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Per- and Polyfluoroalkyl Substances (PFAS) in Breast Milk: Concerning Trends for Current-Use PFAS

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ABSTRACT: This is the first study in the last 15 years to analyze per- and polyfluoroalkyl substances (PFAS) in breast milk collected from mothers (n = 50) in the United States, and our findings indicate that both legacy and current-use PFAS now contaminate breast milk, exposing nursing infants. Breast milk was analyzed for 39 PFAS, including 9 short-chain and 30 long-chain compounds, and 16 of these PFAS were detected in 4−100% of the samples. The ∑PFAS concentration in breast milk ranged from 52.0 to 1850 pg/mL with a median concentration of 121 pg/mL. Perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) were the most abundant PFAS in these samples (medians 30.4 and 13.9 pg/mL, respectively). Two short-chain PFAS, including perfluoro-*n*-hexanoic acid (PFHxA, C6) and perfluoro-*n*-heptanoic acid (PFHpA, C7), were detected in most of the samples with median concentrations of 9.69 and 6.10 pg/mL, respectively. Analysis of the available breast milk PFAS data from around the world over the period of 1996−2019 showed that while the levels of the phased-out PFOS and PFOA have been declining with halving times of 8.1 and 17 years, respectively, the detection frequencies of current-use short-chain PFAS have been increasing with a doubling time of 4.1 years.

KEYWORDS: *short-chain PFAS, perfluorooctanoic acid (PFOA), perfluorooctanesulfonic acid (PFOS), breast milk, transfer efficiency, lactation exposure, PFAS regulation*

INTRODUCTION

Per- and polyfluoroalkyl substances (PFAS), a group of more than 9000 distinct compounds, have been widely used as water-, grease-, and stain-repellents, surfactants, lubricants, and processing aids in paper, textiles, polishes, food packaging, aqueous film-forming foams (AFFFs), and manufacturing for more than 80 years.[1,2] Due to their persistence, bioaccumulation, and toxicity to wildlife and humans, production and use of two major PFAS, perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), have been phased out by major global manufacturers during the last two decades.[3] In 2006, the U.S. Environmental Protection Agency (EPA) launched the PFOA Stewardship program on the elimination of PFOA and its precursors by 2015.[4] PFOS and its salts were added to the Annex B of the Stockholm Convention on Persistent Organic Pollutants in 2009, and PFOA and its salts were listed under the Annex A of the Stockholm Convention in 2019 calling for the worldwide restriction on their use.[5−7] In 2020, the U.S. EPA issued a Significant New Use Rule under the Toxic Substances Control Act that prohibits companies from manufacturing, importing, processing, or using select long-chain PFAS for certain uses without prior EPA review and approval.[8] Manufacturers have largely moved to replacement PFAS with shorter carbon chains (<C8), such as perfluorobutanoic acid (PFBA, C4), perfluoro-1-butanesulfonic acid (PFBS, C4), and perfluoro-*n*-hexanoic acid (PFHxA, C6), which can be found in carpets and other textiles, food packaging, and AFFFs.[9−12] In addition, several long-chain (>C8) perfluoroalkyl carboxylic acids (PFCAs), such as perfluoro-*n*-decanoic acid (PFDA, C10), have been reported as impurities in fluorotelomer-containing products such as textiles.[13,14] Although restrictions on PFOS and PFOA have led to a decline in the body burden of these compounds in the general population of the United States, Europe, and Australia in recent years,[13−18] the detection and concentrations of short- and long-chain PFAS have been increasing.[3,13,14,18,19] For example, blood concentrations of PFBS (C4), perfluoro-*n*-nonanoic acid (PFNA, C9), and PFDA (C10) increased at a rate of about 11% per year in Swedish women between 1996

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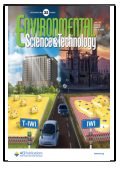

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and 2010.[14] These trends are concerning as growing evidence shows that replacement PFAS can have toxicities similar to the phased-out C8 compounds, including disruption of thyroid hormone signaling and lipid metabolism.[20−23]

Breastfeeding constitutes a major exposure pathway to environmental contaminants, including PFAS, for nursing infants.[24−26] Previous studies have shown that breastfeeding can contribute up to 94% of PFAS intake for 6 month old infants[27] and lead to elevated body burden.[28,29] Infants and children are particularly susceptible to the adverse effects of PFAS exposure because of their unique physiology and rapid development.[24,30,31] This exposure may result in adverse health effects later in life as exposure to PFAS has been significantly associated with dyslipidemia, pregnancy-induced hypertension, liver damage, decreased immune function, increased risk of thyroid disease, reduced fertility, and cancer.[24,32,33]

There is very limited information on lactational PFAS intake for U.S. infants, and the two available studies date back to 2004.[34,35] This previous research reported PFOS (median 106 pg/mL) and PFOA (36.1 pg/mL) as predominant among nine measured PFAS in breast milk collected from U.S. women.[35] Alarmingly, more recent studies from Asia reported elevated detection and concentrations of the current-use PFAS in breast milk, including PFBA (not detected [n.d.] −3.1 pg/mL), perfluoropentanoic acid (PFPeA (C5), 2.4−58 pg/mL), and PFHxA (n.d. −47 pg/mL).[36,37] Moreover, the concentrations of PFHxA, perfluoro-*n*-tetradecanoic acid (PFTeDA, C14), and perfluoro-*n*-tridecanoic acid (PFTrDA, C13) have also been increasing at a rate of 10−20% per year between 2007 and 2016 in breast milk from Swedish mothers.[18] Considering the changing PFAS market and increasing reports of exposure to current-use PFAS, it is essential to assess the levels of both legacy and current-use PFAS in breast milk from U.S. mothers. The goals of this study were threefold: (1) to determine the levels of 9 short- (PFCAs with ≤7 carbons and perfluoroalkane sulfonic acids [PFSAs] with ≤5 carbons) and 30 long-chain (PFCAs with >7 carbons and PFSAs with >5 carbons) PFAS in breast milk collected from U.S. mothers; (2) to estimate the lactational daily intake of PFAS by nursing infants; and (3) to evaluate the implications of the changed PFAS market on the detection and concentrations of legacy and current-use PFAS in breast milk during 1996−2019 using previously published data.

