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Novel Chlorinated Polyfluorinated Ether Sulfonates and Legacy Per-/Polyfluoroalkyl Substances: Placental Transfer and Relationship with Serum Albumin and Glomerular Filtration Rate

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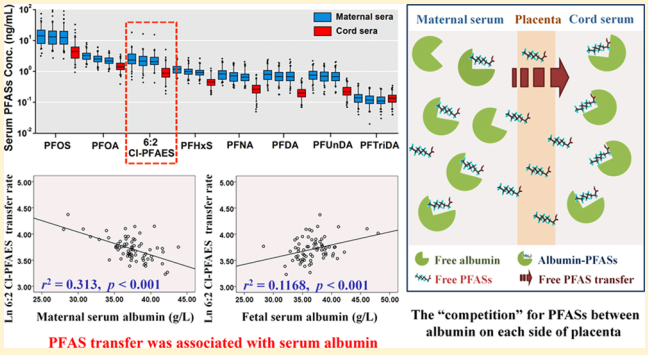
Supporting Information

ABSTRACT: Per- and polyfluoroalkyl substances (PFASs) may cross the placental barrier and lead to fetal exposure. However, little is known about the factors that influence maternal-fetal transfer of these chemicals. PFAS concentrations were analyzed in 100 paired samples of human maternal sera collected in each trimester and cord sera at delivery; these samples were collected in Wuhan, China, 2014. Linear regression was used to estimate associations of transfer efficiencies with factors. Chlorinated polyfluorinated ether sulfonates (Cl-PFAESs, 6:2 and 8:2) were frequently detected (>99%) in maternal and cord sera. A significant decline in PFAS levels during the three trimesters was observed. A U-shape trend for transfer efficiency with increasing chain length was observed for both carboxylates and sulfonates. Higher transfer efficiencies of PFASs were associated with advancing maternal age, higher education, and lower glomerular filtration rate (GFR). Cord serum albumin was a positive factors for higher transfer efficiency (increased 1.1−4.1% per 1g/L albumin), whereas maternal serum albumin tended to reduce transfer efficiency (decreased 2.4−4.3% per 1g/L albumin). Our results suggest that exposure to Cl-PFAESs may be widespread in China. The transfer efficiencies among different PFASs were structure-dependent. Physiological factors (e.g., GFR and serum albumin) were observed for the first time to play critical roles in PFAS placental transfer.



INTRODUCTION

Per- and polyfluoroalkyl substances (PFASs) are a group of anthropogenic fluorinated chemicals that have been widely used for the past six decades.[1] Because of their unique characteristics, such as water and oil repellency, high surface activity, and thermal stability, PFASs have been used in many different industrial and commercial applications, including surface repellent coatings (e.g., food contact paper, textiles, leather, cookware, and upholstery), surfactants (e.g., fire-fighting foams, mist suppressants, and cleaning products), photographic devices, and pesticides.[2,3] Perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) are two of the most predominant PFASs found in humans due to their historical usage and bioaccumulative properties.[4] After the phase-out of PFOS,[5] together with its global regulation[6] and the introduction of the PFOA Stewardship Program,[7] most industrial emissions have been reduced.[8] Serum PFOS

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concentrations in U.S.[9,10] and European populations[11,12] have also decreased steadily since 2000. In contrast, many classes of novel PFASs, including polyfluoroalkyl phosphate diesters (diPAPs), fluorotelomer sulfonates (FTSAs), and polyfluoroalkyl ether sulfonates (PFAESs), have emerged as alternatives to legacy PFOS, and have been identified in human blood.[13−15]

Chlorinated polyfluorinated ether sulfonates (including 6:2 Cl-PFAES and 8:2 Cl-PFAES) with the trade name F-53B have been used in the Chinese metal plating industry for three decades.[16] As alternatives to PFOS, the environmental levels of Cl-PFAESs are expected to increase in China over the coming years. Recent studies in China have detected Cl-PFAESs in surface water,[16] sewage sludge,[17] and freshwater fish,[18] with measured levels comparable to those of PFOS. Although China is the only known emission source, 6:2 Cl-PFAES has also been detected in Arctic wildlife,[19] suggesting long distance transportation and global contamination. To the best of our knowledge, only one study on Cl-PFAES detection in occupationally exposed workers and high fish consumers has been reported.[15] The levels of Cl-PFAES exposure in humans, especially in the general population and biologically sensitive populations (e.g., pregnant women and infants) remain unknown.

Animal exposure and epidemiology studies suggest some PFASs (e.g., PFOA and PFOS) are developmental toxicants, with evidence that prenatal exposure to PFOA and PFOS might result in adverse effects on fetal growth,[20−23] thyroid hormone secretion,[24] and reproductive system development.[25] These findings highlight the necessity to evaluate fetal PFAS exposure during pregnancy, which is a critical time window of development impacting health in later life.[26] A number of studies have reported on the levels of PFASs in maternal and infant sera.[22,24,27−38] The levels of PFAS in maternal sera were found to decline during pregnancy,[11,39] probably due to the dilution effect caused by the increased body weight and blood volume during pregnancy.[40] The transfer of the chemicals from mother to fetal tissues (e.g., fetal lung and liver) may be another reason for the decrease.[41] Therefore, serum PFAS levels at different stages during pregnancy might give a misleading evaluation of fetal PFAS exposure. It is, therefore, scientifically important to determine the best sampling time during pregnancy at which maternal PFAS levels could give the best estimate of fetal PFAS exposure.

Detection of PFASs in cord blood has demonstrated that PFASs might cross the placental barrier.[27,29,39] Placental transfer efficiency (the ratio of PFAS concentration in cord blood to that in maternal blood) is an important marker in assessing fetal PFAS burden.[38,42] Studying transfer efficiency could also help understand the mechanism for transportation of PFASs between mother and fetus. Functional group, chain length, and degree of PFAS branching are important determinants of transfer efficiency.[24,29,38,42] Studies suggest that sociodemographic, perinatal, and physiological factors influence maternal PFAS exposure levels.[39,43] However, further studies are needed to evaluate if these factors affect placental transfer efficiency. To the best of our knowledge, only one preliminary study has suggested that maternal age can influence PFAS placental transfer.[34] Aside from these determinants, limited studies explored other potential factors, for example, maternal glomerular filtration rate (GFR, a kidney function marker that influences renal clearance of PFASs)[44] and serum albumin (primary binding protein for PFASs in serum),[45] for the transfer efficiency of PFASs.

