Letter

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Isomer-specific Transplacental Efficiencies of Perfluoroalkyl Substances in Human Whole Blood

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ABSTRACT

Data on isomer-specific transplacental transfer of perfluoroalkyl substances (PFASs) are very scarce. This study investigates transplacental transfer of 23 PFASs, including isomers of perfluorooctanoate (PFOA), and perfluorooctane sulfonate (PFOS), by analyzing 63 paired maternal and cord whole blood samples collected in Hubei, China. Significant correlations ($r = 0.311$-0.888, $p \leq 0.013$) were observed between the concentrations in maternal and cord blood for most PFASs, indicating that PFASs could be efficiently transported from mother to fetus. For perfluorocarboxylates, a U-shape trend of transplacental transfer efficiencies (TTEs) with carbon chain length increasing was confirmed. For PFOA and PFOS branched isomers, TTEs generally increased as the branching point moved closer to the carboxyl or sulfonate moiety, and branched isomers transferred more efficiently relative to their linear isomers. This is the first time to report the TTEs of PFAS isomers based on human whole blood samples, and to calculate the TTEs of perfluorooctane sulfonamide. For almost all PFASs, the TTEs we reported are lower than the existing studies based on serum or plasma. Whole blood is recommended for risk assessment of PFAS placental transfer considering that PFASs have different partitioning behaviors between blood matrices. More accurate parameters on health risks of PFASs during prenatal exposure are provided here.

1. INTRODUCTION

Perfluoroalkyl substances (PFASs) are widely used in many commercial products and have become ubiquitous pollutants in the environment.[1,2] Because of their potentials for bioaccumulation, PFASs have been found in various biotic samples worldwide.[3,4] PFASs have also been reported in human tissues, such as blood, urine, placenta, and amniotic fluid.[5-8] Large amount of studies documented that PFASs may pose potential health risks on humans, especially on children, such as thyroid hormone disruption,[9] impaired response inhibition,[10] immunotoxicity,[11] elevated serum adiponectin concentration.[12] Exposure to PFASs during critical periods of fetal development, including prenatal period, could adversely affect fetal growth and development.[13,14]

PFASs are synthesized mainly in electrochemical fluorination (ECF) and telomerization. ECF produces a mixture consisting of 70-80% linear isomers and 20-30% branched isomers, while telomerization produces almost completely linear isomers with even number of carbon chains.[1,15,16] Since 3M Company voluntarily phased out perfluorooctane sulfonate (PFOS) and its related products as well as perfluorooctanoate (PFOA) in 2002, telomerization becomes the predominant method to manufacture PFOA worldwide.[1] However, the manufacture of PFASs by ECF method is still used in China.[17,18] In addition, PFOS and related substances are still being manufactured and used in relatively large quantities in China. About 15 enterprises produced PFOS and its derivatives in 2012, which are mainly located in Hubei and Fujian provinces, leading to around 4.8 and 1.6 tons of PFOS released into the environment annually.[19]

Previous reports demonstrated that PFASs in human blood could cross placenta barrier into fetus. However, the transplacental transfer efficiencies (TTEs) of PFAS isomers were not included in most of these studies (Table 1). Jiang et al.[20] reported that the health risks of PFOS and PFOA to newborns could be isomer-specific. Animal studies also indicated that the toxicities or bioaccumulation of PFASs were isomer specific.[21-24] Up to now, there were only two reports on the isomer profiles of PFASs in matched maternal-cord sera samples with relatively small sample size of 20 [25] and 32 [7] pairs, respectively. Additionally, the sampling time was in the early 15 weeks upon pregnancy of the mothers.[25] Studies suggested that PFAS concentrations in maternal serum declined during pregnancy,[26,27] and correlation of cord serum concentrations with maternal serum taken in the third trimester was stronger than that in the earlier two trimesters.[8] What is more, as summarized in Table

1, most of the studies on maternal-cord samples used serum or plasma. Jin et al.[28] observed isomer-specific distribution of PFASs between whole blood and plasma, and indicated that PFOA and/or PFOS precursors had strong binding affinity to red blood cells. Therefore, TTEs measured at the time of delivery could reflect the transplacental effect of the entire pregnancy process more accurately, and TTEs obtained from whole blood would be more accurate to reflect the transplacental risks of PFASs for newborns than serum or plasma.

The objectives of this study are to examine 23 PFASs (including the isomers of PFOA and PFOS) in 63 pairs of maternal-cord blood samples, and to evaluate the impacts of carbon chain length and isomerization on placenta transfer of PFASs. To our knowledge, this is the first study on isomer-specific concentrations of PFOA and PFOS in maternal-cord whole blood (Table 1).

