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Preliminary Associations between the Detection of Perfluoroalkyl Acids (PFAAs) in Drinking Water and Serum Concentrations in a Sample of California Women

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S Supporting Information

ABSTRACT: This study compared detection of perfluoroalkyl acids (PFAAs) in public drinking water with PFAA serum concentrations for 1566 California women. PFAA occurrence in drinking water from U.S. EPA's third Unregulated Contaminant Monitoring Rule (UCMR3) database was linked by residential zip code to study participants. Detectable water concentrations of perfluorooctanoic acid (PFOA) ranged from 0.020 to 0.053 $\mu\text{g}/\text{L}$ and of perfluorooctanesulfonic acid (PFOS) from 0.041 to 0.156 $\mu\text{g}/\text{L}$. Forty percent of detectable concentrations exceeded the 2016 Health Advisory Level of 0.07 $\mu\text{g}/\text{L}$ for combined PFOA and PFOS concentrations. Serum concentrations of PFOS and PFOA significantly differed between participants with and without detectable measures of these compounds in water (Wilcoxon $P \leq 0.0007$). Median serum concentrations of PFOS and PFOA were 29% and 38% higher, respectively, among those with detectable levels in water compared to those without detectable levels. Validation of this approach and replication of these results in other study populations are warranted.



I INTRODUCTION

Perfluoroalkyl acids (PFAAs) are a subset of the poly- and perfluoroalkyl substances (PFASs), a class of compounds that have been widely used for over 60 years to impart nonstick, waterproof and stain-resistant coatings to a variety of consumer products, including cookware, food packaging, clothing, carpeting, and textiles.^{1–3} PFASs are also active ingredients in aqueous film forming foams (AFFF) used to extinguish hydrocarbon-based fuel fires at airports, oil refineries, military bases, and firefighter training facilities.⁴ PFAAs are highly resistant to biodegradation and are among the most persistent of environmental pollutants.^{1,3,5} A growing body of scientific evidence for the two most studied members of PFASs, perfluorooctanesulfonic acid (PFOS) and

perfluorooctanoic acid (PFOA), suggests potentially toxic effects including tumor induction, hepatotoxicity, developmental toxicity, immunotoxicity, endocrine disruption, and neurotoxicity.^{2,3,6–13} Consequently, PFASs, especially PFOS and PFOA, have become the focus of considerable public health concern.

Although U.S. and California biomonitoring data indicate widespread human exposures,^{14–16} routes of exposure have not been fully elucidated.^{5,17–20} Drinking water can be a significant

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Table 1. PFAA Concentrations Detected in Drinking Water (as reported by UCMR3 Data) Linked to Study Participants' Residences

PFAA contaminant	CAS registry number	minimum reporting level ($\mu\text{g/L}$)	PFAA concentration ($\mu\text{g/L}$)		
			no. ^a	mean	min.–max.
perfluorooctanesulfonic acid (PFOS)	1763–23–1	0.04	52	0.058	0.041–0.156
perfluorooctanoic acid (PFOA)	335–67–1	0.02	31	0.028	0.020–0.053
perfluorohexanesulfonic acid (PFHxS)	355–46–4	0.03	12	0.064	0.032–0.120
perfluoroheptanoic acid (PFHpA)	375–85–9	0.01	7	0.015	0.010–0.022
perfluorononanoic acid (PFNA)	375–95–1	0.02	0		
perfluorobutanesulfonic acid (PFBS)	375–73–5	0.09	0		

^aNo. = Number of water samples in which PFAA concentration \geq minimum reporting level (MRL) of UCMR3 data among public water systems (PWS) that serviced a residential zip code of study participants.

route of exposure among populations whose water has known “significant environmental contamination”,^{21–27} but it is unclear whether drinking water may serve as an important route of exposure among the general population. The use of AFFF at airports and military bases and the land application of biosolids have both been observed to contaminate surrounding groundwater and surface water with PFASs^{28–31} and may contribute to PFAS levels in drinking water sources far from PFAS manufacturers.