In the present investigation, a series of maternal sera during gestation and matched cord sera at term were collected among Chinese pregnant women and analyzed for PFASs, including Cl-PFAESs. Our main objectives were to (1) determine the levels of PFASs, especially novel PFOS alternative Cl-PFAESs, in paired samples of maternal sera and cord serum; (2) determine the most representative sampling time during gestational trimesters for the estimation of fetal exposure; and (3) explore whether maternal sociodemographic and physiological factors are potential factors for PFAS transfer efficiency.

MATERIALS AND METHODS

Study Population. In this study, 100 mother-newborn pairs were recruited during August 2014 to December 2014 at the Women and Children Medical and Healthcare Center in Wuhan, China. Pregnant women included in this study were: ≤ 12 weeks of gestation, age ≥18 years, had a single gestation, and native Chinese women. All participants provided written informed consent. The research protocol was approved by the ethics committees of the Tongji Medical College, Huazhong University of Science and Technology, and the study hospital. For each pair, three maternal blood samples [at the first (12.9 ± 1.3 weeks), second (26.0 ± 1.6 weeks), and third trimesters (38.4 ± 1.6 weeks), respectively] and one umbilical cord blood sample (at the time of newborn delivery) were collected. Blood samples were centrifuged immediately after collection, with sera then transferred to prescreened polypropylene tubes and stored at −80 °C until further analysis.

Data Collection. A face-to-face interview was conducted with each participant by a well-trained nurse to collect information on demographic characteristics (e.g., maternal age, prepregnancy weight, education, employment, household income) and lifestyle factors (e.g., active smoking, passive smoking, alcohol consumption). Additional data (e.g., mother's weight at delivery, parity, disease, infant gender, gestational age, birth weight) were obtained from medical records. Passive smoking was defined as exposure to secondhand smoke on at least one occasion per week, for at least 15 min per occasion, either at home or in public areas. Gestational age was calculated based on last menstrual period. Each mother's body mass index (BMI) was calculated using prepregnancy weight in kg divided by the square of height in m. Serum creatinine (in third trimester) and albumin (in third trimester and cord serum) were measured using the Biochemical Analyzer 7180-ISE (Hitachi High-Technology Science Systems Corporation, Tokyo, Japan). Estimated GFR was calculated based on the Cockroft−Gault (GFR-CG) formula [GFR-CG = (140 − age) × weight (kg) × 1.04/serum creatinine (μmol/L)].

Measurements of PFASs in Serum. The 24 target PFASs included perfluoroalkyl carboxylates (PFCAs) with 4 to 14 carbon atoms (i.e., PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTriDA, PFTeDA), perfluoroalkyl sulfonates (PFASs) with 4, 6, 8, and 10 carbon atoms (i.e., PFBS, PFHxS, PFOS, PFDS), fluorotelomer sulfonates (4:2 FTSA, 6:2 FTSA, 8:2 FTSA), methyl perfluorooctanesulfonamidoacetate (MeFOSAA), ethyl perfluorooctanesulfonamidoacetate (EtFOSAA), polyfluoroalkyl phosphate ester diesters (6:2 diPAP and 8:2 diPAP), 6:2 Cl-PFAES, and 8:2 Cl-PFAES.

Serum PFASs were extracted using an ion-pair liquid−liquid extraction method.[46] In brief, 200 μL of serum was spiked with mass-labeled standard, 1 mL of tetra-*n*-butylammonium

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hydrogen sulfate solution (TBAS, 0.5 M), and 2 mL of $NaHCO_3/Na_2CO_3$ buffer solution (pH = 10) were added to the spiked sera; the mixture was vortex-mixed, and 4 mL of methyl *tert*-butyl ether (MTBE) was added to the mixture. The mixture was shaken at 250 rpm for 20 min and centrifuged at 4000 rpm for 15 min to separate the organic and aqueous phases. Approximately 3.5 mL of supernatant was transferred to a new tube. Another 4 mL of MTBE was added to the remaining tube, and the extraction procedure was repeated twice as described above. All three extracts were combined and evaporated to dryness under a gentle stream of nitrogen at 40 °C and reconstituted with 200 μL of methanol.

Target analytes were analyzed by the Acquity UPLC coupled to a Xevo TQ-S triple quadrupole mass spectrometer (Waters, Milford, MA, USA) in negative electrospray ionization (ESI-) mode. Chromatographic separation was accomplished using an Acquity BEH C18 column (100 mm × 2.1 mm, 1.7 μm, Waters, MA, USA) with mobile phases: 10 mM ammonium acetate in water (A) and methanol (B) at a flow rate of 0.4 mL/min. Calibration curves (range = 0.01−20 ng/mL) exhibited excellent linearity ($R^2 > 0.99$).

Extraction blank, matrix recovery, measurement of standard reference materials (SRM1957, nonfortified human blood serum, National Institute of Standards and Technology, USA), and limit of quantification (LOQ) were used as the quality assurance and control (QA/QC) measures. For every batch of extraction, two extraction blanks and two SRM samples were included to ensure no contamination occurred and to ensure the compatibility of data from batch to batch. No detectable levels of PFASs were found in the extraction blank. Matrix recoveries were validated by spiking known amounts of standards into newborn bovine serum and subjected to the extraction method discussed above; the values were within 79%−109%. The measured PFASs in SRM were within the reported range. The LOQs were defined as the lowest standard in the calibration curve with measured concentrations within 70−130% of the theoretical concentrations, and were 0.01 ng/mL for PFSAs and Cl-PFAESs; 0.02 ng/mL for C8−C14 PFCAs; and 0.05 ng/mL for all remaining compounds. Further details on standards and reagents, sample extractions, instrumental analyses, and QA/QC measures are provided in the Supporting Information (SI).