2. MATERIALS AND METHODS

2.1. Nomenclature, Acronyms and Standards.

The nomenclature for specific PFOS and PFOA isomers was adopted from previous study,[29] and the chromatograms of brPFOSK, TPFOA, perfluorooctane sulfonamide (PFOSA) standards are shown in Figure S1-S2. All analyte acronyms used in the present study are listed in Table S1. The PFAC-MXB, MPFAC-MXA, brPFOSK, TPFOA, *n*-PFOSA, N-ethyl perfluorooctane sulfonamide (N-EtFOSA) and M_8FOSA-M standards were purchased from Wellington Laboratories (ON, Canada). The detailed information was already described by Zhang et al.[5] Another PFOSA standard was purchased from J&K Scientific, China.

2.2. Sample Collection.

Sixty-three pairs of maternal and cord whole blood samples were collected in May and June 2014 at the People's Hospital of Hong'an County, Hubei, China. The study protocol was approved by the College of Environmental Science and Engineering, Nankai University, China, and People's Hospital of Hong'an County. All the participants were provided with information about the study purpose, and they agreed to participate voluntarily in the investigation. Table S2 shows the characteristics of these participants. About 5 mL of blood samples were collected by venipuncture to polypropylene (PP) tubes without anticoagulant from mothers 1-3 days before delivery; and same amount of cord blood was collected immediately after tying and cutting off the umbilical cord, and

kept in PP tubes. Six field blanks (5 mL of HPLC-grade water) were accompanied. All the samples were stored in a freezer at -20 °C and transported to the laboratory in coolers with ice and subsequently stored at -20 °C until analyzed.

2.3. Sample Extraction and Analysis.

All the blood samples were extracted using an ion pair method as described earlier.[28] PFASs and the isomers were separated and quantified on a Waters Ultra Performance Liquid Chromatography system coupled with a Waters XEVO TQ-S mass spectrometer (UPLC-MS/MS). Ten microliters of extracted samples were injected onto a FluoroSep-RP Octyl column (ES Industries, West Berlin, NJ). Gradient elution condition was previously described in detail.[28] Table S1 shows the m/z, cone voltage and collision energy used for each PFASs and isomers.

2.4. Quality Control.

All the 6 field blank samples were extracted by the same method to monitor for any contamination. To minimize the background signal of all PFASs from the UPLC instrument, a Waters Isolator Column was added at upstream of the injector to trap the PFASs of instrumental sources. HPLC-grade methanol was used as instrumental blank and was injected every 10 samples to monitor carryover. Two standard solutions (PFAC-MXB, n-PFOSA and N-EtFOSA at 5 ng/mL, brPFOSK and TPFOA at 10 ng/mL) were run every 10 samples to monitor instrumental reproducibility. The relative standard deviation of the instrumental analysis was <10% for all linear PFASs, and <22% for all branched PFASs. The limit of detection (LOD) was defined as the concentration with a signal-to-noise ratio of 3 if the specific PFAS was not detected in the field blanks. For the analytes detected in the field blanks, the LODs were defined as the mean blank concentration plus three times the standard deviation of the blank. Table S3 shows the LODs (0.001-0.210 ng/mL) and recoveries of the PFASs.

2.5. Statistical analysis.

Concentrations below the LOD were replaced by LOD divided by the square root of 2 in the statistical analysis. All the data were log-transformed before the paired *t* tests for the paired maternal and cord blood samples. Spearman rank correlation analysis was performed to examine the relationship between PFAS concentrations in paired maternal-cord blood samples. All analyses were performed with IBM© SPSS Statistics version 20.0 (SPSS, Inc., IBM, Chicago, IL), and significance

was set to p-value < 0.05.

3. RESULTS AND DISCUSSION

3.1. PFAS Concentrations.

Concentrations of PFASs in the paired maternal-cord blood samples are shown in Figure 1 and Table S4-S5. Among the 23 PFASs examined (including the isomers), 17 PFASs were identified in the maternal and cord blood samples. The detection frequency of PFBS, PFHxA, PFHpA, 3*m*-PFOA and N-EtFOSA was less than 5%. Thus, these compounds were not listed in Table S4-S5, and would not be discussed further. High detection frequency (>84%) was observed for most PFASs in both maternal and cord blood, except PFTrDA (69.8%) in maternal blood, and PFDoA (77.8%), PFHxS (73.0%) and *n*-PFOSA (49.2%) in cord blood samples.

ΣPFOS was predominant in both maternal and cord blood with median concentration of 6.59 and 1.35 ng/mL, respectively. For other PFASs, the median concentrations were lower than 1 ng/mL in both maternal and cord blood (Table S4-S5). The median concentration of ΣPFOS (6.59 ng/mL) in the maternal blood was close to that in the industrial city of Norilsk (5.79 ng/mL) in Russia,[30] but lower than in Tianjin, China (12.4 ng/mL).[6] If the whole blood concentration of PFOS was converted to serum concentration by multiplying by a factor of 1.53,[28] the obtained median PFOS serum concentration (10.1 ng/mL) was similar to two recent studies in Wuhan, China (12.32 ng/mL[8] and 7.0 ng/mL[7], respectively).

