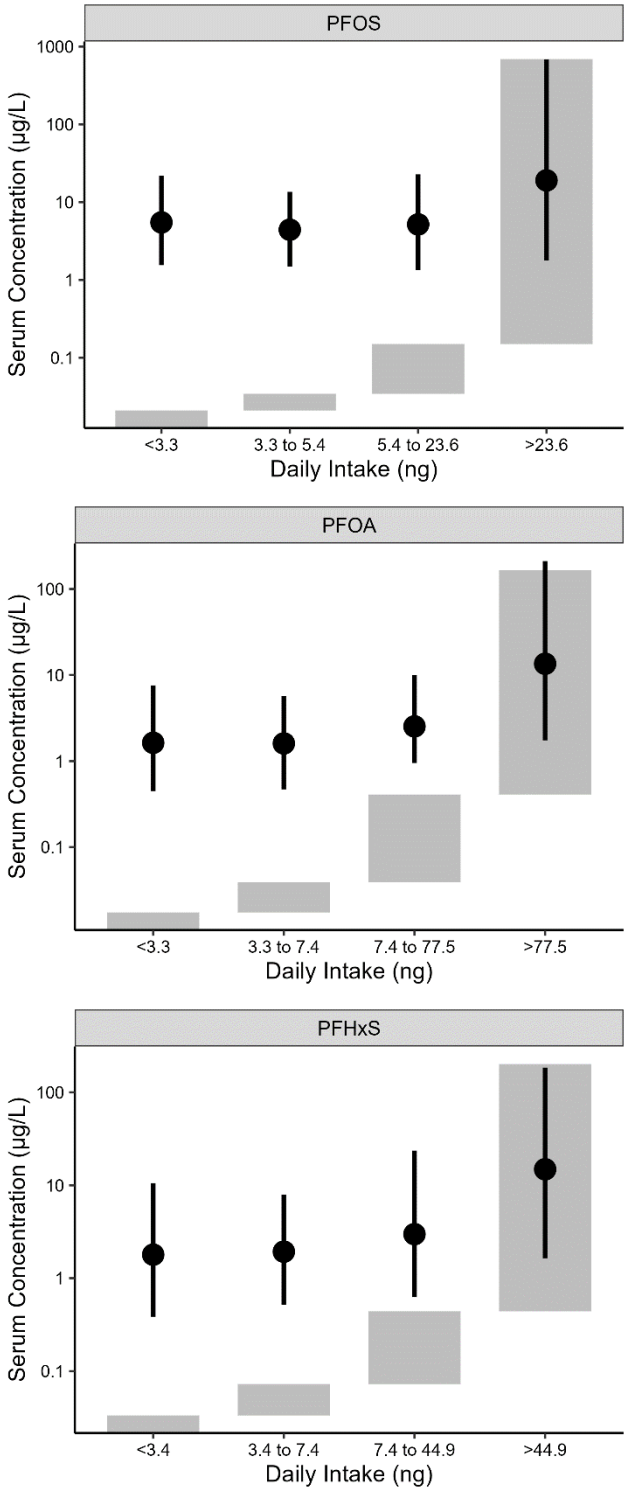


Figure 6A: PFAS daily intake from drinking water in ng/day compared to serum PFAS concentration grouped by self-reported duration of living in the home with contaminated drinking water.