Statistical Analysis. Descriptive statistics were provided for subject demographics and PFAS concentrations in maternal and cord sera. When the concentrations of the PFASs were below the LOQ, a value of LOQ/$\sqrt{2}$ was employed. Since the PFAS levels did not have equal variances, paired *t* tests were used for pairwise comparisons of PFAS serum concentrations. Correlations among PFAS concentrations in maternal sera in the three trimesters and in cord serum were evaluated by Spearman Rank correlations. To estimate the variability of PFAS levels during pregnancy, intraclass correlation coefficients (ICC) were calculated based on one-way random effects models with unstructured symmetry covariance matrices. The ICC values can be interpreted as a measure of reliability of repeated measures over time, which range from 0 (poor reliability) to 1 (high reliability).

The percentage ratio of PFAS concentrations in cord serum to those in third trimester maternal serum (C:T3 ratio) was calculated to indicate PFAS transfer efficiency across the placental barrier (higher ratios mean higher transfer efficiency). To better estimate the actual transfer efficiency (C:T3 ratio) of these chemicals, only paired samples with quantifiable concentrations (>LOQ) in both T3 and cord serum were included (92, 99, 14, and 8 pairs were used for PFDoDA, 8:2 Cl-PFAES, PFHpA and PFTeDA, respectively, and 100 pairs were used for all other compounds). One-way analysis of variance (ANOVA) followed by Duncan's multiple range test was used to compare the differences in the transfer efficiency of PFASs. Linear regression models were performed between the C:T3 ratios of PFASs (PFAS transfer efficiencies) and possible covariates (factors of transfer efficiency). Because of a skewed distribution, the C:T3 ratios were natural log (ln) transformed to better achieve the normality assumption of linear models. The following covariates were included one at a time: maternal age (continuous), prepregnancy BMI [underweight (<18.5), normal (18.5−23.9), overweight (≥24 kg/m^2), categorical], gestational week (continuous), household income (<50 K, 50−100 K, ≥100 K yuan per year, categorical), maternal education (higher than high school, high school, less than high school, categorical), employment (unemployed and employed, dichotomous), parity [0 (nulliparous) and ≥1 (multiparous), dichotomous], infant gender (male and female, dichotomous), passive smoking status (yes and no, dichotomous), GFR (continuous), and serum albumin (continuous). Levels of GFR and serum albumin were also divided into tertiles with the lowest category used as reference. The beta coefficient from the linear model was used to calculate the percentage change in the PFAS transfer efficiencies for each factor [percentage change = $(e^{\beta} - 1) \times 100\%$]. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC). Two-tailed *p*-values of less than 0.05 were considered statistically significant in all models.

RESULTS

Population Characteristics. Demographic characteristics of the 100 pregnant women are shown in Table 1. The average age at delivery and prepregnancy BMI were 28.6 and 20.9, respectively. Among the participants, 76% had received university or higher education; 62% were employed; and 47% had household income higher than 100 K Yuan per year; 88% were first time mothers; and 42% reported passive smoking during pregnancy. No participants reported active smoking or alcohol consumption. The mean values of GFR, maternal serum albumin, and fetal serum albumin were 169.3 (mL/min per 1.73 m^2), 37.4 (g/L), and 36.6 (g/L), respectively. On average (±SD), maternal serum samples were collected at 12.9 ± 1.3, 26.0 ± 1.6, and 38.4 ± 1.6 gestational weeks.

PFAS Concentrations. In most paired samples, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTriDA, PFHxS, PFOS, 6:2 Cl-PFAES, and 8:2 Cl-PFAES were detected (>92%, Table 2). PFHpA and PFTeDA were only detected in 26% and 34% of cord sera, respectively; the detection rate in maternal sera was even lower (8−28%). No other PFASs were detected in any samples. Because of the low detection rate of PFHpA and PFTeDA, only the transfer efficiencies of these two chemicals were evaluated.

A significant decline in PFAS levels during the three trimesters was observed (Table 2 and Figure 1A). The concentrations of total PFAS and individual PFAS significantly decreased 6.9−25.6% between the first and second trimesters (all paired *t* test *p* values <0.05; Table S3). A decline (2.0−16.1%) occurred between the second and third trimesters, but was statistically significant for only PFOA, PFNA, PFHxS, and 8:2 Cl-PFAES. The levels in cord serum were 0.6−2.5-fold

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Table 1. Characteristics of the Pregnant Women (n = 100) in the Study

characteristic	mean ± SD or n (%)
maternal age at delivery (year)	28.6 ± 3.2
prepregnancy BMI (kg/m^2)	20.9 ± 3.0
gestational age (week)	39.4 ± 1.3
prenatal GFR (mL/min per 1.73 m^2)[a]	169.3 ± 37.5
maternal serum albumin (g/L)	37.4 ± 2.7
fetal serum albumin (g/L)	36.6 ± 3.2
infant gender	
boy	51 (51%)
girl	49 (49%)
parity	
0	88 (88%)
1	12 (12%)
education	
more than high school	76 (76%)
high school	16 (16%)
less than high school	8 (8%)
annual household income (yuan)	
<50 K	22 (22%)
50 K−100 K	31 (31%)
≥100 K	47 (47%)
employment	
unemployed	38 (38%)
employed	62 (62%)
passive smoking during pregnancy	
yes	42 (42%)
no	58 (58%)
gestational week of maternal sera	
first trimester	12.9 ± 1.3
second trimester	26.0 ± 1.6
third trimester	38.4 ± 1.6

[a]GFR was calculated based on the Cockroft−Gault (GFR-CG) formula.

lower than those in the third trimester, except for PFTriDA, which was 12.8% higher (all paired t test p values <0.001).

In all samples, PFOS was the predominant compound, followed by PFOA > 6:2 Cl-PFAES > PFHxS > PFNA ≈ PFDA ≈ PFUnDA > PFTriDA > PFDoDA ≈ 8:2 Cl-PFAES (Table 2). The composition profiles of PFASs in maternal sera in different trimesters and in cord sera are shown in Figure 1B. The compositions varied between different trimesters. For instance, the percentage contribution of PFOA in maternal sera significantly decreased from 14.5% (first trimester) to 11.8% (third trimester). The proportion of PFOS increased from 57.9% (first trimester) to 60.8% (third trimester), but the change did not reach a statistical significance.