For ∑PFOA, the converted maternal serum concentration (median, 1.1 ng/mL, blood concentration multiplying by a factor of 1.2[28]), was marginally lower than the pregnant women in Wuhan (1.42 ng/mL[7] and 2.16 ng/mL,[8] respectively). It is worth noting that long carbon-chain length perfluoroalkyl carboxylates (PFCAs) were detected with high frequency in both maternal and cord blood samples, especially PFUnA, which was detected in all the maternal blood samples with similar concentration (0.747 ng/mL) to PFOA (0.907 ng/mL).

The concentrations of all the individual PFASs in the maternal blood samples were significantly (paired t test, $p \leq 0.008$) higher than in the cord blood samples, except PFTrDA with markedly ($p <$ 0.001) lower concentration in maternal blood samples (Figure 1). Relatively high inter-correlations were observed between all the detected PFASs in the paired maternal and cord samples (r = 0.311-0.888, $p \leq 0.013$), except 4*m*-PFOA and 5*m*-PFOA (Table S6). The findings suggested that

PFASs in maternal blood could transfer to fetus through cord blood. Thus, mothers exposed to PFASs could exert potential threats, such as growth and development retardation on their newborns.[13,31].

3.2. Isomeric Compositions of PFASs.

Figure 2 shows the isomer compositions of PFOS and PFOA isomers in the maternal and cord blood samples compared to authentic Chinese products and 3M ECF products.[18] *n*-PFOS contributed 81.6% of total PFOS in maternal blood and 79.7% in cord blood without significant difference (paired *t* test, $p = 0.275$), which was very close to the delivering women from Wuhan, China (83%, serum),[7] and south central Vietnam (81%, plasma).[32] Nonetheless, the *n*-PFOS % was much higher than that reported for the general human plasma or serum from China, e.g. Tianjin (59.2%),[33] Shijiazhuang (43.0% and 50.6%) and Handan (53.7%),[34] and other countries, e.g. Australia (58.7%) and England (59.6%).[35] We also observed higher *n*-PFOS % in 1st trimester pregnant women serum (66.7%)[20] than non-pregnant young women in Tianjin (62.5%),[33] which might be due to the relatively preferential transplacental transfer of *br*-PFOS to *n*-PFOS.[25] The average *n*-PFOS % in most reported products is about 70%.[18] Given the high *n*-PFOS % in maternal and cord blood, and similar high *n*-PFOS % in one PFOS product manufactured in Wuhan (78.2%),[17] it was speculated that exposure to higher *n*-PFOS % ECF products could also cause this phenomenon.

n-PFOA was the dominant isomer, with a range of 94.6-100% (mean, 98.2%) and 92.3-100% (97.6%), in the maternal and cord blood respectively. The mean proportions of *n*-, *iso*- and 5*m*-PFOA in 131 maternal serum samples in Tianjin China were respectively 99, 0.96 and 0.04%,[20] which was quite similar to the maternal results in the present study (Figure 2). Additionally, Beesoon *et al*.[25] also found similar contribution of the branched PFOA isomers (mean 1.9%) in Canadian pregnant women. The percentage of *n*-PFOA in the maternal blood was statistically higher ($p = 0.009$) than the cord blood. Opposite trend was observed for *iso*- and 5*m*-PFOA, with lower percentage in the maternal blood ($p \leq 0.006$). The results suggested that branched PFOA isomers were more easily transferred to fetus than *n*-PFOA.

Although we observed that PFOSA standard contained both *n*- and *br*-PFOSA (Figure S2), we cannot quantify the concentration of *br*-PFOSA due to lack of isomeric composition information. Thus, the proportions of *n*- and *br*-PFOSA in the maternal and cord blood (Figure S3) were just compared based on the peak area in the chromatogram as discussed later. We also observed probable

br-PFHxS isomers in some samples (Figure S4). However, this was not common in most of the blood samples. Since commercial standards of *br*-PFHxS isomers were not available, and they were also easily misleading using the m/z 399/80 ion pair,[29] we would not report the concentrations of *br*-PFHxS isomers.