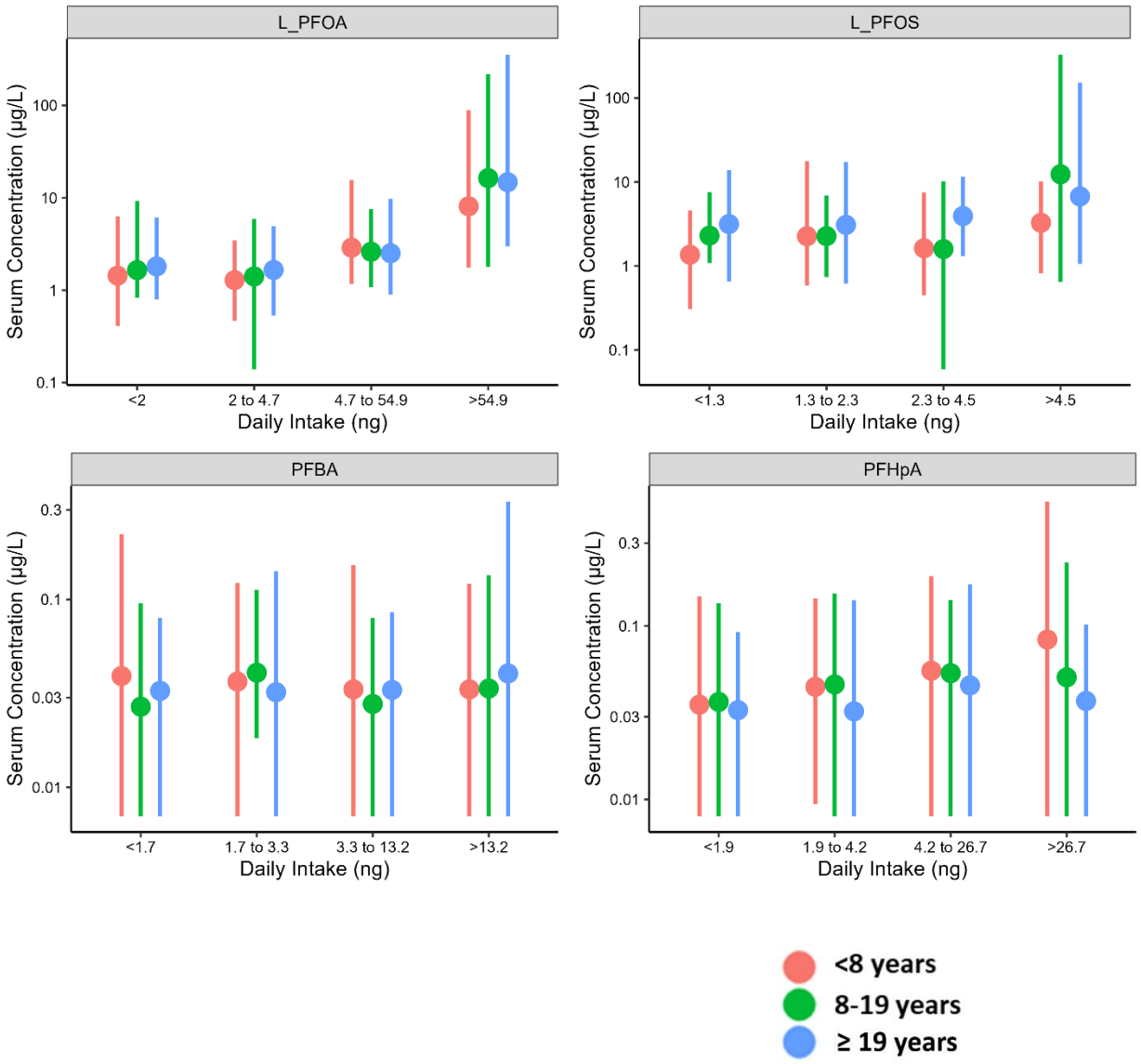


Figure 6B: PFAS daily intake from drinking water in ng/day compared to serum PFAS concentration grouped by self-reported duration of living in the home with contaminated drinking water.

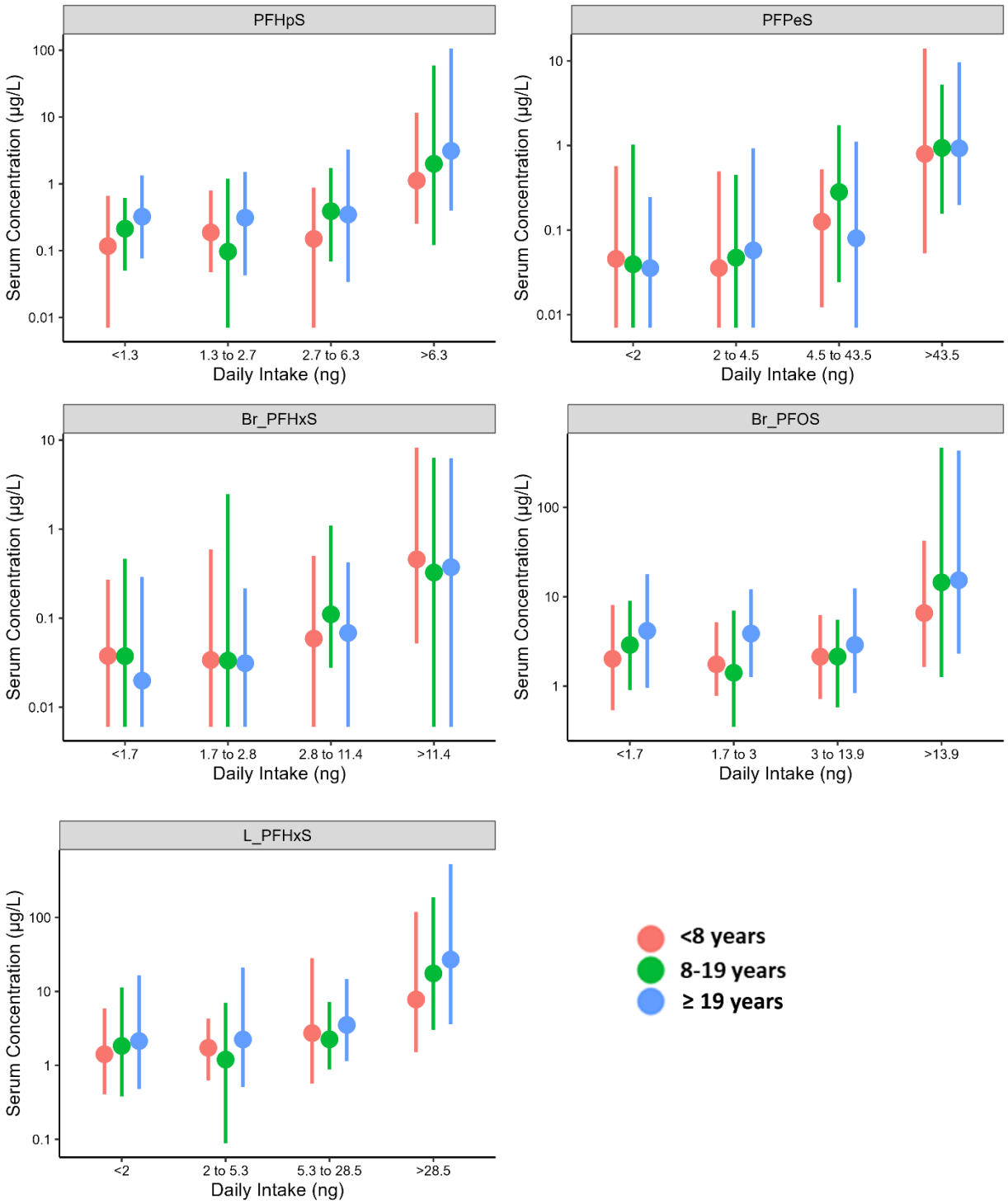
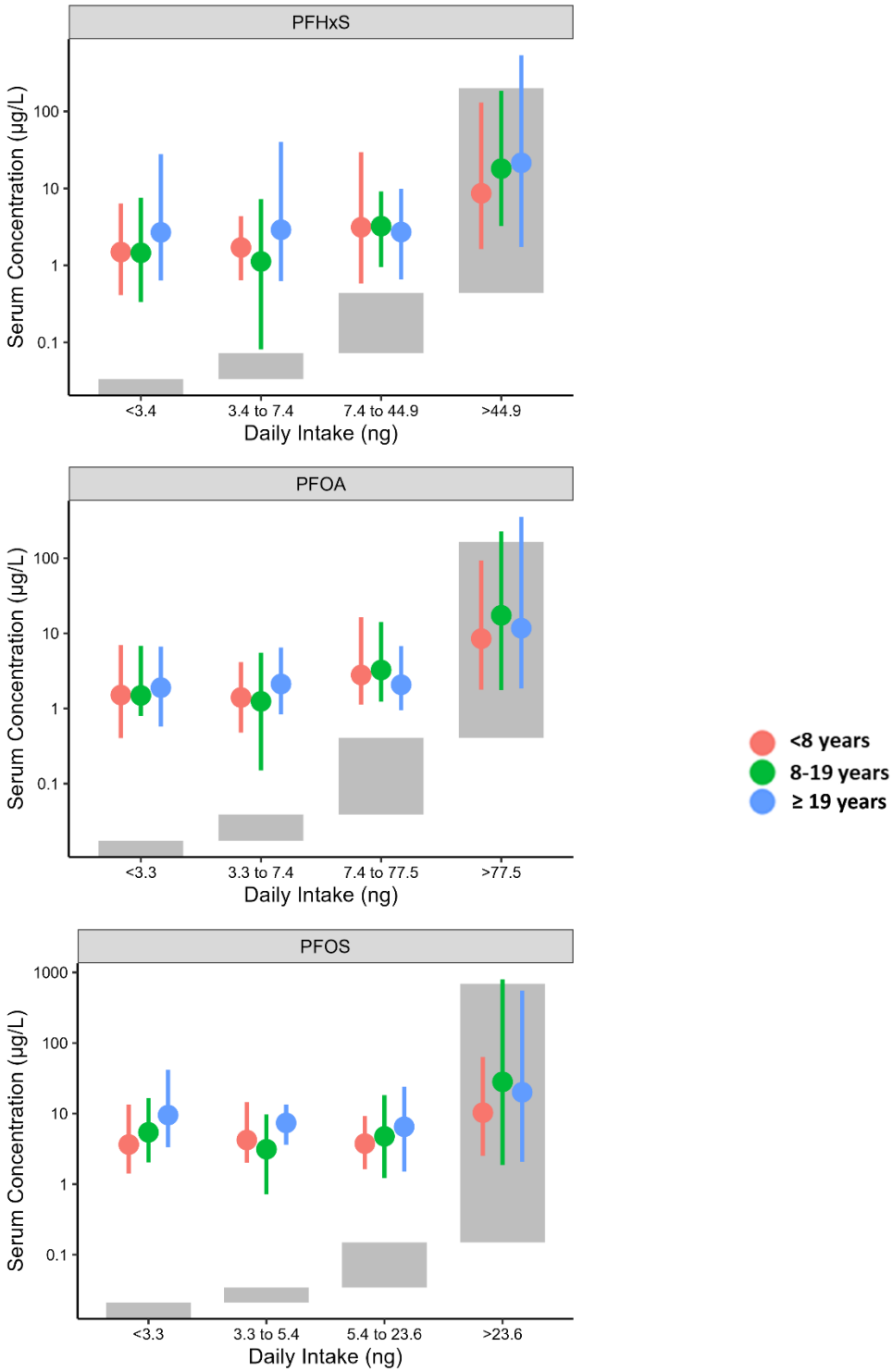