Spearman correlation coefficients between PFAS concentrations in maternal sera in different trimesters and in cord sera are listed in Table 3. The PFAS concentrations of maternal sera between different trimesters were highly correlated (r = 0.77−0.97). Correlations between concentrations in maternal and cord sera were also high (r = 0.62−0.93). The coefficients between PFAS levels in cord serum and third trimester maternal serum were slightly higher than those between cord serum and sera collected in the first or second trimesters. The ICC for serial PFAS measurements among trimesters presented high reproducibility of PFASs during pregnancy (ICC = 0.84−0.97) (Table S4).

Placental Transfer Efficiency of PFASs and Related Factors. The distributions of PFAS transfer efficiencies are shown in Figure 2 and Table S5. The transfer efficiencies of PFASs were less than 100%, except for PFHpA (median = 112%), PFTriDA (119%), and PFTeDA (135%). Carboxylates were more efficiently transferred than sulfonates with the same perfluoroalkyl chain length (e.g., PFOA with a median of 66% was 2-fold higher than PFOS with a median of 35%). A U-shape trend for transfer efficiency with increasing molecular chain length was observed in carboxylates as well as sulfonates (6:2 Cl-PFAES contains eight carbons plus an oxygen atom in the backbone, considered one molecule longer than PFOS).

The associations between PFAS transfer efficiencies and demographic, prenatal, and physiological factors are presented in Table 4. Transfer efficiencies of PFASs were higher for older women, but only PFTriDA, PFHxS and 8:2 Cl-PFAES reached statistical significance. The transfer efficiency of PFTriDA was negatively associated with gestational week. The transfer efficiencies of PFOA, PFHxS, and PFOS were statistically associated with lower educational attainment. PFAS transfer efficiencies were inversely associated with GFR. Negative associations were observed between the transfer efficiencies of PFASs and the level of maternal serum albumin. In contrast, the transfers of PFASs were positively associated with cord serum albumin levels. No significant associations were found between PFAS transfer efficiencies and prepregnancy BMI, parity, infant gender, household income, or passive smoking.

DISCUSSION

The results of the present investigation demonstrated that PFAS exposure maybe widespread in Chinese pregnant women and newborns, even after the voluntary phase-out of PFOS, its global regulation,[5,6] and the introduction of the PFOA Stewardship Program.[7] The levels of PFOS and PFOA (median = 14.23 and 3.24 ng/mL in T1) in the present investigation were lower or comparable to the values reported in pregnant women collected from different regions before or around the time when PFOS started to phase out (e.g., 35.3 and 5.6 ng/mL in Denmark,[22] 1996−2002; 15.0 and 2.1 ng/mL in Sweden,[47] 1978−2001; and 19.7 and 4.2 ng/mL in U.S.,[36] 2000); but were higher than those reported in studies almost 10 year after the phase-out of PFOS (e.g., 3.07 and 1.05 ng/mL in France,[27] 2010−2013; 4.70 and 1.70 ng/mL in Canada,[48] 2008−2011). In addition, the levels of PFOS were approximately 2−3-fold higher than those reported in pregnant women from two other Chinese cities (6.7 ng/mL in Tianjin,[49] 2012; 4.41 ng/mL in Beijing,[50] 2013), suggesting higher PFOS exposure in Wuhan.

For legacy PFAS, the observed concentration sequences (PFOS ≫ PFOA > PFHxS ≈ PFNA ≈ PFDA ≈ PFUnDA > PFTriDA > PFDoDA) in maternal and cord sera were similar to those from prior studies.[22,27,28,33,39] However, other PFASs, such as FTSAs, MeFOSAA, EtFOSAA, and diPAPs, were not present in our samples. Another major difference in PFAS composition was the relatively high contribution of Cl-PFAESs in the Chinese samples; with 6:2 Cl-PFAES being the third highest PFAS in maternal and cord sera, accounting for over 10.0% of total PFASs (Figure 1B). Earlier research reported that known PFASs only accounted for 30−70% of extractable organic fluorine in human blood.[51] The identification of Cl-PFAESs might explain a significant proportion of the unknown fraction in Chinese blood. This is the first study to report baseline concentrations of 6:2 Cl-PFAES and 8:2 Cl-PFAES among pregnant women and fetuses. Our results suggest a

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Table 2. Levels of PFASs (ng/mL) in Maternal Sera in Different Trimesters (T1−T3) and in Cord Sera (n = 100)

				percentile				
analytes	trimester	detection rate (%)	geometric mean	5th	25th	50th	75th	95th
PFOA	T1	100	3.15	1.83	2.44	3.24	3.88	5.61
	T2	100	2.52	1.44	2.05	2.50	3.13	4.33
	T3	100	2.19	1.24	1.81	2.16	2.73	3.85
	cord	100	1.42	0.80	1.14	1.41	1.84	2.63
PFNA	T1	100	0.84	0.45	0.56	0.83	1.06	1.92
	T2	100	0.70	0.37	0.48	0.72	0.92	1.54
	T3	100	0.67	0.34	0.50	0.65	0.82	1.46
	cord	100	0.26	0.09	0.20	0.26	0.36	0.57
PFDA	T1	100	0.78	0.37	0.55	0.81	1.07	1.77
	T2	100	0.69	0.34	0.50	0.68	0.94	1.44
	T3	100	0.68	0.31	0.49	0.68	0.95	1.49
	cord	100	0.20	0.08	0.15	0.20	0.26	0.42
PFUnDA	T1	100	0.76	0.38	0.56	0.75	1.01	1.59
	T2	100	0.69	0.34	0.48	0.70	0.97	1.43
	T3	100	0.68	0.34	0.50	0.68	0.92	1.33
	cord	100	0.22	0.10	0.17	0.22	0.31	0.46
PFDoDA	T1	98	0.07	0.03	0.05	0.08	0.10	0.17
	T2	99	0.07	0.03	0.05	0.07	0.10	0.14
	T3	99	0.07	0.03	0.05	0.07	0.09	0.13
	cord	92	0.04	<LOQ	0.03	0.04	0.06	0.09
PFTriDA	T1	100	0.15	0.07	0.11	0.16	0.22	0.39
	T2	100	0.14	0.05	0.10	0.14	0.18	0.31
	T3	100	0.13	0.06	0.09	0.13	0.18	0.31
	cord	100	0.15	0.06	0.11	0.16	0.21	0.32
PFHxS	T1	100	1.16	0.61	0.88	1.18	1.46	2.42
	T2	100	0.99	0.56	0.81	0.98	1.18	1.79
	T3	100	0.95	0.56	0.77	0.92	1.09	1.81
	cord	100	0.46	0.24	0.35	0.46	0.55	1.04
PFOS	T1	100	14.1	5.56	7.99	14.23	21.68	38.84
	T2	100	13.0	4.82	7.62	13.20	20.38	38.25
	T3	100	12.7	4.84	7.61	12.32	20.03	37.21
	cord	100	4.33	1.66	2.68	4.38	6.19	12.54
6:2 Cl-PFAES	T1	100	2.30	0.90	1.70	2.22	3.45	5.46
	T2	100	1.99	0.81	1.51	1.93	2.96	4.82
	T3	100	1.97	0.86	1.53	1.89	2.59	4.40
	cord	100	0.80	0.30	0.60	0.80	1.13	2.13
8:2 Cl-PFAES	T1	100	0.05	0.02	0.03	0.05	0.08	0.18
	T2	100	0.05	0.02	0.03	0.05	0.07	0.13
	T3	100	0.05	0.02	0.03	0.05	0.07	0.13
	cord	99	0.03	0.01	0.02	0.03	0.04	0.07