MATERIALS AND METHODS

Participant Recruitment and Sample Collection. Primiparous women pregnant and planning to breastfeed or currently breastfeeding and residing in or near Seattle, Washington, United States, were recruited using materials approved by the Indiana University Institutional Review Board. Recruitment took place over social media channels, through parenting groups and via paper flyers. Breast milk samples (n = 50) were collected during March−October 2019. Participants were instructed to manually express breast milk, which was transferred into polypropylene jars precleaned with water, isopropyl alcohol, and methanol. The samples were retrieved from participants within 24 h after collection and stored at −4 °C until shipment to Indiana University, where they were stored at −20 °C until analysis. Participants also provided answers to a questionnaire to collect demographic and housing data (Table 1).

Sample Analysis. Breast milk samples (2 mL, thawed at room temperature) fortified with surrogate standards (Tables S1 and S2) were ultrasonicated in 4 mL of acetonitrile for 1 h. The samples were then centrifuged (3000 rpm, 5 min), and the supernatants were transferred to new tubes. Each sample was re-extracted twice (total of 3 extractions), and the supernatants were combined. The sample was further concentrated to ∼2 mL under a gentle stream of N_2 and diluted with 4 mL of water. The resulting extract was loaded on an Oasis weak anion-exchange (WAX) cartridge subsequently conditioned with 3 mL of 0.5% ammonium hydroxide in methanol, 3 mL of methanol, and 3 mL of water. The column was then washed with 3 mL of water and 3 mL of methanol/water (1:9, v/v), and target analytes were eluted with 3 mL of 0.5% ammonium hydroxide in methanol. The extract was evaporated to dryness using N_2, reconstituted in 200 μL of methanol, and filtered through a 0.2 μm nylon syringe filter. Internal standards (Tables S1 and S2) were spiked to each sample before instrumental analysis for the quantitation of target compounds. The details on standards and reagents used in this study are provided in the Supporting Information.

Instrumental Analysis. Thirty-nine PFAS were analyzed in these samples, and the complete list of analytes is given in Tables S1 and S2. An ultraperformance liquid chromatograph coupled with a triple-quadrupole mass spectrometer (Agilent 1290 Infinity II UPLC, 6470 QQQ-MS) in the negative electrospray ionization (ESI-) mode was used to analyze 10 PFSAs, 12 PFCAs, 3 fluorotelomer sulfonates (FTSs), and 3 perfluorooctane sulfonamides (FOSAs). Chromatographic separation was achieved on an Acquity UPLC BEH C18 column (50 mm, 2.1 mm i.d., 1.7 μm thickness, Waters) at 40 °C. Mobile phases consisted of 2 mM ammonium acetate in water (A) and 2 mM ammonium acetate in methanol (B). The gradient was 10% B for 0.5 min initially, ramped to 40% B at 1 min, and then increased to 100% B at 17.5 min. The instrument was equilibrated for 3.5 min after every run. The

Table 1. Summary of Participants' Demographic Characteristics

parameters		N	percentage, %
age (years)	<33	15	30
	>33	34	68
	missing	1	2
education	some college	1	2
	college degree	17	34
	advanced degree	31	62
	missing	1	2
census tract median income	low (<$45 000)	1	2
	moderate ($45 000−70 000)	8	16
	middle ($70 000−100 000)	23	46
	upper middle (>$100 000)	18	36
residence time (years)	<20	34	68
	>20	15	30
	missing	1	2
child's age (at the time of collection)	<6 months	22	44
	>6 months	26	52
	missing	2	4
BMI (kg/m^2)	underweight, <18.5	0	0
	normal, 18.5−24.9	29	58
	overweight, 25−29.9	11	22
	obese, >30	7	14
	missing	3	6

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injection volume was 5 μL. The nebulizer, gas flow, gas temperature, capillary voltage, sheath gas temperature, and sheath gas flow were set to be 25 psi, 10 L/min, 300 °C, 2800 V, 330 °C, and 11 L/min, respectively. Data acquisition was conducted in the dynamic multiple reaction monitoring (dMRM) mode.

Four fluorotelomer alcohols (FTOHs), three fluorotelomer acrylates (FTACs), two fluorotelomer methacrylates (FTMACs), and two perfluorooctane sulfonamidoethanols (FOSEs) were analyzed using an Agilent 7890 gas chromatograph (GC) coupled to an Agilent 5975C mass spectrometer (MS) in the electron capture positive ionization (PCI) mode. The injection temperature was 200 °C, and the injection volume was 2 μL. The carrier gas was helium at a constant flow rate of 1 mL/min. The separation was achieved on a CP-WAX 57 CB capillary column (25 m, 250 μm i.d., and 0.2 μm film thickness, Agilent J&W). The oven temperature was programmed to increase from 60 °C (3 min) to 85 °C at a rate of 25 °C/min, then to 190 °C at 3 °C/min, and kept for 8 min. The MS ion source, quadrupole, and GC/MS transfer line temperatures were maintained at 200, 106, and 200 °C, respectively. The target compounds were analyzed using the selected ion monitoring (SIM) mode. The optimized monitoring fragment ions for all analytes are included in Tables S1 and S2. Quantification of target compounds was performed by isotope dilution using calibration curves with concentrations ranging from 0.1 to 5 ng/mL. The regression coefficients of linearity tests were all >0.99.