Figure 6C: PFAS daily intake from drinking water in ng/day compared to serum PFAS concentration grouped by self-reported duration of living in the home with contaminated drinking water. Grey bars for PFOS, PFOA, and PFHxS are the predicted ranges of steady state serum concentrations from drinking water exposure within the respective groups. These are calculated using the modified equation 5.



Statistical Analyses: Daily Intake and Other Factors That Can Affect Serum PFAS Concentrations

In a model to assess the association between various factors that may affect serum PFAS concentrations and serum PFAS concentrations by analyte, age was a significant predictor of many analytes including PFOS, L-PFOS, Br-PFOS, and PFHpS (all increasing with age) and PFHpA (which decreased with age) (Table 7). Sex was also a significant predictor of serum PFAS for many PFAS, with males having statistically higher serum PFAS concentrations than females for PFOA, L-PFOA, PFOS, L-PFOS, Br-PFOS, PFBA, PFHxS, L-PFHxS, and PFHpS. Models for other analytes showed no statistically significant differences between men and women.

Eating hunted deer from anywhere was statistically significantly associated with an increase in serum levels of L-PFOS (Table 7). Eating hunted deer from inside the study area and eating hunted game from inside the study area were significantly negatively associated with serum PFHpA. Eating hunted game from anywhere, eating eggs from chickens, and eating vegetables from inside the study area or anywhere else were all factors not statistically significantly associated with serum PFAS concentrations for any other PFAS. Eating wild-caught fish from inside or outside the study area was significantly associated with higher serum concentrations of PFOS, L-PFOS, and PFBA. The number of years spent living in the home (residence duration) was significantly associated with increased PFHpA concentrations but was not significantly associated with any of the other analytes.

In models including only participants aged 18 or over, all serum PFAS except PFHpA were negatively associated with blood/plasma donation. Results show a decrease in serum PFAS of between 3%-7% per each additional yearly blood or plasma donation (Table 8). Having ever been diagnosed with kidney disease was also highly associated with lower serum PFAS concentrations for most PFAS. Of the 14 adults who reported ever having been diagnosed with kidney disease, 7% also reported having been on dialysis. Only serum PFHpA concentrations had an association with ever having been diagnosed with diabetes, with an estimated 77% increase in serum PFHpA in those who were ever diagnosed with diabetes. No associations were found with self-reported ever having been diagnosed with anemia.

No associations were found with self-reported work history in an industry that uses PFAS (Table 8). Only 13 participants had ever worked for Wolverine Worldwide, Inc. Among these former workers, most of the jobs they described having at Wolverine were unlikely to have had much involvement in production, and the few individuals with job descriptions that could have involved contact with fluorochemicals had left their position(s) by 1987. Similarly, of the 10 individuals who had a history of living or working on a military base, few of the self-reported roles on the military base were likely to have had much contact with fluorochemicals, and most positions were held prior to the 2000s. The 46 individuals who reported working in another type of PFAS-related job in the past 20 years described positions with a wide range of likelihood of PFAS exposure.

In models including only adult females, although no statistically significant associations were found between serum PFAS concentrations and number of months spent breastfeeding children, number of births, or having menstruated in the three years before the blood draw, the estimated percent change in serum PFAS was negative in almost all cases (Table 9).

In an analysis regressing serum PFAS on total months a minor (aged less than 18 years) spent breastfeeding as an infant (adjusted for the age of the minor and household income), no statistically

significant associations were found. However, it is worth noting that for 10 of the 12 analytes measured, a positive association was found between time spent breastfeeding and serum PFAS concentrations (Table 10. Percent change in serum PFAS, by analyte, per one month increase in having been breastfed among participants less than 18 years old.).