widespread exposure of Cl-PFAESs in China; however, further studies are needed to better understand the exposure pattern of Cl-PFAESs, especially in the general population from different regions.

Strong correlations between serial maternal sera samples from the first to third trimesters and cord sera (Table 3) were consistent with previous mother-infant paired studies.[11,27,39] After combining these results with the high reproducibility of maternal PFAS levels during pregnancy (Table S4), our findings suggest the feasibility of using PFAS levels in one maternal serum sample during pregnancy to assess PFAS fetal exposure. Samples in the first and second trimesters were slightly less correlated with cord sera than samples in the third trimester (Table 3), which might be due to longer time interval before delivery. Maternal physiological changes, including blood volume expansion and renal clearance increase in this period,[40] might cause serum PFAS decline, leading to higher variability in PFAS levels. To obtain nonbiased assessment of PFAS exposure between individuals, a relatively narrow time window for maternal blood sampling is recommended. If there is a window of vulnerability to affect fetal growth or even long-term health consequence, the exposure level at that particular trimester might be most important. Further investigation is required in this aspect.

Using maternal sera collected at early pregnancy (before full expansion of blood volume and renal clearance) could overestimate the actual PFAS concentration at delivery. Therefore, we used PFAS levels in cord sera over PFAS levels in maternal samples taken in the third trimester (38.4 ± 1.6 week, within 1 week before delivery) to better estimate the actual transfer efficiency of PFASs. Selective placental transfer among PFASs was observed, with comparable transfer efficiencies to those found in previous studies.[22,24,27−30,32−34,36−38,42] An earlier study suggested that PFAS transfer efficiencies decrease with each increasing unit of $-CF_2$ chain.[32] However, some long-chain PFASs, including

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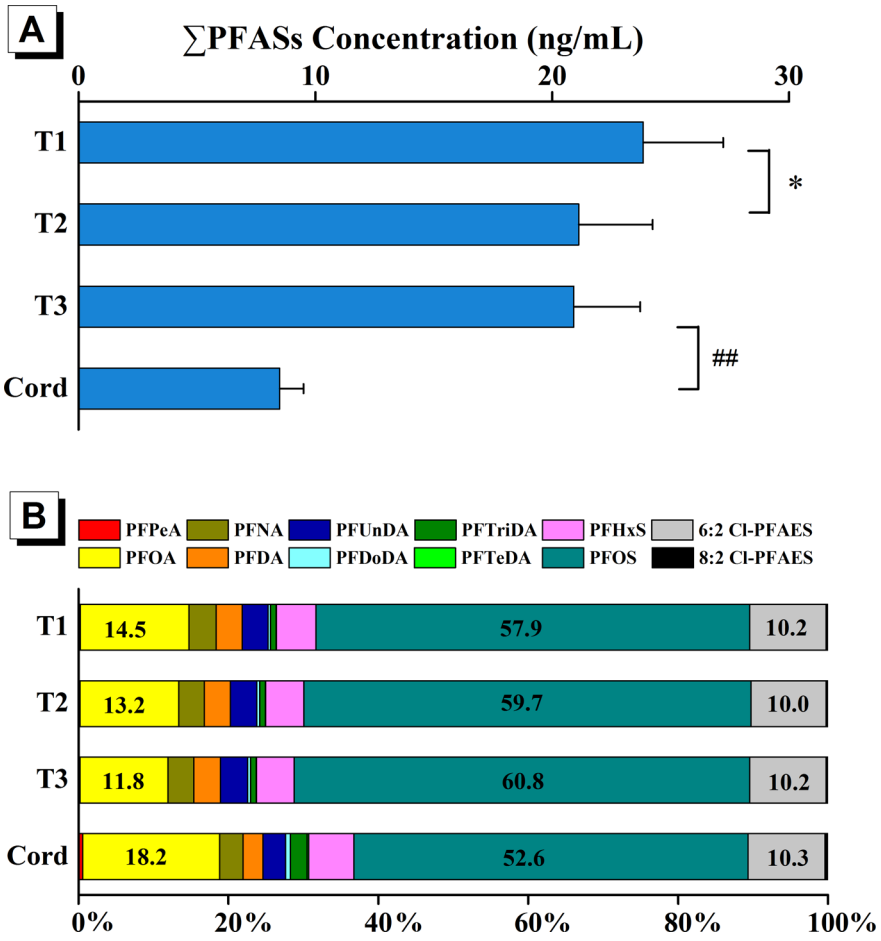

Figure 1. (A) Concentrations of ΣPFAS (sum of all detectable PFASs) and (B) composition profile (percentage mean mass fraction of individual compounds) in maternal sera during the three trimesters and in cord sera. * indicates significant difference in ΣPFAS levels between first and second trimesters (paired *t* test *p*-value = 0.02). ## indicates significant difference in ΣPFAS levels between maternal sera taken in the third trimester and cord sera (paired *t* test *p*-value <0.001).