3.3. Transplacental Transfer of PFASs.

To explore transplacental transfer of PFASs via blood, TTEs were calculated by dividing the PFAS concentrations in cord blood by those in maternal blood (Table 1). For PFCAs, the TTE decreased with carbon chain length increasing from PFOA (C8) to PFDA (C10), and then increased to PFTrDA (C13). This confirmed the U-shaped trend of TTEs of C8-C13 PFCAs. Possible explanations for this U-shaped result were discussed by Zhang *et al*.[6] and Pan *et al*.[8]

The order of TTEs of the two perfluoroalkane sulfonates (PFSAs) and PFOSA was PFHxS > PFOS > PFOSA, agreeing with the result we calculated with the original data from Hanssen *et al.*[30] (Table 1). The TTEs of all PFASs, except PFDoA and PFTrDA in this study were considerably lower than those obtained based on serum/plasma data reported in previous studies (Table 1). This could be attributed to the lower packed cell volume (PCV) in pregnant women (0.38) than in newborn (0.60),[30] and most PFASs preferred to partition to serum/plasma than blood cells. The observed TTEs of PFDoA and PFTrDA were greater than previous studies based on serum/plasma samples (Table 1). The relevant reason is unclear currently and needs to be further studied. It is worth noting that some PFAS, such as PFOSA, prefer to partition to blood cells than serum/plasma.[28,30] This could explain the low detection frequency or low concentration of PFOSA in human. For these compounds, the TTEs based on serum/plasma would be inaccurate. Therefore, whole blood is recommended for measuring the levels and TTEs of these compounds.

All the detected *br*-PFOA isomers (*iso*-, 5*m*- and 4*m*-PFOA) were transferred more efficiently (TTEs 0.71, 0.94, and 2.00) than *n*-PFOA (0.56) (Figure 3), consistent with the results reported by Beesoon et al.[25] The TTE order of PFOA isomers in this study (4*m* > 5*m* > *iso* > *n*) was generally in line with their elution order from the reverse phase chromatography, and thus consistent with their hydrophilicity (Figure S1). The TTEs of the *br*-PFOA isomers increased as the branching point moved closer to the carboxyl moiety. The median TTE of *n*-PFOA (0.56) was lower than that reported by Beesoon *et al*.[25] (0.61) and Chen *et al.* (0.82),[7] which could be due to different blood matrices. It was reported that newborns have higher PCV (0.60) than pregnant women (0.38).[30] For

most PFASs with greater binding affinities with human serum albumin (HSA), the TTEs calculated based on serum data could be higher than those based on whole blood. Nevertheless, the TTEs of *iso*-PFOA (0.67), 5*m*-PFOA (0.54) and 4*m*-PFOA (0.68) calculated by Beesoon *et al.*,[25] were lower than this study and Chen *et al.* (1.29).[7] This could be due to lower binding affinity of branched PFOA isomers to HSA than *n*-PFOA, which suggests that branched PFOA isomers are more easily eliminated and transferred to fetus than *n*-PFOA during pregnancy.[36] Furthermore, giving that the cord blood was always sampled right after mother delivery, the sampling time of maternal blood should affect the calculated TTEs. Previous studies reported that the PFAS concentrations in maternal blood decreased with time during pregnancy.[26,27] This may explain the higher calculated TTEs of branched PFOA isomers at delivery (this study and Chen *et al.*[7]) than the time at early 15 weeks (Beesoon *et al.*[25]). The whole blood samples in current study were more representative of the pregnancy, and the results could better reflect the impacts of pregnancy on transplacental efficiencies of PFASs.

Like PFOA, the TTEs of *br*-PFOS isomers, including 1*m*, 4*m*, 3+5*m* and m_2, were all greater than *n*-PFOS; and the TTEs of *br*-PFOS isomers increased as the branching point moved closer to the sulfonate moiety: 1*m* > 4*m* > 3+5*m* > *iso* (Figure 3). This could be explained by the much weaker binding affinity of branched isomers to HSA relative to *n*-PFOS.[36] Due to higher PCV in newborns than pregnant women (0.60 vs. 0.38),[30] and preferential partition to serum/plasma fraction,[28] TTEs of all the PFOS isomers obtained from whole blood samples in this study were generally lower than that obtained from serum samples reported by Chen *et al.*[7] (Table 1).

To our knowledge, there was no report on TTEs of PFOSA. This could be because PFOSA was not measured, or measured but below LODs. The possible explanation is that PFOSA has strong binding affinity to red blood cells,[28] and was rarely present in serum or plasma. We found PFOSA in 92.1% maternal blood samples, and 49.2% cord blood samples. The median TTE of *n*-PFOSA was 0.12, lower than the TTE of all the other PFASs we calculated (Figure 3). The lower *n*-PFOSA proportion (paired *t* test, $p = 0.004$, N = 30) in the maternal blood (mean, 56.9%) than in the cord blood (mean, 80.4%), suggested a lower TTE for *br*-PFOSA than *n*-PFOSA. This is different from the TTE results of *br*-PFOS and *br*-PFOA isomers. It could be explained by the passive diffusion mechanism of drugs crossing the placental barrier,[37] namely, more hydrophilic compounds show lower TTEs compared to more hydrophobic compounds.[38] Based on the earlier elution (Figure

S2-S3), *br*-PFOSA isomers are more hydrophilic than *n*-PFOSA. Further studies are warranted to better understand the isomer-specific transplacental behavior of PFOSA.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed information on list of perfluorinated compounds monitored in the present study and their acronyms, HPLC-MS/MS parent and product ions, characteristics of the sample population, LOD and recoveries for PFASs, individual concentrations of PFAS in maternal and cord blood, spearman correlation coefficients between the concentrations of individual PFAS in matched maternal and cord blood samples, chromatograms of TPFOA, brPFOSK and PFOSA standards, chromatograms of PFHxS and PFOSA in some blood samples.