Quality Assurance and Control. One procedural blank was included in each batch of 10 samples, and two field blanks were collected using empty collection jars briefly opened during sampling. All data were blank-corrected by subtracting the average procedural blank concentrations from sample concentrations. Method detection limits (MDLs) were set at three times the standard deviation of the target analyte levels detected in procedural blanks. For compounds not detected in blanks, MDLs were based on a signal-to-noise ratio of 3. MDLs, average field, and procedural blank concentrations for all analytes are included in Table S3. One matrix spike sample was included in each batch of 10 samples, and the absolute matrix spike recoveries for target analytes ranged from 48 to 100% (Table S4). Surrogate standards were spiked to each sample, and their recoveries ranged from 60 ± 2 to 82 ± 6% (mean ± standard error; Table S5). The concentrations were not recovery-corrected.

Data Analysis. PFAS lactational (blood-to-milk) transfer efficiencies (TE, %) were calculated using eq 1 adapted from Liu et al.[38]

$$\mathrm{TE} = \frac{C_{\mathrm{BM}}}{C_{\mathrm{S}} \times 1000} \times 100 \tag{1}$$

where C_{BM} is a median concentration of a PFAS measured in breast milk, pg/mL; and C_S is a median serum concentration of that PFAS reported for women in the 2015−2016 National Health and Nutrition Examination Survey (NHANES), ng/mL (serum PFAS concentrations were not measured in this study). An MDL value of 0.1 ng/mL was used for PFHxA, PFHpA, and PFDoA reported as not detected in NHANES,[39] resulting in lower-bound TE estimates for these compounds. The TE for PFNA was not calculated because serum PFNA concentrations were not available in the NHANES.[39]

Lactational estimated daily intakes (EDIs; ng/kg body weight [bw]/day) of PFAS were calculated using eq 2 adapted from Zhu et al.[40]

$$\mathrm{EDI} = \frac{C_{\mathrm{BM}} \times \mathrm{FIR}}{1000} \tag{2}$$

where C_{BM} is a median concentration of a PFAS in breast milk, pg/mL; and FIR is a food ingestion rate (mL/kg bw/day) representing the average daily intake of breast milk (150, 140, 110, and 83 mL/kg bw/day for <1, 1−3, 3−6, and 6−12 months old infants, respectively).[41]

Descriptive statistics were calculated using IBM SPSS Statistics 24 and Microsoft Excel 2016. Plots were generated using Sigma Plot 13 and R studio. Statistical tests included the analysis of variance (ANOVA) using logarithmically transformed concentrations (Minitab 13). Correlation heat maps and hierarchical clustering were based on Pearson correlation coefficients of the logarithmically transformed concentrations of individual PFAS with detection frequencies of >50%. Multivariate linear regression was used to analyze the relationships between PFAS levels and participants' demographic and behavioral characteristics. Concentrations below MDLs were replaced with MDL/2 values for the descriptive statistics and correlation analyses. The significance level was set at $p < 0.05$.

For the temporal trend analysis, logarithmically transformed concentrations of PFOS and PFOA were fitted with a first-order linear regression model, as shown in eq 3

$$\ln C_t = a_0 + a_1 \times t \tag{3}$$

where C_t is the mean concentration in year t, a_0 and a_1 are the fitted constants, and t is the sampling year. The same model was used for the temporal trend analysis of the short-chain PFAS detection frequencies.

Halving times ($t_{1/2}$, years) and doubling times (t_2, years) were calculated as follows

$$t_{1/2} = \frac{-\ln(2)}{a_1} \ (\text{for } a_1 < 0) \tag{4}$$

$$t_2 = \frac{\ln(2)}{a_1} \ (\text{for } a_1 > 0) \tag{5}$$

In the temporal trend analysis for the detection frequencies of the short-chain PFAS, the detection frequencies of each analyte were normalized ($DF_{normalized}$, %) to the highest limit of detection (LOD) reported across the studies included in the analysis to address the improved sensitivity of the analytical methods developed during the time period covered in the analysis (1996−2019)

$$\mathrm{DF}_{\mathrm{normalized}} = \frac{\mathrm{DF}_{\mathrm{original}}}{\mathrm{LOD}_{\mathrm{highest}}} \times \mathrm{LOD}_{\mathrm{actual}} \tag{6}$$

where $DF_{original}$ is the detection frequency of a PFAS (%), and LOD_{actual} is its reported LOD (pg/mL). $LOD_{highest}$ is the highest LOD reported for that PFAS across the studies included in the analysis (3.1, 37, 24, 27, and 20 pg/mL for PFBA, PFBS, PFPeA, PFHxA, and PFHpA, respectively). If the $LOD_{highest}$ was higher than the reported maximum concentration of that PFAS, the $DF_{normalized}$ was assigned to 0%. The data were collected from the studies where the detection frequencies of short-chain PFAS, their detection limits, and maximum concentrations were reported. The data before and