The U.S. Environmental Protection Agency (U.S. EPA), under its third Revisions to the Unregulated Contaminant Monitoring Rule (UCMR3) for Public Water Systems began testing public water supplies in 2013 for six PFAAs.³² These data are collected to provide scientifically valid information on the occurrence of unregulated chemicals that are of potential public health concern and are used by the U.S. EPA to inform regulatory decisions. The UCMR3 now offers the most comprehensive population-based data set of PFAA occurrence in drinking water. The current analysis compares biomonitoring data on PFAAs in a sample of California women with UCMR3-derived PFAA drinking water detections. To our knowledge, this is the first study to link PFAA biomonitoring data for the general population to PFAA detections in U.S. public water supplies.

MATERIALS AND METHODS

Study Population. The study population was composed of 1566 women residing in California who are participants in the California Teachers Study (CTS), an ongoing cohort study of over 133 000 female professional public school employees.³³ These women provided a blood sample as part of their participation in a breast cancer case-control study nested within the CTS. The characteristics of the study population reflect that of the larger CTS study from which it was drawn. As shown in the Supporting Information (Table S1), the study population was predominantly composed of non-Hispanic white (77%) and middle-aged or older women, with nearly 70% between the ages of 60–79 years. Approximately 40% had been diagnosed with breast cancer prior to blood collection.

Serum Collection. Blood samples were collected from participants by licensed phlebotomists from January 2011 to September 2013. Addresses at blood draw were confirmed with participants by the phlebotomists prior to blood collection. Blood samples were collected in Tiger Top (SST) tubes (10 mL BD collection tube catalog #367985), kept on cool packs, and within several hours were spun down using portable centrifuges to separate the serum. Processed samples were then frozen and transported to the laboratory where they remained frozen and stored at $-20\text{ }^{\circ}\text{C}$ until thawed for the PFAA analysis.

Serum PFAS Measurements. Serum measurements of 12 PFASs were conducted using an online SPE-HPLC-MS/MS

method as described in detail previously.³⁴ Briefly, 100 μL of serum was diluted in formic acid and spiked with isotopically labeled internal standards before injection into the online SPE-HPLC-MS/MS system (Symbiosis Pharma, IChrom Solutions, Plainsboro, NJ, and ABSciex 4000 QTrap mass spectrometer, ABSciex, Redwood City, CA) for cleanup and analysis. Native and isotopically labeled PFAS standards were purchased from Wellington Laboratories (Shawnee Mission, KS). Within each batch analysis of 20 samples, two in-house spiked calf serum samples and NIST 1958 Standard Reference Material were run in duplicate together with the other quality control samples.

The current study is restricted to the four PFAAs that were detected in California UCMR3 data: PFOS, PFOA, perfluorohexanesulfonic acid (PFHxS), and perfluoroheptanoic acid (PFHpA). Limits of detection (LOD) and detection frequency (DF) for each of the compounds were as follows: PFOS (LOD = 0.066 ng/mL, 99.87% DF); PFOA (LOD = 0.110 ng/mL; 99.87% DF); PFHxS (LOD = 0.021 ng/mL; 99.04% DF); PFHpA (LOD = 0.026 ng/mL; 74.8% DF).

PFAAs in UCMR3 Drinking Water. Proxy indicators for PFAAs in study participants' drinking water were derived by linking their residence at the time of blood draw to information on PFAA occurrence in the UCMR3 data. Drinking water samples included in UCMR3 were collected from all U.S. public water systems (PWSs) serving $\geq 10\,000$ people and 800 representative smaller PWSs between January 2013 and December 2015. Water samples were taken at the entry point to the distribution system. Minimum reporting levels ranged from 0.01 to 0.09 $\mu\text{g/L}$, depending on the analyte (Table 1). Further details of the UCMR3 data monitoring are available elsewhere.³⁵ In California, water was sampled from 452 PWSs. One or more PFAAs were detected in drinking water samples collected from 28 PWSs (6.2% detection rate). Because perfluorononanoic acid (PFNA) and perfluorobutanesulfonic acid (PFBS) were not detected in any PWSs in California, these compounds were not included in our analysis.