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Notes

The authors declare no competing financial interest.

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development.

Table 1. Summary of existing studies on maternal–fetal transfer of PFASs (Maternal blood was sampled in the third trimester or within the first week after deliver).

	PFOA					PFNA	PFDA	PFUnA	PFDoA	PFTrDA	PFHxS	PFOS							*n*-PFOSA	Sample type	Sample size	Sampling year	Location	Reference
	n	*iso*	5*m*	4*m*	total							*n*	*iso*	3+5*m*	4*m*	1*m*	m_2	total						
Mean	0.59	0.81	1.7	2.0	0.59	0.30	0.18	0.27	0.82	3.1	0.36	0.21	0.22	0.29	0.51	0.48	0.30	0.22	0.21					
Median	0.56	0.71	0.94	2.0	0.57	0.27	0.17	0.22	0.61	2.3	0.35	0.20	0.17	0.23	0.34	0.39	0.25	0.20	0.12					
Min	0.31	0.22	0.20	0.33	0.31	0.13	0.073	0.089	0.18	0.23	0.11	0.098	0.028	0.031	0.027	0.021	0.053	0.09	0.010	Blood	≤ 63	2014	China	This study
Max	1.1	2.9	10	5.0	1.1	0.61	0.40	0.62	3.3	13	0.88	0.42	1.3	2.1	5.0	2.1	1.0	0.53	1.5					
N[†]	63	49	36	7	63	63	59	62	43	42	46	63	59	63	38	61	19	63	30					
Mean	0.84	1.27			0.81						0.90	0.38	0.39	0.68	0.70	0.84	0.98	0.43		Serum	≤ 32	2015-2016	China	7
Median	0.82	1.29			0.77						0.86	0.37	0.39	0.58	0.65	0.79	0.96	0.40						
Median[‡]					0.65	0.40	0.29	0.32	0.57	1.23	0.50							0.36		Serum	≤100	2014	China	8
Mean					0.84						0.57							0.35		Serum	59	2011	South Korea	39
Median					0.80						0.50							0.32						
Mean[§]					0.58	0.36	0.25	0.30	0.80		0.34							0.29		Blood	29	2010	China	6
Median[§]					0.58	0.32	0.25	0.28	0.79		0.29							0.18						
Mean					0.91	0.61	0.42	0.54		1.84	0.95							0.57		Serum	≤50	2009	China	40
Median					0.89	0.57	0.39	0.52		1.74	0.73							0.54						
Median[‡]					0.70						0.40							0.29		Serum	27	2007-2009	Germany	41
Mean[‖]					0.82	0.40	0.40	0.32		1.17	0.68							0.33		Plasma	123	2007-2008	Norway	42
Median[‡]					0.79	0.35	0.57	0.25		1.00	0.71							0.30						
Mean					0.69	0.47	0.33	0.29			0.64							0.36		Serum	20	2007	South Korea	43
Median					0.67	0.48	0.33	0.29			0.65							0.37						
Median[‡]					1	0.4					0.6							0.44		Serum	≤58	2005-2006	South Africa	44
Mean[‖]					0.87	1.18					1.25							0.44		Serum	≤101	2004-2005	Canada	45
Median[‡]					0.87	1.04					1.28							0.42						
Mean					1.26													0.60		Plasma	11	2003	Germany	46
Median					1.24													0.59						
Mean[§]					ND													0.32		Serum	15	2003	Japan	47
Median[§]					ND													0.31						
Mean[§]					0.65	0.42		0.50			0.45	0.36						0.32	0.17[*]	Blood	≤7	2001	Russia	30
Median[§]					0.66	0.37		0.45			0.45	0.35						0.31	0.17[*]					
Mean[§]					0.81	0.54		0.41			0.63	0.42						0.38	1.10	Plasma	7			
Median[§]					0.84	0.53		0.41			0.54	0.38						0.35	1.12					
Mean					0.72	0.50	0.29				0.74							0.34		Serum	12	2000	Faroe Islands	14

[†]Number of maternal-cord pairs that were available for calculating TTE. When concentrations were not detected in maternal or cord samples, that pair was excluded in the analysis.
[‡]Calculated by the median concentration data; [§] Calculated by the original concentration data; [‖]Calculated by the mean concentration data. [*]Calculated by sum of PFOSA

REFERENCES

(1) Prevedouros, K.; Cousins, I.T.; Buck, R.C.; Korzeniowski, S.H. Sources, fate and transport of perfluorocarboxylates. *Environ. Sci. Technol.* **2006**, *40*, 32-44.