When evaluating the associations between estimated daily intake of PFAS by analyte (in ng/day) from contaminated drinking water and PFAS concentration in serum of the same analyte, all measured analytes (except for PFBA, which showed no association) showed positive and highly statistically significant associations (Table 11). Results are reported in the table as the percent change in serum PFAS concentration associated with a 1% increase in estimated daily intake from drinking water.

Table 7. Percent change in serum PFAS, by analyte, per one unit/level change in predictor variable.

Predictor variable	N	Serum PFOA % change (p-value)	Serum L-PFOA % change (p-value)	Serum PFOS % change (p-value)	Serum L-PFOS % change (p-value)	Serum Br-PFOS % change (p-value)	Serum PFBA % change (p-value)
Age (per 1 year increase)	413	-0.18 (0.46)	-0.18 (0.48)	**1.03 (<0.01)**	**1.10 (<0.01)**	**1.00 (<0.01)**	-0.47 (0.06)
Sex (% change male over female)	413	**14.29 (<0.05)**	**14.38 (<0.05)**	**56.14 (<0.01)**	**39.13 (<0.01)**	**76.52 (<0.01)**	**0.36 (<0.05)**
Years spent living in home (per 1 year increase)	365	0.53 (0.46)	0.55 (0.44)	0.85 (0.24)	1.04 (0.16)	0.69 (0.39)	0.49 (0.43)
Eating hunted deer from anywhere*	351	0.84 (0.93)	1.31 (0.89)	22.89 (0.06)	**34.39 (<0.05)**	13.59 (0.28)	-7.59 (0.38)
Eating deer hunted from inside the study area*	363	2.27 (0.87)	1.18 (0.93)	-2.69 (0.86)	7.67 (0.65)	-16.02 (0.31)	1.30 (0.92)
Eating wild-caught fish from anywhere*	350	-3.44 (0.62)	-3.08 (0.66)	**18.29 (0.05)**	**35.58 (<0.01)**	6.58 (0.50)	**16.20 (<0.05)**
Eating wild-caught fish from inside the study area*	363	-12.95 (0.23)	-12.38 (0.26)	16.98 (0.25)	**34.18 (<0.05)**	6.06 (0.70)	-0.27 (0.98)
Eating other hunted game from anywhere*	353	-9.57 (0.40)	-9.19 (0.42)	15.26 (0.34)	27.55 (0.10)	4.75 (0.78)	-10.48 (0.37)
Eating hunted game from inside the study area*	362	6.67 (0.81)	6.98 (0.81)	55.28 (0.18)	67.95 (0.11)	34.19 (0.42)	25.40 (0.40)
Eating eggs from chickens raised inside the study area*	333	-2.18 (0.81)	-2.19 (0.81)	17.08 (0.12)	**30.26 (<0.05)**	2.68 (0.82)	0.15 (0.99)
Eating vegetables grown inside the study area*	351	3.75 (0.70)	3.66 (0.71)	1.94 (0.86)	9.23 (0.42)	-6.32 (0.59)	3.27 (0.72)

*Food consumption data was categorized as never consuming the food, consuming the food a few times per year or less, and consuming the food once per month or more. Log-transformed serum PFAS concentration was regressed on each of these three-level food variables and results are shown as the percent change in serum PFAS concentration associated with a one-level increase in food consumption.

Statistically significant findings ($p<0.05$) are in **bold typeface.**

Table 7. Percent change in serum PFAS, by analyte, per one unit/level change in predictor variable.

Predictor variable	N	Serum PFHxS % change (p-value)	Serum L-PFHxS % change (p-value)	Serum Br-PFHxS % change (p-value)	Serum PFHpA % change (p-value)	Serum PFHpS % change (p-value)	Serum PFPeS % change (p-value)
Age (per 1 year increase)	413	0.49 (0.12)	0.005 (0.15)	-0.35 (0.41)	**-1.35 (<0.01)**	**1.42 (<0.01)**	-0.23 (0.46)
Sex (% change male over female)	413	**37.96 (<0.01)**	**38.49 (<0.01)**	-17.13 (0.12)	-4.84 (0.57)	**68.73 (<0.01)**	5.40 (0.53)
Years spent living in home (per 1 year increase)	356	0.26 (0.75)	0.24 (0.77)	0.03 (0.98)	**1.25 (<0.05)**	0.84 (0.38)	0.54 (0.59)
Eating hunted deer from anywhere*	351	12.49 (0.28)	12.85 (0.27)	-3.65 (0.81)	-10.89 (0.20)	14.49 (0.32)	-16.06 (0.18)
Eating deer hunted from inside the study area*	363	-15.82 (0.30)	-16.72 (0.28)	-18.29 (0.38)	**-23.73 (<0.05)**	-10.47 (0.59)	-27.46 (0.11)
Eating wild-caught fish from anywhere*	350	-2.28 (0.78)	-1.75 (0.83)	-1.75 (0.83)	12.93 (0.09)	-3.70 (0.72)	2.51 (0.80)
Eating wild-caught fish from inside the study area*	363	4.55 (0.75)	4.89 (0.73)	-5.26 (0.78)	-13.51 (0.20)	2.53 (0.88)	-8.94 (0.56)
Eating other hunted game from anywhere*	353	20.44 (0.19)	20.34 (0.20)	9.90 (0.64)	**-26.54 (<0.05)**	4.87 (0.79)	5.94 (0.73)
Eating other hunted game from inside the study area*	362	23.68 (0.51)	24.01 (0.51)	28.84 (0.58)	-10.15 (0.70)	24.56 (0.58)	2.16 (0.96)
Eating eggs from chickens raised inside the study area*	333	-5.73 (0.58)	-4.94 (0.64)	-20.18 (0.12)	7.95 (0.35)	11.39 (0.41)	-6.46 (0.60)
Eating vegetables grown inside the study area*	351	7.61 (0.51)	8.05 (0.49)	9.35 (0.52)	-8.81 (0.30)	-0.13 (0.99)	-9.42 (0.45)

*Food consumption was categorized as never consuming the food, consuming the food a few times per year or less, and consuming the food once per month or more. Log-transformed serum PFAS concentration was regressed on each of these three-level food variables and results are shown as the percent change in serum PFAS concentration associated with a one-level increase in food consumption.