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Table 2. Detection Frequencies (DF, %), Minimum, 25th Percentile, Median, 75th Percentile, and Maximum Concentrations of PFAS in Breast Milk (pg/mL; n = 50), and a Contribution (%) of each PFAS Compound to the ∑PFAS Concentrations (Calculated Based on Median Concentrations)

compound (carbon chain)	DF	min.	25th	median	75th	max.	contr.
			Short-Chain				
PFPeS (C5)	8	<0.10	<0.10	<0.10	<0.10	2.01	
PFHxA (C6)	64	<9.1	<9.1	9.69	18.6	111	10
4:2 FTS (C6)	14	<0.60	<0.60	<0.60	<0.60	35.3	
PFHpA (C7)	98	<0.20	4.54	6.10	7.15	45.7	6
∑short-chain		7.00	10.7	17.2	28.0	157	15
			Long-Chain				
PFHxS (C6)	90	<6.1	5.25	6.55	7.45	16.7	7
PFHpS (C7)	74	<0.30	<0.30	1.05	1.59	7.42	1
PFOS (C8)	100	6.35	16.8	30.4	63.0	187	32
PFOA (C8)	86	<16	10.6	13.9	25.3	50.7	15
PFNS (C9)	58	<0.30	<0.30	0.440	0.920	1.43	1
PFNA (C9)	100	2.00	4.13	5.98	8.40	36.3	6
PFDS (C10)	4	<1.0	<1.0	<1.0	<1.0	1.37	
PFDA (C10)	94	<0.80	5.97	7.40	11.1	697	8
PFUdA (C11)	84	<0.20	3.00	4.43	6.03	18.0	5
PFDoA (C12)	94	<1.0	4.20	5.26	7.78	374	6
PFTrDA (C13)	78	<1.2	1.69	3.16	5.29	313	3
PFTeDA (C14)	18	<15	<15	<15	<15	409	
∑long-chain		40.5	82.6	99.6	142	1830	85
∑PFAS		52.0	103	121	190	1850	100

after the normalization are included in Table S6. Because the data used for the temporal trend analyses were not normally distributed, the data set was naturally log-transformed and the transformed data were found to be normally distributed based on the Skewness−Kurtosis normality test. Nondetects were not included in the analyses. We tested the appropriateness of using eq 6 to normalize by assessing the relationship between detection frequency and LOD using our own data for the most abundant short-chain PFAS detected in this study; the association was strong and linear (r^2 > 0.94; p < 0.05).

RESULTS AND DISCUSSION

Population Characteristics. A summary of participants' demographic characteristics is given in Table 1. All women were breastfeeding their first child during the time of sampling. The majority of participants were Caucasian with ages ranging from 24 to 42 years old (mean ± standard deviation 34 ± 4 years). All participants resided in or around Seattle, Washington, United States, with an average residence time of 13 ± 11 years. Ninety-four percent of participants had attained higher education, and 82% lived in the middle- or upper-middle-class neighborhoods (based on census tract data).[42] Postpartum body mass index (BMI) values ranged from 18.9 to 39.6, and 58% of participants had a BMI within the normal range (18.5−24.9), while 22% were overweight and 14% were obese.

Concentrations. Table 2 presents the results of the descriptive statistics for the 16 PFAS detected in breast milk, including 4 short-chain PFAS defined as perfluorocarboxylic acids (PFCAs) with ≤7 carbons and perfluorosulfonic acids (PFSAs) with ≤5 carbons and 12 long-chain PFAS defined as PFCAs with >7 carbons and PFSAs with >5 carbons. Twelve PFAS were detected in more than half of the samples and the other four were detected in 18% or fewer. The rest of the PFAS analytes (Tables S1 and S2) were not detected in any of the samples and are not discussed further.

Total PFAS concentrations (∑PFAS, the sum of 16 PFAS concentrations) ranged from 52.0 to 1850 pg/mL (median 121 pg/mL). Overall, PFOS and PFOA were the predominant PFAS (medians 30.4 and 13.9 pg/mL, respectively) and contributed on average 32 and 15% to the ∑PFAS concentrations, respectively (Table 2). The concentrations of these two compounds were generally lower than those found in breast milk samples from the United States in 2004 (medians 106 and 36.1 pg/mL, respectively)[35] and from Asia and Europe in 1996−2019 (range 6.81−317 and 41−181 pg/mL, respectively).[43] The decreasing levels of these two PFAS in breast milk mirror the decline in U.S. serum levels reported in NHANES between 2004 and 2015.[39] Perfluoro-1-hexanesulfonic acid (PFHxS, C6) was found in 90% of the samples with a median concentration of 6.55 pg/mL, which was comparable to the levels reported for breast milk from Japanese (median 6.45 pg/mL), Malaysian (median 6.68 pg/mL), and Korean (median 7.2 pg/mL) women in 2003−2010[44,45] but lower than those from Europe (median 70 pg/mL).[13] Perfluoro-1-heptanesulfonic acid (PFHpS, C7) was detected in 74% of the samples with a lower median concentration of 1.05 pg/mL.