(2) Lindstrom, A.B.; Strynar, M.J.; Libelo, E.L. Polyfluorinated compounds: Past, present, and future. *Environ. Sci. Technol.* **2011**, *45*, 7954-7961.

(3) Mueller, C.E.; De Silva, A.O.; Small, J.; Williamson, M.; Wang, X.; Morris, A.; Katz, S.; Gamberg, M.; Muir, D.C.G. Biomagnification of perfluorinated compounds in a remote terrestrial food chain: Lichen-caribou-wolf. *Environ. Sci. Technol.* **2011**, *45*, 8665-8673.

(4) Delinsky, A.D.; Strynar, M.J.; McCann, P.J.; Varns, J.L.; McMillan, L.; Nakayama, S.F.; Lindstrom, A.B. Geographical distribution of perfluorinated compounds in fish from minnesota lakes and rivers. *Environ. Sci. Technol.* **2010**, *44*, 2549-2554.

(5) Zhang, Y.; Beesoon, S.; Zhu, L.; Martin, J.W. Biomonitoring of perfluoroalkyl acids in human urine and estimates of biological half-life. *Environ. Sci. Technol.* **2013**, *47*, 10619-10627.

(6) Zhang, T.; Sun, H.; Lin, Y.; Qin, X.; Zhang, Y.; Geng, X.; Kannan, K. Distribution of poly- and perfluoroalkyl substances in matched samples from pregnant women and carbon chain length related maternal transfer. *Environ. Sci. Technol.* **2013**, *47*, 7974-7981.

(7) Chen, F.; Yin, S.; Kelly, B.C.; Liu, W. Isomer-specific transplacental transfer of perfluoroalkyl acids: Results from a survey of paired maternal, cord sera, and placentas. *Environ. Sci. Technol.* **2017**, *51*, 5756-5763.

(8) Pan, Y.; Zhu, Y.; Zheng, T.; Cui, Q.; Buka, S.L.; Zhang, B.; Guo, Y.; Xia, W.; Yeung, L.W.; Li, Y. Novel chlorinated polyfluorinated ether sulfonates and legacy per-/polyfluoroalkyl substances: Placental transfer and relationship with serum albumin and glomerular filtration rate. *Environ. Sci. Technol.* **2017**, *51*, 634-644.

(9) Kim, S.; Choi, K.; Ji, K.; Seo, J.; Kho, Y.; Park, J.; Kim, S.; Park, S.; Hwang, I.; Jeon, J.; Yang, H.; Giesy, J.P. Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones. *Environ. Sci. Technol.* **2011**, *45*, 7465-7472.

(10) Gump, B.B.; Wu, Q.; Dumas, A.K.; Kannan, K. Perfluorochemical (PFC) exposure in children: Associations with impaired response inhibition. *Environ. Sci. Technol.* **2011**, *45*, 8151-8159.

(11) Grandjean, P.; Andersen, E.W.; Budtz-Jorgensen, E.; Nielsen, F.; Molbak, K.; Weihe, P.; Heilmann, C. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *Jama-J Am Med Assoc*. **2012**, *307*, 391-397.

(12) Lin, C.-Y.; Wen, L.L.; Lin, L.-Y.; Wen, T.-W.; Lien, G.-W.; Chen, C.-Y.; Hsu, S.H.J.; Chien, K.-L.; Sung, F.-C.; Chen, P.-C.; Su, T.-C. Associations between levels of serum perfluorinated chemicals and adiponectin in a young hypertension cohort in taiwan. *Environ. Sci. Technol.* **2011**, *45*, 10691-10698.

(13) Robledo, C.A.; Yeung, E.; Mendola, P.; Sundaram, R.; Maisog, J.; Sweeney, A.M.; Barr, D.B.; Louis, G.M.B. Preconception maternal and paternal exposure to persistent organic pollutants and birth size: The life study. *Environ. Health. Persp.* **2015**, *123*, 88-94.

(14) Needham, L.L.; Grandjean, P.; Heinzow, B.; Jorgensen, P.J.; Nielsen, F.; Patterson, D.G.; Sjodin, A.; Turner, W.E.; Weihe, P. Partition of environmental chemicals between maternal and fetal blood and tissues. *Environ. Sci. Technol.* **2011**, *45*, 1121-1126.

(15) Paul, A.G.; Jones, K.C.; Sweetman, A.J. A first global production, emission, and environmental inventory for perfluorooctane sulfonate. *Environ. Sci. Technol.* **2009**, *43*, 386-392.

(16) Butt, C.; Berger, U.; Bossi, R.; Tomy, G. Levels and trends of poly-and perfluorinated compounds in the arctic environment. *Sci. Total Environ.* **2010**, *408*, 2936-2965.