Statistically significant findings ($p<0.05$) are in **bold typeface.**

Table 8. Percent change in serum PFAS, by analyte, per one unit/level change in predictor variable among adult participants only (18 years old or over).

Predictor variable	N	Serum PFOA % change (p-value)	Serum L-PFOA % change (p-value)	Serum PFOS % change (p-value)	Serum L-PFOS % change (p-value)	Serum Br- PFOS % change (p-value)	Serum PFBA % change (p-value)
Ever had diabetes (yes vs. no)	286	11.38 (0.51)	11.09 (0.53)	19.62 (0.38)	14.87 (0.49)	21.20 (0.40)	-1.13 (0.95)
Ever had kidney disease (yes vs. no)	282	**-44.07 (<0.05)**	**-44.83 (<0.05)**	**-64.65 (<0.01)**	**-62.48 (<0.01)**	**-66.52 (<0.01)**	33.97 (0.24)
Ever had anemia	318	-9.11 (0.59)	-8.73 (0.61)	0.33 (0.99)	-2.16 (0.92)	-0.08 (1.00)	22.65 (0.29)
Number of blood/plasma donations per year (% change per yearly donation)	268	**-5.24 (<0.01)**	**-5.23 (<0.01)**	**-5.14 (<0.01)**	**-3.85 (<0.01)**	**-7.70 (<0.01)**	1.44 (0.18)
Ever worked in an industry that uses PFAS (yes vs. no)	286	2.03 (0.88)	1.66 (0.90)	-13.51 (0.35)	-9.62 (0.51)	-17.35 (0.28)	10.65 (0.45)

Predictor variable	N	Serum PFHxS % change (p-value)	Serum L-PFHxS % change (p-value)	Serum Br-PFHxS % change (p-value)	Serum PFHpA % change (p-value)	Serum PFHpS % change (p-value)	Serum PFPeS % change (p-value)
Ever had diabetes (yes vs. no)	286	15.18 (0.47)	15.14 (0.48)	-38.06 (0.12)	**77.04 (<0.01)**	19.50 (0.47)	28.11 (0.28)
Ever had kidney disease (yes vs. no)	282	**-60.16 (<0.01)**	**-61.19 (<0.01)**	-29.53 (0.41)	49.45 (0.09)	**-58.37 (<0.05)**	-43.49 (0.09)
Ever had anemia	318	-2.44 (0.91)	-3.06 (0.89)	62.34 (0.14)	-18.85 (0.21)	0.18 (0.99)	14.52 (0.54)
Number of blood/plasma donations per year (% change per yearly donation)	268	**-7.12 (<0.01)**	**-7.23 (<0.01)**	**-3.99 (<0.05)**	-0.72 (0.46)	**-6.85 (<0.01)**	**-4.47 (<0.05)**
Ever worked in an industry that uses PFAS (yes vs. no)	286	-16.07 (0.26)	-16.15 (0.26)	**-39.13 (<0.05)**	-11.93 (0.31)	-6.26 (0.74)	-21.39 (0.20)

Statistically significant findings (p<0.05) are in **bold typeface.**

Table 9. Percent change in serum PFAS, by analyte, per one unit change in predictor variable among adult female participants.

Predictor variable	N	Serum PFOA % change (p-value)	Serum L-PFOA % change (p-value)	Serum PFOS % change (p-value)	Serum L-PFOS % change (p-value)	Serum Br-PFOS % change (p-value)	Serum PFBA % change (p-value)
Total months spent breastfeeding children	148	-0.97(0.22)	-0.98 (0.22)	-1.11 (0.20)	-0.77 (0.35)	-1.90 (0.07)	-0.11 (0.87)
Number of births	136	-3.48 (0.71)	-3.43 (0.71)	-8.88 (0.37)	-3.79 (0.69)	-16.59 (0.16)	15.68 (0.11)
Menstruated in last 3 years (yes vs. no)	160	-5.25 (0.85)	-5.13 (0.86)	-2.66 (0.93)	5.23 (0.86)	-20.93 (0.15)	-10.16 (0.67)

Predictor variable	N	Serum PFHxS % change (p-value)	Serum L-PFHxS % change (p-value)	Serum Br-PFHxS % change (p-value)	Serum PFHpA % change (p-value)	Serum PFHpS % change (p-value)	Serum PFPeS % change (p-value)
Total months spent breastfeeding children	148	-1.63 (0.10)	-1.64 (0.10)	-1.82 (0.13)	-0.04 (0.94)	-1.45 (0.18)	0.15 (0.89)
Number of births	136	-11.24 (0.30)	-11.42 (0.30)	-5.94 (0.65)	6.94 (0.36)	-6.55 (0.60)	7.07 (0.60)
Menstruated in last 3 years (yes vs. no)	160	-15.28 (0.63)	-17.70 (0.57)	61.40 (0.26)	-23.29 (0.23)	-28.89 (0.39)	51.59 (0.31)

Table 10. Percent change in serum PFAS, by analyte, per one month increase in having been breastfed among participants less than 18 years old.

Predictor variable	N	Serum PFOA % change (p-value)	Serum L-PFOA % change (p-value)	Serum PFOS % change (p-value)	Serum L-PFOS % change (p-value)	Serum Br-PFOS % change (p-value)	Serum PFBA % change (p-value)
Total months spent breastfeeding	77	1.39 (0.29)	1.38 (0.28)	2.38 (0.28)	3.21 (0.25)	2.29 (0.32)	1.06 (0.62)

Predictor variable	N	Serum PFHxS % change (p-value)	Serum L- PFHxS % change (p-value)	Serum Br-PFHxS % change (p-value)	Serum PFHpA % change (p-value)	Serum PFHpS % change (p-value)	Serum PFPeS % change (p-value)
Total months spent breastfeeding	77	0.46 (0.71)	0.46 (0.71)	-0.49 (0.73)	0.83 (0.70)	-2.05 (0.27)	1.51 (0.46)

Table 11. Percent change in serum PFAS, by analyte, per one percent increase in estimated daily intake of that analyte from drinking water.