The UCMR3 occurrence data were downloaded from the EPA Web site³⁵ on April 12, 2016. For each chemical, the UCMR3 database contains a record for each water sample that includes the following information: whether the chemical was detected at or above its LOD, the concentration detected ($\mu\text{g/L}$), collection date, and identifiers for the PWS provider and facility. The UCMR3 data also contain information identifying the zip codes served by each large PWS (i.e., serving $\geq 10,000$ people). These data were cross classified by PWSs to create a file that summarized for each California zip code whether any PFAA had been detected at least once during the 3 year UCMR3 monitoring period. This file was then linked to our study participants based on the zip code of residence at the time of blood collection. Through this process, a proxy indicator for the occurrence of each

Table 2. PFAAs: Comparison of Serum Concentrations (ng/mL) among 1333 Study Participants with and without Detectable Levels in Drinking Water^a

PFAA compound detected in drinking water ^b	PFAA serum concentration (ng/mL) ^c								
	<i>n</i> ^a	% ^d	mean	geo. mean	median	percentile		max.	<i>P</i> ^e
						P ₂₅	P ₇₅		
PFHpA									
detected	35	2.2	0.12	0.07	0.07	0.03	0.14	0.95	0.36
not detected	1,298	82.9	0.09	0.06	0.05	0.03	0.11	1.61	
PFHxS									
detected	31	2.0	1.87	1.35	1.48	0.91	2.91	5.07	0.60
not detected	1,302	83.1	2.29	1.66	1.60	1.04	2.57	21.80	
PFOA									
detected	70	4.5	4.06	3.47	3.46	2.54	4.83	17.00	<0.0001
not detected	1,263	80.7	2.99	2.45	2.51	1.69	3.64	39.10	
PFOS									
detected	93	5.9	11.02	8.51	9.11	5.02	13.70	39.40	0.0007
not detected	1,240	79.2	8.42	6.76	7.08	4.45	10.60	99.80	

^aNumber of study participants excludes 233 participants whose residential zip code at blood draw was not included in the UCMR3 database.

^bDetected = the particular PFAA compound was detected in a public water system (PWS) that serves the zip code of residence at blood draw; not detected = the particular PFAA compound was not detected in a PWS that serves the zip code of residence at blood draw (as reported by UCMR3 Occurrence Data, 2013–2015).³⁵ ^cgeo. mean = geometric mean; P₂₅ = 25th-percentile; P₇₅ = 75th-percentile; max. = maximum. ^dPercentages are expressed as percent of total number of study participants, including those that did not link to the UCMR3 (*n* = 1,566) and therefore do not sum to 100%. ^e*P* = *p*-value calculated from Wilcoxon Rank Sum Test.

PFAA in the drinking water of study participants was created and defined as follows: “detected” indicating that the particular PFAA had been detected in at least one PWS that serves their residential zip code; “not detected” indicating that the particular PFAA had not been detected in any of the PWSs that serve their residential zip code; and “not tested” indicating that their residential zip code was not supplied by a PWS contained in the UCMR3 database.

Statistical Analysis. Prior to statistical analyses, serum samples with PFAA concentrations below the LOD were imputed as LOD/√2 for each analyte. Descriptive statistics, including mean values, median values, geometric mean values, and percentiles for the serum PFAA concentrations were calculated and are presented separately for those with and without detectable measures of each of the PFAAs in drinking water (Table 2). Wilcoxon Rank-Sum tests were performed to evaluate formally whether the distributions of serum concentrations differed in a statistically significant way between those with and without detectable levels of the given PFAA in drinking water. These analyses excluded the 233 participants whose residence was located in a zip code that was not included in the UCMR3 data.