(17) Benskin, J.P.; Yeung, L.W.Y.; Yamashita, N.; Taniyasu, S.; Lam, P.K.S.; Martin, J.W. Perfluorinated acid isomer

profiling in water and quantitative assessment of manufacturing source. *Environ. Sci. Technol.* **2010**, *44*, 9049-9054.

(18) Jiang, W.; Zhang, Y.; Yang, L.; Chu, X.; Zhu, L. Perfluoroalkyl acids (PFAAs) with isomer analysis in the commercial PFOS and PFOA products in China. *Chemosphere*. **2015**, *127*, 180-187.

(19) Xie, S.; Wang, T.; Liu, S.; Jones, K.C.; Sweetman, A.J.; Lu, Y. Industrial source identification and emission estimation of perfluorooctane sulfonate in China. *Environ. Int.* **2013**, *52*, 1-8.

(20) Jiang, W.; Zhang, Y.; Zhu, L.; Deng, J. Serum levels of perfluoroalkyl acids (PFAAs) with isomer analysis and their associations with medical parameters in chinese pregnant women. *Environ. Int.* **2014**, *64*, 40-47.

(21) Loveless, S.E.; Finlay, C.; Everds, N.E.; Frame, S.R.; Gillies, P.J.; O'Connor, J.C.; Powley, C.R.; Kennedy, G.L. Comparative responses of rats and mice exposed to linear/branched, linear, or branched ammonium perfluorooctanoate (APFO). *Toxicology*. **2006**, *220*, 203-217.

(22) Sharpe, R.L.; Benskin, J.P.; Laarman, A.H.; MacLeod, S.L.; Martin, J.W.; Wong, C.S.; Goss, G.G. Perfluorooctane sulfonate toxicity, isomer‐specific accumulation, and maternal transfer in zebrafish (danio rerio) and rainbow trout (oncorhynchus mykiss). *Environ. Toxicol. Chem.* **2010**, *29*, 1957-1966.

(23) Benskin, J.P.; De Silva, A.O.; Martin, L.J.; Arsenault, G.; McCrindle, R.; Riddell, N.; Mabury, S.A.; Martin, J.W. Disposition of perfluorinated acid isomers in sprague-dawley rats; part 1: Single dose. *Environ. Toxicol. Chem.* **2009**, *28*, 542-554.

(24) De Silva, A.O.; Benskin, J.P.; Martin, L.J.; Arsenault, G.; McCrindle, R.; Riddell, N.; Martin, J.W.; Mabury, S.A. Disposition of perfluorinated acid isomers in sprague-dawley rats; part 2: Subchronic dose. *Environ. Toxicol. Chem.* **2009**, *28*, 555-567.

(25) Beesoon, S.; Webster, G.M.; Shoeib, M.; Harner, T.; Benskin, J.P.; Martin, J.W. Isomer profiles of perfluorochemicals in matched maternal, cord, and house dust samples: Manufacturing sources and transplacental transfer. *Environ. Health Perspect.* **2011**, *119*, 1659-1664.

(26) Kato, K.; Wong, L.-Y.; Chen, A.; Dunbar, C.; Webster, G.M.; Lanphear, B.P.; Calafat, A.M. Changes in serum concentrations of maternal poly- and perfluoroalkyl substances over the course of pregnancy and predictors of exposure in a multiethnic cohort of cincinnati, ohio pregnant women during 2003-2006. *Environ. Sci. Technol.* **2014**, *48*, 9600-9608.

(27) Glynn, A.; Berger, U.; Bignert, A.; Ullah, S.; Aune, M.; Lignell, S.; Darnerud, P.O. Perfluorinated alkyl acids in blood serum from primiparous women in sweden: Serial sampling during pregnancy and nursing, and temporal trends 1996–2010. *Environ. Sci. Technol.* **2012**, *46*, 9071-9079.

(28) Jin, H.; Zhang, Y.; Jiang, W.; Zhu, L.-Y.; Martin, J.W. Isomer–specific distribution of perfluoroalkyl substances in blood. *Environ. Sci. Technol.* **2016**, *50*, 7808-7815.

(29) Benskin, J.P.; Bataineh, M.; Martin, J.W. Simultaneous characterization of perfluoroalkyl carboxylate, sulfonate, and sulfonamide isomers by liquid chromatography-tandem mass spectrometry. *Anal. Chem.* **2007**, *79*, 6455-6464.

(30) Hanssen, L.; Dudarev, A.A.; Huber, S.; Odland, J.O.; Nieboer, E.; Sandanger, T.M. Partition of perfluoroalkyl substances (PFASs) in whole blood and plasma, assessed in maternal and umbilical cord samples from inhabitants of arctic Russia and Uzbekistan. *Sci. Total Environ.* **2013**, *447*, 430-437.

(31) Fei, C.Y.; McLaughlin, J.K.; Tarone, R.E.; Olsen, J. Perfluorinated chemicals and fetal growth: A study within the Danish national birth cohort. *Environ. Health. Persp.* **2007**, *115*, 1677-1682.