Several long-chain PFAS, including perfluoro-n-nonanoic acid (PFNA, C9), perfluoro-n-decanoic acid (PFDA, C10), perfluoro-n-undecanoic acid (PFUdA, C11), perfluoro-n-dodecanoic acid (PFDoA, C12), and perfluoro-n-tridecanoic acid (PFTrDA, C13), were frequently detected in these breast milk samples. Perfluoro-1-nonanesulfonic acid (PFNS, C9), perfluoro-1-decanesulfonic acid (PFDS, C10), and perfluoro-n-tetradecanoic acid (PFTeDA, C14) were detected less frequently than the other long-chain PFAS (detection frequencies of 58, 4, and 18%, respectively). PFNA was found in all of the samples with a median concentration of 5.98 pg/mL, which was lower than the levels detected in breast milk from the United States and China in 2004 (medians 6.97 and 18.1 pg/mL, respectively)[35,46] and from Spain in 2014 (40 pg/mL).[47] PFDA was detected in 94% of the samples with a

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median concentration of 7.40 pg/mL and was the most abundant among the C10−C13 PFAS ($p < 0.05$ based on a one-way analysis of variance [ANOVA]). PFDA concentrations were lower than those reported in breast milk from China in 2004 (median 7.2 pg/mL)[46] and 2009 (17 pg/mL)[38] and Spain in 2014 (20 pg/mL).[47] PFUdA was found in 84% of the samples with a median concentration of 4.43 pg/mL, and PFDoA and PFTrDA were detected in up to 94% of the samples at similar concentrations (medians 5.26 and 3.16 pg/mL, respectively). These three long-chain PFAS were also previously detected in breast milk from Asia and Europe in 2004−2009 but at lower concentrations.[46,48,49] Increasing detection of the long-chain PFAS (≥C9) was observed in Swedish breast milk collected between 1972 and 2016.[18] Frequent detection of these long-chain PFAS in breast milk is of particular concern because of their high persistence and bioaccumulation potential due to their strong binding affinities to blood proteins.[5] Our findings show continued human exposure to these compounds, likely due to a combination of exposure from diet and the indoor environment. Exposure to C9−C12 PFAS has been linked to seafood exposure,[50] and previous studies of long-chain PFAS in house dust from the United States and Europe report frequent detection,[51,52] suggesting indoor sources of these compounds, such as treated carpets and home textiles as well as after-market stain-protection treatments.[14,53−56] In addition, indirect exposure to dipolyfluoroalkyl phosphates (diPAPs), perfluorooctane sulfonamides (FOSAs), fluorotelomer alcohols (FTOHs), and perfluorooctane sulfonamidoethanols (FOSEs) from diet, air, or dust can be a potential source of these long-chain PFAS.[57−62] For example, air concentrations of 10:2 FTOH were significantly correlated with serum PFOA and PFNA levels and air concentrations of 2-(N-methylperfluoro-1-octanesulfonamido)-ethanol (MeFOSE) were positively associated with serum PFOS levels.[57]

Four short-chain current-use PFAS were also detected in these breast milk samples. Perfluorohexanoic acid (PFHxA, C6) was detected in 64% of the samples and was the most abundant compound among these short-chain PFAS with a median concentration of 9.69 pg/mL. Alarmingly, the concentrations of PFHxA, a PFAS with an increasing toxicity concern,[63−65] in these samples were comparable to those of PFOA ($p > 0.05$ based on a one-way ANOVA; Figure 1). Perfluoro-*n*-heptanoic acid (PFHpA, C7) was detected in 98% of the samples with a median concentration of 6.10 pg/mL. The levels of PFHxA and PFHpA in this study were up to 4 times lower than those in breast milk from Korean women (medians 47 and 28 pg/mL, respectively).[36] It was suggested that the higher levels of PFHxA and PFHpA in Korean breast milk were due to the widespread occurrence of these two compounds in drinking water and foodstuff in Korea.[66−68] These two PFAS were rarely detected in the blood of U.S. women reported in NHANES (2013−2014),[39] suggesting increased exposure present in our cohort and/or potential preferential bioaccumulation in breast milk, although this comparison should be interpreted with caution given the improved sensitivity of the analytical method used in the current study compared to the NHANES. Both PFHxA and PFHpA have been shown to form as a result of biotic transformation or atmospheric oxidation of 6:2 FTOH found in high concentrations in stain-protected textiles, food packaging, waxes, and sealers and to increase in concentration with weathering of textiles.[56,62,69,70] The 6:2 FTOH has been

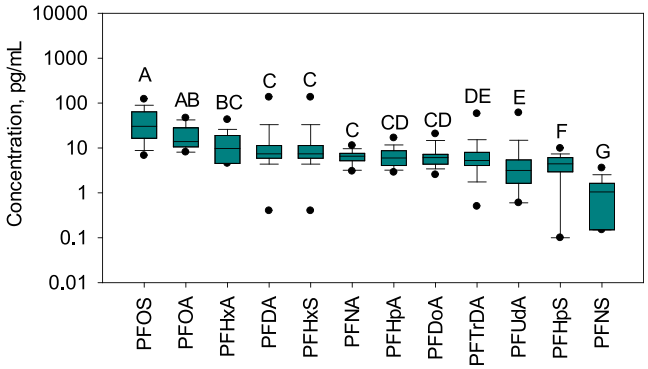

Figure 1. Concentrations of PFAS detected in >50% of the breast milk samples (n = 50, pg/mL). Concentrations are shown as box plots, representing the 25th and 75th percentiles; black lines represent the median; the whiskers represent the 10th and 90th percentiles; and the dots represent the 5th and 95th percentiles. The letters represent the results of the one-way analysis of variance (ANOVA); the concentrations are ranked from the highest to lowest in alphabetic order, and concentrations sharing the same letter are not statistically different at $p < 0.05$.

detected in indoor air as well as in indoor dust.[51,59] Finally, 1*H*,1*H*,2*H*,2*H*-perfluorohexane sulfonic acid (4:2 FTS, C6) and perfluoro-1-pentanesulfonic acid (PFPeS, C5) were detected in 14 and 8% of the samples, respectively. To the best of our knowledge, this is the first report on the occurrence of 4:2 FTS in breast milk. This compound is a component of waxes and sealers and has been associated with AFFFs.[19]

Overall, there was a wide variation in exposure to specific and ∑PFAS in the breast milk from 50 mothers. In some of the cases with particularly high exposure levels, questionnaire data provided information that may offer a partial explanation. Several of the mothers with the highest levels had water-proofing sprays used in their homes; in other cases, high concentrations of long-chain compounds (≥C9) suggest exposure through fish consumption.[50] One of the mothers lives in a household with a firefighter, but the PFAS levels in her breast milk were below the median ∑PFAS concentration.