Predictor variable	N	Serum PFOA % change in serum concentration per 1% change in daily intake from water (p-value)	Serum L-PFOA % change in serum concentration per 1% change in daily intake from water (p-value)	Serum PFOS % change in serum concentration per 1% change in daily intake from water (p-value)	Serum L-PFOS % change in serum concentration per 1% change in daily intake from water (p-value)	Serum Br-PFOS % change in serum concentration per 1% change in daily intake from water (p-value)	Serum PFBA % change in serum concentration per 1% change in daily intake from water (p-value)
Estimated daily intake of corresponding PFAS analyte from drinking water	409	**0.41 (<0.01)**	**0.38 (<0.01)**	**0.31 (<0.01)**	**0.32 (<0.01)**	**0.32 (<0.01)**	0.16 (0.71)

Predictor variable	N	Serum PFHxS % change in serum concentration per 1% change in daily intake from water (p-value)	Serum L-PFHxS % change in serum concentration per 1% change in daily intake from water (p-value)	Serum Br-PFHxS % change in serum concentration per 1% change in daily intake from water (p-value)	Serum PFHpA % change in serum concentration per 1% change in daily intake from water (p-value)	Serum PFHpS % change in serum concentration per 1% change in daily intake from water (p-value)	Serum PFPeS % change in serum concentration per 1% change in daily intake from water (p-value)
Estimated daily intake of corresponding PFAS analyte from drinking water	409	**0.43 (<0.01)**	**0.42 (<0.01)**	**0.50 (<0.01)**	**0.08 (<0.05)**	**0.58 (<0.01)**	**0.56 (<0.01)**

Statistically significant findings (p<0.05) are in **bold typeface.**

Discussion

This exposure assessment measured serum and drinking water concentrations of 30 PFAS among a sample of residents in the North Kent County area. By several measures, the PFAS concentrations in many participants' drinking water were elevated compared to health-based drinking water comparison levels and compared to levels found in most Michigan public water supplies and private drinking water wells.[39]

By multiple measures, serum PFAS concentrations for several PFAS (most notably PFOA, Br-PFOS, and PFHxS) were higher among residents in the investigation area with detectable concentrations of PFAS in their private drinking water well than among the general U.S. population as described in NHANES.[40]

A relationship was observed between increasing PFAS concentrations in participants' unfiltered drinking water and increasing concentrations in their serum for some PFAS, but for other PFAS, no relationship was observed. It was not expected that a relationship would be observed for every PFAS mainly due to limitations in the timing of the blood collections compared to when exposures ended or were reduced. Some PFAS, like PFBA and PFBS for example, are eliminated from the body much more quickly than other PFAS (differences in half-life of days vs. years[1]) after the end of exposure. For most, if not all, participants, exposure was significantly reduced in 2017 or 2018 when whole-house filters were installed, or household members chose to only consume bottled water. Since NKCEA data collection took place from November 2018 through June 2019, a year or more may have passed since drinking water exposure mitigation. Therefore, by the time blood was drawn for the study, these PFAS, had they originated from a water exposure, had likely already been eliminated from the body. This also means that participants' serum PFAS concentrations reported here are not likely the highest that they have ever been. This is especially true for those with the highest exposures from their drinking water. The overlap in the highest water PFAS concentration groups and the highest daily intake amount groups between measured and predicted serum PFAS is very good (e.g., there is no overprediction of measured serum PFAS concentrations and only some underprediction). That means that for this group, most if not all the PFAS measured in their serum at the time of the study can be explained from drinking contaminated private drinking well water prior to intervention. Other exposure sources could still contribute to serum PFAS concentrations, but in general, the amount from the drinking water was likely a dominant contributing source.

Definitions:

Overprediction: when comparing the measured and estimated serum PFAS concentration and the estimated concentration is much higher than what was measured, there is a situation of overprediction. There are many explanations for this, but in this study, it mainly indicates the exposure was overestimated. In other words, the average concentration of PFAS in the water was lower over time than measured, or people drank less of the contaminated water, or were not drinking it at all, or had not consumed the contaminated water for as long as the model estimated. These are many more reasons the information provided could led to overprediction, but these are some of the most common.

Underprediction: when comparing the measured and estimated serum PFAS concentration and the measured concentration is much higher than what was estimated, there is a situation of underprediction. For this study, this likely indicates that there was a greater exposure than what the model alone is estimating. Since the model only estimates the contribution from drinking water, there are likely many other sources that contributed to the PFAS in participants' serum. It is also possible that the exposure from water was larger due to more PFAS in the water in the past than what is measured now. These are many more reasons the information provided could led to underprediction, but these are some of the most common.

Evidence from the statistical models and analysis of participants' serum PFAS stratified by residence duration in the affected home indicates that duration of exposure is less important than the recent intake of PFAS in water. This is likely due to constant exposure via drinking water causing serum PFAS concentrations to reach steady state.[41] Other exposure assessments, such as those done by ATSDR in Berkeley County, WV,[42] and Hampden County, MA,[43] have found associations between length of residency in an area and increased PFAS concentrations in serum; this was even after accounting for participant age. An important distinction between the two exposure assessments is that in the ATSDR analysis, participants were asked about living in the community for the past 20 years. NKCEA participants were asked about the full duration of living in the area, and this was numerically analyzed. This is an important difference and might account for the dispersant observations.

The strongest associations observed from the statistical models were between estimated daily intake of PFAS by analyte in nanograms/day from contaminated drinking water and serum PFAS concentrations of that same analyte. For all measured analytes except for PFBA (which showed no association), the associations between estimated daily intake of PFAS from drinking water and serum PFAS concentrations were positive and highly statistically significant. This strongly suggests that drinking contaminated water from this area contributed greatly to elevated serum PFAS concentrations in households on private wells in the investigation area.

In addition to the exposure through drinking water, the results show that there are other past or present non-drinking water exposures to PFAS, especially PFOA, PFOS, and PFHxS. This is not unexpected, as there are sources of these and many other PFAS beyond drinking water. Other exposure assessments have come to similar conclusions that drinking water exposure can explain most but not all the PFAS detected in participants serum.[44] Looking at the lowest water PFAS concentration groups and

daily intake amount groups, the overlap between measured and predicted serum PFAS is very poor. The predicted range is much lower than what was measured in the serum. This result highlights that for participants in these groups, their home drinking water was likely not the only source of PFAS currently in their serum. Importantly, for participants in these groups, their serum PFAS concentrations are similar to those in the general U.S. population.