RESULTS AND DISCUSSION

Of the 1566 participants in our study, 109 (7%) lived in a residence whose zip code was supplied by a PWS that had detected at least one PFAA in its water at least once during the UCMR3 monitoring period, 1224 participants (78%) linked to a zip code whose water was supplied by a PWS that had not detected any PFAA in its water, and the remaining 233 (15%) lived in a zipcode whose water was not tested. The racial/ethnic characteristics and distribution of breast cancer cases and age were similar across the three categories of PFAA water detections (Table S1).

PFOS and PFOA were the PFAA compounds most frequently detected by the UCMR3 monitoring, found in the drinking water linked to 5.9% and 4.5% of participants, respectively. PFHpA and PFHxS were detected in the drinking water linked to about 2% of participants. The distributions of detectable PFAAs in the UCMR3 that linked to our study participants are

summarized in Table 1. The detectable levels of PFOA (mean = 0.028 μg/L; range = 0.020–0.053 μg/L) and PFOS (mean = 0.058 μg/L; range = 0.041–0.156 μg/L) were all below the previous U.S. EPA 2009 Provisional Health Advisory Levels of 0.4 μg/L and 0.2 μg/L, respectively. Under the newly issued 2016 Lifetime Health Advisory Level for PFOA and PFOS (individual or combined concentrations of 0.07 μg/L),³⁶ substantially more exceedances occurred, with 40% of the detectable concentrations exceeding the Advisory Level based on combined concentrations and 16% based on PFOS concentration alone. No samples exceeded the Advisory Level based on PFOA concentration alone. In contrast to the prior provisional US EPA Health Advisories which were intended to be protective for short-term exposures, the new Lifetime Health Advisory Level is designed to protect against chronic exposures. Seventy-one percent of our study participants had been residing in the same zip code for at least 15 years.

The distribution of serum concentrations of PFOS and PFOA significantly differed among study participants with and without detectable measures of PFOA (*P* < 0.0001) and PFOS (*P* = 0.0007) in drinking water (Table 2). Compared to those who linked to drinking water with no detectable PFOA, the median serum PFOA concentration was 38% higher in those that linked to water with detectable PFOA (3.46 ng/mL versus 2.51 ng/mL). For PFOS, the median serum concentration was 29% higher among those for whom it was detected in drinking water compared to those for whom it was not (9.11 ng/mL versus 7.08 ng/mL). In contrast, no statistically significant differences in the distributions of serum concentrations for PFHpA (*P* = 0.36) or PFHxS (*P* = 0.60) between study participants with and without detectable levels in drinking water were observed. When we repeated these analyses after removing the breast cancer cases, the results were similar (Supporting Information Table S2).

To our knowledge, this is the first study to demonstrate an association between serum PFAA levels and detection of PFAAs in drinking water supplies among a population with no previously recognized water contamination. These results, which suggest

that drinking water with relatively low levels of PFAAs may contribute to higher serum levels among exposed women, are consistent with human pharmacokinetic modeling. It has been previously established that, on average, ongoing exposure to PFOA in drinking water increases serum PFOA concentrations in a serum: drinking water ratio of 100:1 or greater;^{25,37} while based on half-lives and clearance factor differences, PFOS in drinking water is estimated to increase serum concentrations at a ratio of 172:1 or more.^{38–40} Therefore, assuming no other significant sources of exposure, at the mean drinking water concentration of 0.028 $\mu\text{g/L}$ among those with detectable levels of PFOA in water, we would expect a mean serum level of 2.8 ng/mL, and at the mean drinking water concentration of 0.058 $\mu\text{g/L}$ among those with detectable levels of PFOS in water, we would expect a mean serum PFOS level of 9.98 ng/mL. The mean serum levels in our participants with detectable measures of PFOA and PFOS in drinking water of 4.06 and 11.02 ng/mL, respectively, are marginally higher, but generally consistent with these predictions. Overall, the PFOA and PFOS data in this study suggest that drinking water can be an important source of human exposure to PFAAs.