Lactational Transfer Efficiencies. The transfer mechanism from blood to milk for PFAS is thought to be different from that for other persistent organic pollutants, such as polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs), because PFAS do not accumulate in lipids.[43] PFAS have strong binding affinities to serum proteins,[71,72] and studies with paired samples have shown that the levels of PFAS in breast milk on average constitute about 1% of those in serum.[35,38] Mechanisms for transfer may include bulk transport along with phospholipids or delivery to the mammary gland membrane via serum proteins.[73] In the latter case, transfer to breast milk may be regulated by binding affinities to those proteins,[73] including human serum albumin,[71,74] fatty acid binding protein,[75−77] and transthyretin.[78−80] Here, compound-specific lactational (blood-to-milk) transfer efficiencies of PFAS (eq 1) were determined based on PFAS concentrations in milk measured in this study and in serum reported in NHANES for U.S. women (2015−2016).[39] Overall, the estimated PFAS lactational transfer efficiencies were below 100%, unlike those for lipophilic compounds such as PCBs, PBDEs, and organochlorine pesticides, which all have transfer efficiencies over 100% and a stronger tendency to accumulate in breast milk.[81] In our

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analysis, we observed a U-shaped relationship between estimated PFAS transfer efficiencies and the length of the PFAS carbon chain (Figure S1), a trend similar to that found for PFAS placental transfer.[82] Transfer efficiencies decreased with the increasing number of carbons in the PFAS structure for C6−C8 compounds and then increased for C9−C12 compounds. The highest lactational transfer efficiency was determined for PFHxA (9.7%) [MDL values were used for PFAS not detected in NHANES], suggesting a potentially stronger ability to partition from blood to milk for this short-chain PFAS (Table S7). Overall, the transfer efficiencies ranged from 9.7% for PFHxA (C6) to 6.1% for PFHpA (C7) to ∼1.0% for PFOS (C8) and PFOA (C8) and back to 7.4% for PFDA (C10) and 5.3% for PFDoA (C12). Similarly, a low lactational transfer efficiency of 2% was previously reported for PFOS.[38] Our analysis has limitations as it compares 2019 breast milk data from a local population with 2015−2016 serum data from a national population and PFAS use patterns may have changed in that time period. NHANES serum PFAS data for women were used here because paired milk and blood samples were not collected in this study. Even though we used two different data sets for milk and blood for estimating PFAS transfer efficiencies, this approach has been previously used and can provide important information on PFAS ability to partition to milk.[38] Another complicating factor is the possibility that serum measurements of compounds like PFHxA do not accurately represent blood concentrations, as whole blood has been found to have higher concentrations than serum.[83] However, the potential for high transfer efficiencies for short-chain and some long-chain PFAS found here highlights the importance of measuring these compounds in breast milk and suggests an increase in exposure through breastfeeding with the increase in the use of these compounds.

Concentration Correlations. Correlation heat maps and hierarchical clustering based on Pearson correlation coefficients of logarithmically transformed concentrations of individual PFAS detected in more than half of the samples are shown in Figure S2. The hierarchical clustering shows three distinct PFAS clusters. The first cluster includes strong correlations among long-chain PFCAs, such as PFDA, PFDoA, and PFTrDA (r = 0.71−0.81, p < 0.001). In the second cluster, short-chain PFCAs (e.g., PFHxA and PFHpA) and PFNA were significantly correlated with each other (r = 0.41−0.63, p < 0.05). Clustering of PFHxA and PFHpA likely reflects their shared parent compound, 6:2 FTOH, a building block, and a degradation product of the side-chain fluorinated polymers typically used for water- and stain-repellent treatments.[70] The third cluster included weakly correlated PFHxS, PFHpS, PFOA, and PFOS (r = 0.25−0.38, p < 0.05). Separate clustering for short-chain, long-chain, and legacy PFAS suggests different sources for these three PFAS groups and may reflect market shifts in production and use from legacy toward short- and long-chain PFAS.

Correlations with Demographic and Behavioral Characteristics. A significant positive correlation was observed between the PFHxS concentrations in breast milk and maternal BMI in a multiple linear regression model adjusted for maternal age and household income (slope [β] = 0.417, p = 0.049; Table S8). This finding is consistent with a previous report of a positive association between exposure to PFHxS and the increased risk of obesity and other metabolic diseases.[24] A multiple linear regression analysis adjusted for the maternal age and BMI showed that PFOS concentrations were significantly lower as the duration of breastfeeding (estimated based on infant's age at the time of sampling) increased (β = −0.411, p = 0.047; Table S9). PFOS concentrations in breast milk of mothers who had breastfed for less than 6 months were 1.2 times higher than in those who had breastfed over 6 months. This finding indicates that lactation is an important excretion pathway for breastfeeding mothers and a transfer mode to nursing infants. Similarly, Thomsen et al. reported that PFOS concentrations in breast milk declined by about 37% after a year of breastfeeding.[84] No significant relationships were found between the concentrations of other PFAS, including ∑PFAS, and demographic or behavioral characteristics, possibly due to a limited sample size.