Table 3. Spearman Correlation Coefficients between Levels of Selected PFASs in Maternal Sera in Different Trimesters (T1−T3) and in Cord Sera (n = 100)

	T1 and T2	T1 and T3	T2 and T3	T1 and cord	T2 and cord	T3 and cord
PFOA	0.91	0.85	0.92	0.73	0.74	0.78
PFNA	0.96	0.93	0.97	0.82	0.85	0.86
PFDA	0.94	0.91	0.97	0.81	0.89	0.89
PFUnDA	0.95	0.90	0.95	0.81	0.87	0.89
PFDoDA	0.80	0.77	0.85	0.62	0.75	0.77
PFTriDA	0.89	0.76	0.88	0.71	0.80	0.87
PFHxS	0.95	0.87	0.92	0.82	0.82	0.81
PFOS	0.96	0.89	0.93	0.83	0.88	0.92
6:2 Cl-PFAES	0.94	0.93	0.96	0.84	0.92	0.91
8:2 Cl-PFAES	0.89	0.85	0.93	0.83	0.92	0.93

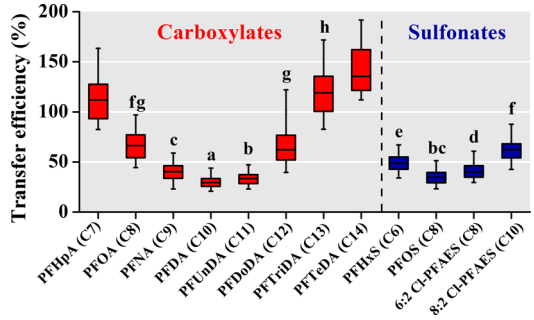

Figure 2. Transfer efficiencies of PFASs with increasing molecular chain length. PFASs with different letters indicate statistically significant differences in transfer efficiencies by Duncan's multiple range test at $p < 0.05$. PFHpA and PFTeDA are excluded from Duncan's test due to their limited sample size (14 and 8 pairs for PFHpA and PFTeDA, respectively).

PFDoDA, PFTriDA, and MeFOSAA, were reported to have greater efficiency than expected.[24,38,39] In the present investigation, the transfer efficiency of PFTriDA was over 100%, consistent with other research.[24,33] For the first time, we reported on the transfer efficiency of PFTeDA (even higher than PFTriDA), indicating no placental impediment for these chemicals. With the detection of these longer chain PFASs (e.g., PFUnDA, PFDoDA, PFTriDA, PFTeDA for carboxylates, and 6:2 and 8:2 Cl-PFAESs for sulfonates), we observed a U-shape trend with increasing chain length, rather than a falling line. To date, this is the first study to report a U-shape trend in sulfonates, as well as the most comprehensive study for carboxylates (C7−C14). In addition, there was similar transfer efficiencies between 8:2 Cl-PFAES (geometric mean 61%) and PFOA (65%), which was significantly higher than that of PFDA (29%) having the same carbon chain length. The unique

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Table 4. Percentage Change (95% CI) in PFAS Transfer Efficiencies Associated with Selected Factors (n = 100)[a]