At a group level, statistical models were used to explore the contribution of breastfeeding, eating fish or wild game, and several other self-reported exposure sources and elimination routes using multilevel models, but it is not possible to pinpoint which one and how much each are responsible for the gap between predicted and measured serum PFAS concentrations. As expected, multilevel models showed that increasing age and male sex were significant predictors of increased serum PFAS for most analytes. This was also observed in ATSDR exposure assessments and in the New York State Department of Health's investigation of PFOA exposure in Hoosick Falls.[45] This is likely because PFAS are bioaccumulative and males lack female-specific PFAS excretion routes such as menstruation, pregnancy, and breastfeeding. These findings are similar to those observed in ATSDR exposure assessments and exposure assessments conducted at Hoosick Falls, NY.[42,43,46,47,48,49,50,51]

This assessment also shows that eating wild-caught fish was associated with increased serum PFOS, L-PFOS, and PFBA. Other studies and exposure assessments have found associations between fish consumption and serum PFAS concentrations, but not necessarily those identified here:

- ATSDR's exposure assessment in Spokane County near the Fairchild Air Force Base identified an association (with limited data) for PFDA and eating locally caught fish.[48] No relationship between wild-caught fish consumption and serum PFAS concentrations was observed in other ATSDR PFAS exposure assessment locations due to small or nonexistent number of participants who ate locally caught fish.[42,43,46,47,49,50,51]
- Christensen et al. (2017) analyzed serum PFAS and fish consumption data collected via NHANES and identified associations between fish consumption and PFDE, PFNA, and PFuDA.[52]
- Christensen et al. (2016) identified primarily weak associations between serum PFAS and fish consumption, but stronger associations were identified between serum PFDA and PFHpS and consumption of locally caught and restaurant-purchased fish in Wisconsin male anglers 50 years old and older.[53]
- In a study of women in five locations throughout the U.S., higher fish intake was associated with lower linear PFOA, branched PFOS, and Et-FOSAA serum levels and higher serum PFNA levels.[54]
- In licensed New York anglers, more Great Lake Basin fish meals in the past year were associated with increased serum PFO, PFDA, PFHxS, and PFNA. A significant association was also identified between number of years consuming fish and higher serum PFOS and PFDA.[55]

For adults, blood/plasma donation and having ever been diagnosed with kidney disease were both statistically significantly associated with decreased serum PFAS for many analytes. This was somewhat unexpected for kidney disease since decreased kidney function should lead to decreased PFAS excretion and higher PFAS concentrations. This has also been observed in the Pease Tradeport exposure assessment.[56] The best explanation for this for the NKCEA population is that since 7% of the participants

who reported ever having been diagnosed with kidney disease also reported ever having undergone dialysis, this could account for the negative correlation. Dialysis is an excretion method and would be hypothesized to offset the increased retention in the serum from decreased kidney function. For blood donations, decreased serum PFAS have been reported before.[57]

For adults, ever having worked in a PFAS-related industry was not associated with serum PFAS concentrations, likely due to misclassification (i.e., most reported roles were not likely to have had high exposure to PFAS, and roles that were more likely to involve contact with PFAS were typically held decades before the study).

For models that included only adult females, as expected, the number of months spent breastfeeding children, number of births, or having menstruated in the three years before their blood draw were all negatively associated with serum PFAS concentrations for most analytes, although none reached the level of statistical significance. This is possibly due to the small sample size. With a larger sample size, these associations may have reached statistical significance.

The results of regressing serum PFAS on total months a child less than 18 years old spent breastfeeding showed no statistically significant associations; however, for ten of the twelve analytes modeled, there was a positive association between time spent breastfeeding and serum PFAS concentrations. This was also observed in the ATSDR Lubbock County Exposure assessment for PFOS.[49]

Limitations

The study had some limitations. First, self-reported questionnaire data on potential exposure sources and elimination mechanisms is subject to recall bias. Second, some analyses were limited by a small sample size. There is also potentially volunteer bias – residents with higher water levels of PFAS participated at higher rates. It is also possible that participants with poorer health participated at higher rates out of interest in PFAS being a possible cause of their poor health. The exposure survey did not capture all possible sources of exposure to PFAS; in particular, it lacked questions usage of consumer products containing PFAS such as ski wax, food packaging, and stain- and water-repellant clothing or other products. This study therefore cannot comment on these sources. Finally, not knowing the starting time for the PFAS exposure via private drinking water wells as represented by the daily intake (calculated with PFAS concentrations from unfiltered samples) was a limitation to assessing the relationship between drinking water PFAS concentrations and serum PFAS as well as between daily intake of PFAS and serum PFAS concentrations.

Conclusions

By several measures, more people under study in the North Kent County investigation area had greater concentrations for PFOA, PFOS, PFHxS, PFHpS, and MeFOSAA than the general U.S. population. Water concentrations of PFAS in private drinking water wells varied greatly among participating households. Sampling and analysis of PFAS concentrations in current and/or filtered drinking water showed that exposure to PFAS via private drinking water wells had been greatly reduced at the time the exposure assessment took place. For certain PFAS, drinking water was a major exposure source for NKCEA participants and a large portion of the elevated serum concentrations can be attributed to this

exposure. However, it is clear that other sources of PFAS also contribute to what is observed in serum, especially for those with a low concentration of PFAS in their drinking water. Estimated daily intake of PFAS from drinking water, increasing age, male sex, and eating wild caught fish were significant predictors for increased serum PFAS concentrations in the NKCEA population. Factors like blood/plasma donation, kidney disease in adults, breastfeeding, and menstruation in women were associated with a decrease in serum PFAS concentrations, although not all reached the level of statistical significance.

MDHHS will continue to analyze the data collected in the exposure assessment, including investigating geospatial patterns in the distribution of the PFAS measured in water and serum. Future analyses may also include an examination of PFAS mixtures. These results are expected to be submitted for peer-reviewed publication.

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Supplemental Information

Table S1. Names, abbreviations, CAS numbers, serum limit of quantitation (LOQ), water method reporting limits (RL), and most recent year of NHANES data available for PFAS measured in the NKCEA.