Exposure Assessment. The lactational estimated daily intakes (EDIs) for PFAS detected in more than half of the samples calculated for infants between the ages of 0 and 12 months old based on the U.S. EPA average age-based daily breast milk consumption rates[41] are presented in Table 3.

Table 3. Lactational Estimated Daily Intakes (EDIs) for PFAS Detected in >50% of the Samples for <1, 1−3, 3−6, and 6−12 Months Old Infants (ng/kg bw/day)

	age, months			
	1	1−3	3−6	6−12
PFHxA	1.5	1.4	1.1	0.80
PFHpA	0.98	0.92	0.72	0.54
PFHxS	0.92	0.85	0.67	0.51
PFHpS	0.16	0.15	0.12	0.090
PFOS	4.6	4.3	3.3	2.5
PFOA	2.1	1.9	1.5	1.2
PFNS	0.90	0.84	0.66	0.50
PFNA	0.070	0.060	0.050	0.040
PFDA	1.1	1.0	0.81	0.61
PFUdA	0.66	0.62	0.49	0.37
PFDoA	0.79	0.74	0.58	0.44
PFTrDA	0.47	0.44	0.35	0.26
∑PFAS	18	17	13	10

Generally, the EDIs decreased with infants' age. The highest ∑PFAS EDI was observed for infants younger than 1 month old (18 ng/kg bw/day), followed by 1−3 months old (17 ng/kg bw/day), 3−6 months old (13 ng/kg bw/day), and 6−12 months old (10 ng/kg bw/day). This change in the intake is driven by both the increasing body weight and EPA breast milk intake reference levels, which decrease with infant's age. These EDIs were more than an order of magnitude higher than those reported for adults through dietary intake (0.58 ng/kg bw/day),[85] indicating that breastfeeding is a significant exposure pathway for nursing infants. The EDI for PFOS was the highest for all age groups (2.5−4.6 ng/kg bw/day), followed by the EDIs for PFOA (1.2−2.1 ng/kg bw/day) and PFHxA (0.80−1.5 ng/kg bw/day). These EDIs for infants were lower than the reference dose (RfD) values established by the U.S. EPA (20 ng/kg bw/day for both PFOS and PFOA).[86,87] It should be noted that the PFOS EDI estimated for the 95th percentile breast milk concentration (16.5 ng/kg bw/day) was close to the established RfD of 20 ng/kg bw/day.[86] Moreover, PFOS EDIs are concerning when compared to the RfDs calculated based on more sensitive immunotoxic end points developed by some states, such as New Jersey, that have established a PFOS RfD of 1.8 ng/kg bw/day.[88] The latter is

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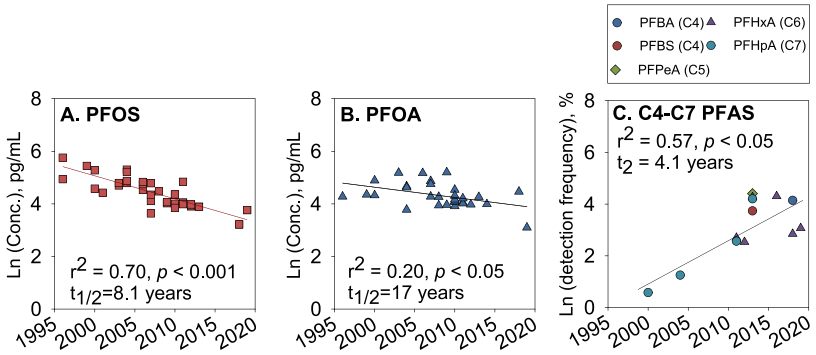

Figure 2. Changes in PFOS (A) and PFOA (B) concentrations (ln-transformed; pg/mL, n = 39 and 30, respectively) and detection frequencies (normalized to the highest detection limit for each compound across all studies and ln-transformed, %, n = 13) of short-chain PFAS (C) in breast milk during 1996−2019. $t_{1/2}$ is the halving time (number of years during which the concentrations are halved) and t_2 is the doubling time (number of years during which the detection frequencies are doubled). Tables S6 and S10 and Figure S3 include the data used in these analyses (PFHpA [2019] and PFPeA [2018] with detection frequencies of 1.0 and 4.8%, respectively, were excluded from this analysis as outliers).

below the PFOS lactational EDIs determined in this study for all four infant age groups.

Effects of PFAS Regulations and Market Changes. Over the last 15 years, since PFAS levels were last measured in U.S. breast milk, major changes have taken place in U.S. production and use of some of these compounds. Most significantly, the primary makers of PFAS in the United States began the phase-out of PFOS in 2000 and of PFOA in 2006.[51] They moved instead to short-chain PFAS and other replacements for grease- and water-repellency treatments for paper and textiles, with products that degrade ultimately to short-chain acids including PFHpA, PFHxA, PFPeA, PFBA, PFPeS, and PFBS.[3] Our study provides an opportunity to measure the impact of this change in production and use practices on the levels and composition of PFAS in U.S. breast milk. In addition, our new data in combination with those reported in other studies in the last 25 years allow us to assess global temporal trends in PFAS contamination of breast milk.