factors	PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTriDA	PFHxS	PFOS	6:2 Cl-PFAES	8:2 Cl-PFAES
maternal age (years)										
age per 1 year	1.5 (−0.1, 3.0)	1.6 (−0.1, 3.4)	1.0 (−0.5, 2.4)	1.0 (−0.3, 2.3)	1.7 (−0.3, 3.7)	**2.0 (0.6, 3.3)**	**1.5 (0.2, 2.7)**	1.0 (−0.5, 2.5)	0.9 (−0.6, 2.4)	**1.5 (0.2, 2.8)**
prepregnancy BMI (kg/m^2)										
normal (18.5−24)	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
underweight (<18.5)	−2.8 (−14.7, 10.8)	4.4 (−9.9, 21.1)	6.9 (−5.3, 20.7)	4.0 (−6.8, 16.0)	0.8 (−15.0, 19.4)	−2.5 (−13.1, 9.5)	−0.1 (−10.3, 11.2)	2.1 (−10.1, 15.8)	−1.3 (−13.6, 12.6)	1.6 (−9.6, 14.3)
overweight (≥24)	−0.8 (−15.0, 15.8)	−2.7 (−18.3, 15.9)	−1.5 (−14.6, 13.7)	−5.0 (−16.5, 8.1)	−5.0 (−22.2, 16.1)	1.7 (−11.3, 16.6)	−2.2 (−13.9, 11.0)	−6.2 (−19.3, 8.9)	−7.3 (−21.2, 9.1)	−1.2 (−14.5, 14.1)
gestational age (weeks)										
gestational age per week	−1.5 (−5.0, 2.2)	−2.3 (−6.2, 1.8)	0.4 (−3.0, 3.8)	−0.3 (−3.3, 2.8)	−2.3 (−6.8, 2.5)	**−5.0 (−7.9, −2.0)**	1.2 (−1.8, 4.2)	0.8 (−2.7, 4.5)	−1.2 (−4.8, 2.6)	−2.3 (−5.4, 0.9)
parity										
0	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
1	1.1 (−13.6, 18.4)	2.0 (−14.6, 21. 9)	−0.6 (−14.2, 15.1)	1.1 (−11.4, 15.4)	10.3 (−10.0, 35.2)	9.6 (−4.5, 25.8)	1.1 (−11.2, 15.1)	−6.9 (−20.0, 8.4)	3.7 (−11.0, 20.9)	5.1 (−8.1, 20.3)
infant gender										
girl	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
boy	−0.6 (−9.9, 9.7)	3.2 (−7.7, 15.3)	8.3 (−1.1, 18.6)	5.2 (−3.1, 14.2)	7.7 (−5.2, 22.2)	1.3 (−7.2, 10.5)	4.5 (−3.6, 13.3)	5.4 (−4.2, 15.9)	2.8 (−7.2, 13.9)	0.1 (−8.6, 9.5)
education										
more than high school	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
high school	1.6 (−8.3, 12.5)	−2.7 (−13.6, 9.7)	2.5 (−7.0, 13.0)	4.3 (−4.5, 14.0)	14.7 (0.3, 31.2)	8.9 (−0.6, 19.4)	1.1 (−7.1, 10.1)	−0.9 (−10.3, 9.5)	1.4 (−9.1, 13.2)	−5.7 (−14.4, 3.9)
less than high school	**−17.4 (−29.0, −3.9)**	−8.1 (−23.0, 9.7)	−11.1 (−23.0, 2.6)	−3.3 (−15.2, 10.2)	−3.2 (−20.6, 18.1)	−4.1 (−16.3, 9.7)	**−12.4 (−22.8, −0.7)**	**−16.8 (−28.2, −3.6)**	−8.0 (−21.9, 8.3)	−3.2 (−16.2, 11.8)
household income (yuan)										
>100 K	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
50−100 K	7.9 (−5.9, 23.7)	13.6 (−2.6, 32.4)	0.9 (−11.3, 14.8)	0.4 (−10.6, 12.8)	−17.3 (−30.6, 1.4)	−5.2 (−15.9, 6.9)	7.4 (−4.0, 20.2)	6.3 (−7.0, 21.4)	3.8 (−9.7, 19.3)	−3.9 (−15.0, 8.7)
<50 K	7.1 (−5.7, 21.6)	11.1 (−3.7, 28.1)	0.1 (−11.2, 12.8)	−0.1 (−10.3, 11.3)	−9.4 (−22.9, 6.6)	−9.7 (−19.2, 1.0)	3.3 (−7.0, 14.6)	6.3 (−6.0, 20.3)	2.8 (−9.9, 17.4)	−4.0 (−14.5, 7.9)
employment										
unemployed	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
employed	6.1 (−4.0, 17.1)	5.5 (−5.9, 18.2)	3.9 (−5.0, 13.8)	2.4 (−5.6, 11.1)	1.5 (−11.0, 15.8)	7.9 (−1.2, 17.9)	4.4 (−3.8, 13.3)	5.4 (−4.3, 16.0)	10.6 (−0.1, 22.5)	9.6 (−0.2, 19.8)
passive smoking during pregnancy										
no	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
yes	−1.4 (−10.8, 8.9)	−2.6 (−13.1, 9.2)	3.6 (−5.4, 13.4)	0.8 (−7.0, 9.4)	−12.1 (−22.6, −0.2)	−4.8 (−12.8, 3.9)	0.4 (−7.5, 9.0)	3.7 (−5.8, 14.2)	−2.2 (−11.8, 8.6)	−6.5 (−14.6, 2.3)
GFR (mL/min per 1.73 m^2)										
tertile 1 (<151.7)	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
tertile 2 (151.7−182.0)	**−13.5 (−23.0, −2.8)**	**−13.8 (−24.5, −1.5)**	**−12.3 (−21.2, −2.3)**	**−10.1 (−18.3, −1.1)**	0.3 (−14.0, 16.9)	3.2 (−7.1, 14.7)	**−11.0 (−19.2, −2.0)**	**−19.3 (−27.4, −10.3)**	**−13.2 (−22.7, −2.4)**	1.5 (−8.7, 12.9)
tertile 3 (>182.0)	**−14.9 (−24.2, −4.5)**	**−15.8 (−26.2, −3.9)**	**−16.5 (−24.9, −7.1)**	**−17.1 (−24.6, −8.9)**	**−15.1 (−27.1, −1.2)**	−7.5 (−16.7, 2.7)	**−11.8 (−19.8, −2.9)**	**−21.0 (−28.9, −12.3)**	**−19.0 (−28.0, −8.9)**	**−10.8 (−19.9, −0.7)**
GFR per 10 mL/min per 1.73 m^2	**−1.3 (−2.6, 0.0)**	−1.0 (−2.5, 0.5)	**−1.3 (−2.4, −0.1)**	**−1.3 (−2.4, −0.2)**	**−1.7 (−3.3, −0.1)**	**−0.6 (−1.8, 0.5)**	−1.0 (−2.0, 0.1)	**−1.8 (−3.0, −0.6)**	**−1.5 (−2.8, −0.2)**	−1.0 (−2.1, 0.2)

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Table 4. continued

factors	PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFTriDA	PFHxS	PFOS	6:2 Cl-PFAES	8:2 Cl-PFAES
maternal serum albumin (g/L)										
tertile 1 (<36.6)	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
tertile 2 (36.6−38.5)	−3.8 (−13.9, 7.4)	−3.3 (−15.2, 10.2)	−4.2 (−13.7, 6.2)	−2.9 (−11.6, 6.7)	−10.5 (−23.3, 4.4)	−4.4 (−13.9, 6.2)	−3.8 (−12.3, 5.5)	−3.4 (−13.5, 8.0)	**−13.0 (−22, −2.9)**	**−10.4 (−19.0, −0.8)**
tertile 3 (>38.5)	**−20.3 (−28.8, −10.7)**	**−18.5 (−28.7, −6.8)**	**−15.5 (−24.0, −6.1)**	**−12.5 (−20.5, −3.7)**	**−16.7 (−28.5, −2.9)**	**−11.4 (−20.2, −1.7)**	**−15.7 (−23.3, −7.4)**	**−16.1 (−25.1, −6.0)**	**−22.2 (−30.7, −12.7)**	**−16.8 (−25.1, −7.6)**
albumin per 1 g/L	**−3.4 (−5.0, −1.8)**	**−3.1 (−5.0, −1.2)**	**−2.9 (−4.4, −1.4)**	**−2.4 (−3.8, −1.0)**	**−2.4 (−4.7, −0.2)**	**−3.1 (−4.5, −1.7)**	**−2.9 (−4.2, −1.5)**	**−2.5 (−4.2, −0.9)**	**−4.3 (−5.7, −2.8)**	**−3.3 (−4.6, −1.9)**
fetal serum albumin (g/L)										
tertile 1 (<35.2)	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
tertile 2 (35.2−37.6)	**19.8 (7.6, 33.4)**	**14.7 (0.5, 31.0)**	**16.2 (5.1, 28.6)**	**12.6 (2.6, 23.6)**	**29.1 (11.0, 50.1)**	**17.2 (5.6, 30.0)**	**15.2 (5.6, 25.6)**	**17.2 (5.7, 30.1)**	8.2 (−4.1, 22.0)	**17.3 (5.7, 30.2)**
tertile 3 (>37.6)	**31.3 (17.8, 46.4)**	**21.4 (6.2, 38.8)**	**23.4 (11.5, 36.6)**	**17.7 (7.0, 29.1)**	**16.2 (0.2, 34.6)**	8.5 (−2.0, 20.0)	**27.8 (17.1, 39.4)**	**31.4 (18.4, 45.9)**	**18.8 (5.3, 33.9)**	**13.5 (2.2, 26.0)**
albumin per 1 g/L	**4.1 (2.7, 5.4)**	**2.7 (1.0, 4.5)**	**2.9 (1.6, 4.3)**	**1.8 (0.5, 3.0)**	**2.3 (0.3, 4.3)**	**2.3 (0.3, 4.3)**	**3.5 (2.5, 4.6)**	**4.1 (2.8, 5.4)**	**2.5 (0.9, 4.1)**	1.1 (−0.4, 2.5)