Abbreviation	Name	CAS Number	Serum Method LOQ (µg/L)	Water Method RL Range (ppt)	Most recent NHANES data year, age 3-11	Most recent NHANES data year, age 12+
	Perfluorocarboxylic acids					
PFBA	Perfluorobutanoic acid	375-22-4	0.0106	2	‡NA	‡NA
PFPeA	Perfluoropentanoic acid	2706-90-3	0.0112	2	‡NA	‡NA
PFHxA	Perfluorohexanoic acid	307-24-4	0.0126	2-5	‡NA	2017-2018
PFHpA	Perfluoroheptanoic acid	375-85-9	0.0124	2	2013-2014	2013-2014
PFOA	Perfluorooctanoic acid (branched and linear)	335-67-1	NA	4	2013-2014	2017-2018
L-PFOA	Perfluorooctanoic acid (linear)	335-67-1	0.0098	2	2013-2014	2017-2018
Br-PFOA	Perfluorooctanoic acid (branched)	335-67-1	0.0101	2	2013-2014	2015-2016
PFNA	Perfluorononanoic acid	375-95-1	0.0103	2	2013-2014	2017-2018
PFDA	Perfluorodecanoic acid	335-76-2	0.0087	2	2013-2014	2017-2018
PFUnA	Perfluoroundecanoic acid	2058-94-8	0.0109	2-5	2013-2014	2017-2018
PFDoA	Perfluorododecanoic acid	307-55-1	0.0082	2-10	2013-2014	2015-2016
PFTeA	Perfluorotetradecanoic acid	376-06-7	0.0102	2-10	‡NA	‡NA
PFTriA	Perfluorotridecanoic acid	72629-94-8	0.01	2-10	‡NA	‡NA
	Perfluorosulfonic acids					
PFBS	Perfluorobutanesulfonic acid	375-73-5	0.0089	2	2013-2014	2013-2014
PFPeS	Perfluoropentanesulfonic acid	2706-91-4	0.0104	2	‡NA	‡NA
PFHxS	Perfluorohexanesulfonic acid (branched and linear)	355-46-4	NA	4	2013-2014	2017-2018
L-PFHxS	Perfluorohexanesulfonic acid (linear)	355-46-4	0.009	2	‡NA	‡NA
Br-PFHxS	Perfluorohexanesulfonic acid (branched)	355-46-4	0.009	2	‡NA	‡NA
PFHpS	Perfluoroheptanesulfonic acid	375-92-8	0.0113	2	‡NA	2017-2018
PFOS	Perfluorooctanesulfonic acid (branched and linear)	1763-23-1	NA	4	2013-2014	2017-2018
L-PFOS	Perfluorooctanesulfonic acid (linear)	1763-23-1	0.0095	2	2013-2014	2017-2018
Br-PFOS	Perfluorooctanesulfonic acid (branched)	1763-23-1	0.0081	2	2013-2014	2017-2018
PFNS	Perfluorononanesulfonic acid	68259-12-1	0.0101	2-5	‡NA	‡NA
PFDS	Perfluorodecanesulfonic acid	335-77-3	0.0095	2-10	‡NA	‡NA
	Fluorotelomer sulfonic acids					
4:2 FTS	1H, 1H, 2H, 2H, perfluorohexane sulfonic acid	757124-72-4	0.0089	2-5	‡NA	‡NA

6:2 FTS	1H, 1H, 2H, 2H, perfluorooctane sulfonic acid	27619-97-2	0.0113	2	‡NA	‡NA
8:2 FTS	1H, 1H, 2H, 2H, perfluorodecane sulfonic acid	39108-34-4	0.0095	2-5	‡NA	‡NA
	Perfluorosulfonamido acetic acids					
EtFOSAA	N-Ethylperfluorooctane sulfonamidoacetic acid	2991-50-6	0.0095	2-5	2013-2014	2011-2012
MeFOSAA	N-Methylperfluorooctane sulfonamidoacetic acid	2355-31-9	0.0107	2-5	2013-2014	2017-2018
	Perfluorosulfonamides					
PFOSA	Perfluorooctanesulfonamide	754-91-6	0.0072	2-10	2011-2012	2013-2014

‡NA = The analyte was not measured in NHANES.

NA = There is no limit of quantification for totals of isomers.

Table S2. Candidate variables for inclusion in multilevel models to assess whether factors thought a priori to be determinants of PFAS exposure were significantly associated with serum PFAS concentrations.

Exposure
Age
Sex
Race
Household income
Years spent living in home (residence duration)
Eating hunted deer from anywhere
Eating hunted deer from inside the study area
Eating wild caught fish from anywhere
Eating wild caught fish from inside the study area
Eating other hunted game from anywhere
Eating other hunted game from inside the study area
Eating eggs from chickens raised inside the study area
Eating vegetables grown inside the study area
Estimated daily intake of corresponding PFAS analyte from drinking water
Ever had kidney disease
Ever had diabetes
Ever had anemia
Ever having worked in an industry that uses PFAS
Number of annual blood or plasma donations
Total months spent breastfeeding children
Total months spent breastfeeding
Number of births
Menstruation in the last three years

Table S3. Minimum sufficient adjustment set for regressing log-transformed serum PFAS concentrations for each of the 12 PFAS of interest on each of the exposure of interest, as determined by directed acyclic graphs (DAGs).

Exposure	Minimum necessary adjustment set
Age	None
Sex	None
Years spent living in home (residence duration)	Age, household income
Eating hunted deer from anywhere	Household income, race
Eating hunted deer from inside the study area	Household income, race
Eating wild caught fish from anywhere	Household income, race
Eating wild caught fish from inside the study area	Household income, race
Eating other hunted game from anywhere	Household income, race
Eating other hunted game from inside the study area	Household income, race
Eating eggs from chickens raised inside the study area	Household income, race
Eating vegetables grown inside the study area	Household income, race
Estimated daily intake of corresponding PFAS analyte from drinking water	Female breastfeeding, sex
Ever had kidney disease	Age, household income, sex
Ever had diabetes	Age, household income
Ever had anemia	Age, menstruation, sex
Ever having worked in an industry that uses PFAS	Household income, race, sex
Number of annual blood or plasma donations	Age, household income, anemia, sex
Total months spent breastfeeding children	Age, sex, household income
Total months spent breastfeeding	Age, household income
Number of births	Age, household income, sex, and menstruation
Menstruation in the last three years	Age, sex

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