This study has a number of limitations worth noting. Most importantly, because UCMR3 monitoring was designed to assess population exposures, not to assign exposures to individuals, it does not provide the data elements necessary to link definitively a contaminated water sample to a specific home. UCMR3 data are based on samples collected from multiple points of entry within a PWS; PFAA detection in one sample does not necessarily represent the PFAA occurrence in water throughout the entire PWS distribution system. Additionally, in the infrequent instance when a residence is located in a zip code that is serviced by more than one PWS it is not possible to definitively identify the PWS. Furthermore, the MRLs of the UCMR3 data are relatively high compared to the levels of detection available from many certified laboratories; thus it is likely that PFAAs were present in some samples but were not detected by the UCMR3 monitoring. Given these limitations of the UCMR3 data, our proxy measure for PFAAs in drinking water is likely to introduce some misclassification of exposure. Thus, the true difference in serum levels between those with and without PFAA exposures from drinking water is likely to be greater than what we observed in this study.

As issues related to drinking water contamination were not part of the original aims of the CTS, additional uncertainties in exposure were introduced by a lack of information about whether participants routinely drink their home tap water or consume water from private wells. Information about other potential sources of PFAA exposure, including diet, indoor dust, and occupational exposures,^{3,17–19,41} also was lacking. Occupational exposures, however, are unlikely to be important in our study population, and there is no reason to postulate that these other exposure sources would be correlated to detection of PFAAs in drinking water. Thus, although it is possible that our findings are spurious due to uncontrolled confounding, it seems unlikely.

It should also be noted that this study population was composed of CTS members who had participated in a nested breast cancer case-control study, and thus the selection of study participants was not designed to produce a representative sample of the California population. Nevertheless, results were similar among the subset of participants who served as controls in the breast cancer study and overall the PFAA serum concentrations in our study population were consistent with levels reported among adult women in recent U.S. biomonitoring data.¹⁵

Under its 2016 PFOA and PFOS Drinking Water Health Advisories, the U.S. EPA recommends that when PFOA and PFOS concentrations, individually or combined, are found to exceed 70 $\mu\text{g/L}$, water systems should “quickly undertake additional sampling to assess the level, scope and localized source of contamination to inform next steps.”³⁶ The UCMR3 data do not provide sufficient information to identify specific localized sources of PFAA contamination to drinking water supplies. California, like many states, however, has known PFAA contamination in groundwater⁴² and in waste water that discharges to surface water from the use of AFFF,⁴³ and this may contribute to PFAA contamination of drinking water supplies. Additional point sources could come from manufacturers who produce or use PFASs industrially. The UCMR3 data could help pinpoint geographic “hot spots”, offering a useful starting point to identify and remediate specific sources of exposure, as well as to target populations for future health evaluations (see California Map of UCMR3 data in [Supporting Information](#), Figure S1).

There is evidence that many of the health end points of concern associated with some of the PFAAs may be elicited by levels in the range of serum PFAAs observed in our study population.^{8,25,44,45} Thus, the elevated serum PFAA concentrations found among our study participants who were potentially exposed to PFAAs in drinking water underscore the potential public health importance of these findings and the need for further study. Given the health implications of these results, validation of our approach and replication of these findings in other study populations with biomonitoring data should be a research priority.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.estlett.6b00154](https://doi.org/10.1021/acs.estlett.6b00154).

Table S1. Demographic Characteristics and Detection of PFAAs in Drinking Water for Study Participants ($n = 1566$). Table S2. PFAAs: Serum Concentrations (ng/mL) among Subset of Study Population that were Controls ($n = 944$): Comparison of Serum Concentrations (ng/mL) between Study Participants with and without Detectable Levels in Drinking Water. Figure S1: Zip codes in California serviced by a public water system (PWS) with detectable levels of PFAAs ([PDF](#)).

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Notes

The authors declare no competing financial interest.

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