[a]Percentage changes were calculated as the exponentiated beta coefficients minus 1. Each factor was run in a separate model. Percentage changes with statistical significance ($p < 0.05$) are presented in bold.

structure of Cl-PFAESs (e.g., ester bond, chlorine atom) might play a role in facilitating the placental transfer.

The U-shape trend might be explained by the binding affinity of PFASs to blood proteins like albumin and fatty acid binding protein (FABP). Since passive diffusion is often the mechanism by which chemicals cross the placental barrier,[52] binding to macromolecules might increase the difficulty in passing through placental membranes, which means the stronger binding affinity to maternal serum proteins, the harder it is for the free PFASs to cross the placental barrier. Zhang et al.[53] reported an inverted U-shape trend for binding affinity to FABP from C7 to C14 PFCAs, the binding affinity increased for increasing chain-length from C8−C11, but started to decrease from C12−C14, which support this hypothesis. Studies on affinity to albumin among different chain-length PFASs are still controversial.[54−56] However, linear PFOS and PFOA are reported to bind to maternal serum albumin more strongly than their branched isomers,[45] which could explain why linear PFASs cross the placenta less efficiently than branched isomers.[29,42]

The main binding protein for PFASs, albumin, may strongly affect the transfer of PFASs from maternal serum to fetal serum. The negative association observed between transfer efficiency and maternal serum albumin and the positive association between cord serum albumin and transfer efficiency (Table 4) led to our hypothesis that maternal serum albumin might sequester PFASs from entering the placenta, while fetal albumin might facilitate the entrance of PFASs into cord blood, thus implying "competition" for PFASs between albumin on each side of the placenta. Passive diffusion of PFASs is more likely involved for the transport of free fraction between each side of the placenta, since albumin can hardly transfer across the placental barrier.[57] The rate of passive diffusion depends on the concentration gradient; the higher fetal albumin level, the more PFASs taken up by fetal albumin, and the less free PFAS in cord blood, which consequently may facilitate the rate of placental transfer via passive diffusion. Future investigation is needed to test this hypothesis. Although the underlying mechanism remains unclear, our study suggests that maternal and fetal albumin are key factors affecting PFAS transport from maternal serum to fetal serum via the placenta.

Aside from serum albumin, other demographic and physiological factors were found to be factors for PFAS transfer efficiency. Consistent with Manzano-Salgado et al.,[34] we found that PFAS transfer efficiencies increased for older mothers (Table 4). It is possible that maternal age might affect placental vascular development, consequently affecting placental function.[58] Mothers with higher education tended to have higher transfer efficiency (Table 4). It is difficult to explain how education attainment could affect PFAS transfer; however, it may be partly due to the positive relationship between maternal age and education attainment (higher educated women have a tendency to give birth later). Insufficient sample size of low educated mothers [less than high school (n = 8)] might be another reason, resulting in selection bias. In addition, we observed lower PFAS transfer efficiency with higher GFR (Table 4). Higher flow rate of filtered fluids represents higher elimination through the kidney,[59] and higher renal clearance during pregnancy may drop the burden of PFASs in maternal blood, consequently reducing their transfer into the fetus. In addition, sufficiently high GFR during pregnancy is essential for normal fetal growth.[59,60] It is not known whether kidney function during pregnancy (indicated by GFR) affects the formation and/or function of the placenta, which could further

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affect the transfer of chemicals such as PFASs across the placenta. Detailed mechanisms behind this relationship requires further investigation. There are limitations to this study. First, due to the difficulty of collecting maternal blood during all three trimesters and corresponding cord blood, the sample size in this study was limited to 100. Second, although a U-shape distribution of transfer efficiency was observed among PFASs, special attention should be given to the interpretation of the data due to the low detection rates of PFHpA and PFTeDA (only 14 and 8 pairs) and relative low levels of PFDoDA and PFTriDA. More sensitive methods or larger sample volume are needed to confirm the trends of these compounds.

In conclusion, the presence of 6:2 Cl-PFAES in sera samples at comparable concentrations to PFOA indicated that exposure to 6:2 Cl-PFAES may be relatively high and widespread among pregnant women and fetuses in China. Toxicological and epidemiological studies are necessary to evaluate their potential adverse effects on fetal growth, given that a relative large amount of 6:2 Cl-PFAES can transfer across the placenta. Structure-dependent transfer efficiencies were observed among different PFASs. Our results suggest both maternal and fetal serum albumin play important roles in PFAS placental transfer. To the best of our knowledge, this is the first epidemiological study to show associations between PFAS transfer efficiencies and physiological factors, such as serum albumin and GFR. These factors might be considered as covariates when estimating PFAS with health outcomes in future epidemiological studies. Our research will hopefully contribute to the understanding of the transport mechanism of PFASs through the placental barrier.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.est.6b04590.

Additional information regarding standards and reagents, sample extraction, instrumental analysis, quality assurance, and quality control (PDF)

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Notes

The authors declare no competing financial interest.

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