We have compiled the available data on PFOS and PFOA in breast milk, including ours (Table S10), and regressed concentrations against the year of sample collection (Figures 2A,B and S3). This analysis (eqs 3−5) shows that the levels of PFOS in breast milk have declined significantly worldwide since 1996 (r^2 = 0.70, p < 0.001) with a halving time of 8.1 years, while a weaker trend was found for PFOA (r^2 = 0.20, p < 0.05), which declined with a halving time of 17 years. Overall, PFOS and PFOA concentrations in breast milk decreased, on average, by 37 and 19% during the period of 1996−2019. These encouraging trends are likely related to the changes in the production and use of PFOS and PFOA during the early 2000s in many developed countries.[5,17] The slower decline in PFOA concentrations may be due to its use in some developing countries until 2019, when it was added to the Stockholm Convention on Persistent Organic Pollutants calling for a global elimination.[7,89] A similar decline has been found for PFOS and PFOA levels in water,[90] sediment,[90] indoor dust,[90] wildlife,[91] human blood,[17] and Swedish breast milk.[18] Comparing the PFOS and PFOA concentrations in the present study with the most recent study from 2004 reporting PFAS in breast milk in the United States,[35] the overall decline in concentrations is 71% for PFOS and 56% for PFOA. These rates are very similar to the decline of 75 and 61% for PFOS and PFOA concentrations, respectively, in blood reported in the NHANES for U.S. women over the same time period.[39]

In contrast with the promising trends described above, several recent studies, including ours, report increasing detection of short-chain PFAS in breast milk. For example, detection frequencies (normalized to the highest detection limit reported across the studies) of PFHpA (C7) in breast milk increased from 1.8% in 2000[45] to 13% in 2011[92] and further to 67% in 2013.[36] Recent studies from Korea (2013) and China (2018) found PFPeA (C5) and PFHxA (C6) in more than half of the samples.[36,37] In addition, these studies also reported PFBA (C4) and PFBS (C4) with detection frequencies of 63 and 42%, respectively.[36,37] Our analysis of all currently available data on short-chain PFAS in breast milk[35−37,46,92] shows that the detection frequency (normalized to the highest detection limit reported for each individual PFAS across the studies included in the analysis; see eqs 3−6) of C4−C7 PFAS has increased since the early 2000s (r^2 = 0.57, p < 0.05; Figure 2C), doubling every 4.1 years for all C4−C7 PFAS included in the analysis. In addition, the reported maximum concentrations have also steadily increased worldwide for PFBS from 2.5 pg/mL in 2004 in China[46] to 56 pg/mL in 2013 in Korea[36] and for PFHpA from 13.9 pg/mL in 1999 in Japan[45] to 117 pg/mL in 2011[92] and 48 pg/mL in 2013 in Korea[36] (Table S6). While these results must be interpreted with caution due to the limited data available for short-chain PFAS in breast milk, these changes likely reflect the shift toward short-chain PFAS as replacements for the C8 compounds.[19,53] Generally, the number of studies reporting short-chain PFAS in consumer products, the environment, and people is steadily increasing.[18,43,93] The makers of these chemicals report the use of short-chain fluorotelomer-based products as the basis for stain- and water-repellent treatments for food packaging, carpets, upholstery, and other textiles, and short-chain PFAS have been found in many consumer products, such as textiles, leather, carpets, food-packaging materials, and cosmetics, as grease-, stain-, and water-repellents.[51,94−99] Short-chain PFAS have high mobility in soil and water, resulting in contamination of surface and groundwater,[100] including drinking water,[101,102] and have been found in wildlife (e.g., polar bears, ringed seals, bald eagle eggs)[91,103] and human tissues.[82,104−106] Short-chain PFAS, such as PFBA, PFBS, PFHxA, and PFHpA, show cytotoxicity in cell-based studies as well as adverse effects on reproduction, development, liver, kidneys, and lipid metabolism in animal studies.[23,63,64,107−112] A recent study also showed that PFBA, PFBS, PFPeA, and PFHxA can cross the placental barrier more

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efficiently compared to long-chain PFAS and pose a higher exposure risk to the fetus.[82]

Strengths and Limitations. This study has several limitations. Transfer efficiencies were calculated using PFAS concentrations from the 2015 to 2016 NHANES data for U.S. women because paired breast milk and blood samples were not collected in this study. Our sample size was small, covered a limited geographic area, and may not be representative of the general U.S. population. Further studies focused on paired blood−milk samples collected from diverse populations are needed to fully evaluate the distribution of both legacy and current-use PFAS in breast milk. The increasing trend of detection frequencies of short-chain PFAS should be interpreted with caution due to the limited number of studies that have measured short-chain PFAS in breast milk.

Nonetheless, this is the first study to measure PFAS concentrations in breast milk from the United States in the last 15 years. Our results indicate that while the legacy PFOS and PFOA are still the most abundant PFAS in breast milk, similar to the studies from the early 2000s, the detection frequencies and concentrations of several current-use short-chain PFAS have significantly increased since then. Moreover, our analysis of the global data available on PFAS in breast milk indicates that the levels of the legacy C8 compounds are declining with halving times of up to 17 years, while the detection frequencies of current-use short-chain PFAS have almost tripled between 1996 and 2019. These findings suggest that the increased use of short-chain PFAS as replacements for the phased-out PFOS and PFOA is reflected in current exposure trends and that some short-chain compounds are bioaccumulative. With the critical role that breastfeeding plays in child and maternal health, these results showing the buildup of current-use PFAS in breast milk clarify the urgency of phase-out where safer alternatives are available.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.0c06978.

List of target analytes and details of the instrumental methods; MDLs and blank concentrations; lactational transfer efficiencies; summary of the available global data on PFAS in breast milk; and the results of the multiple regression analyses (PDF)

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Notes

The authors declare no competing financial interest.

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