(32) Rylander, C.; Duong Trong, P.; Odland, J.O.; Sandanger, T.M. Perfluorinated compounds in delivering women from south central vietnam. *J. Environ. Monit.* **2009**, *11*, 2002-2008.

(33) Zhang, Y.; Jiang, W.; Fang, S.; Zhu, L.; Deng, J. Perfluoroalkyl acids and the isomers of perfluorooctanesulfonate and perfluorooctanoate in the sera of 50 new couples in Tianjin, China. *Environ. Int.* **2014**, *68*, 185-191.

(34) Zhang, Y.; Beesoon, S.; Zhu, L.; Martin, J.W. Isomers of perfluorooctanesulfonate and perfluorooctanoate and total

perfluoroalkyl acids in human serum from two cities in North China. *Environ. Int.* **2013**, *53*, 9-17.

(35) Kärrman, A.; Langlois, I.; van Bavel, B.; Lindstrom, G.; Oehme, M. Identification and pattern of perfluorooctane sulfonate (PFOS) isomers in human serum and plasma. *Environ. Int.* **2007**, *33*, 782-788.

(36) Beesoon, S.; Martin, J.W. Isomer-specific binding affinity of perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) to serum proteins. *Environ. Sci. Technol.* **2015**, *49*, 5722-5731.

(37) Syme, M.R.; Paxton, J.W.; Keelan, J.A. Drug transfer and metabolism by the human placenta. *Clin. Pharmacokinet.* **2004**, *43*, 487-514.

(38) Van Der Aa, E.M.; Peereboom-Stegeman, J.H.C.; Noordhoek, J.; Gribnau, F.W.; Russel, F.G. Mechanisms of drug transfer across the human placenta. *Pharm. World Sci.* **1998**, *20*, 139-148.

(39) Lee, Y.J.; Kim, M.K.; Bae, J.; Yang, J.H. Concentrations of perfluoroalkyl compounds in maternal and umbilical cord sera and birth outcomes in korea. *Chemosphere*. **2013**, *90*, 1603-1609.

(40) Liu, J.Y.; Li, J.G.; Liu, Y.; Chan, H.M.; Zhao, Y.F.; Cai, Z.W.; Wu, Y.N. Comparison on gestation and lactation exposure of perfluorinated compounds for newborns. *Environ. Int.* **2011**, *37*, 1206-1212.

(41) Fromme, H.; Mosch, C.; Morovitz, M.; Alba-Alejandre, I.; Boehmer, S.; Kiranoglu, M.; Faber, F.; Hannibal, I.; Genzel-Boroviczeny, O.; Koletzko, B.; Volkel, W. Pre- and postnatal exposure to perfluorinated compounds (PFCs). *Environ. Sci. Technol.* **2010**, *44*, 7123-7129.

(42) Gutzkow, K.B.; Haug, L.S.; Thomsen, C.; Sabaredzovic, A.; Becher, G.; Brunborg, G. Placental transfer of perfluorinated compounds is selective - a norwegian mother and child sub-cohort study. *Int. J. Hyg. Environ. Health*. **2012**, *215*, 216-219.

(43) Kim, S.K.; Lee, K.T.; Kang, C.S.; Tao, L.; Kannan, K.; Kim, K.R.; Kim, C.K.; Lee, J.S.; Park, P.S.; Yoo, Y.W.; Ha, J.Y.; Shin, Y.S.; Lee, J.H. Distribution of perfluorochemicals between sera and milk from the same mothers and implications for prenatal and postnatal exposures. *Environ. Pollut.* **2011**, *159*, 169-174.

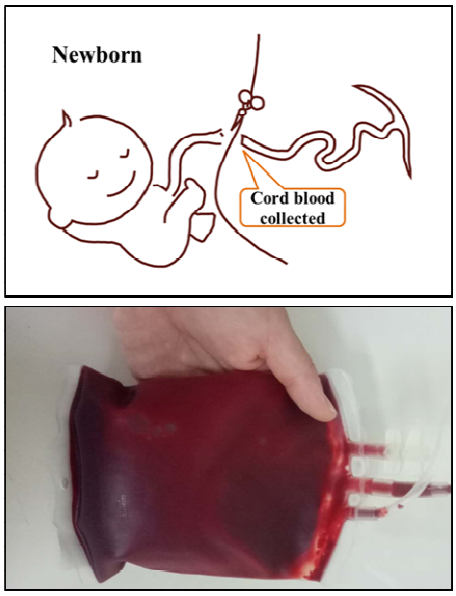
(44) Hanssen, L.; Roellin, H.; Odland, J.O.; Moe, M.K.; Sandanger, T.M. Perfluorinated compounds in maternal serum and cord blood from selected areas of south africa: Results of a pilot study. *J. Environ. Monit.* **2010**, *12*, 1355-1361.

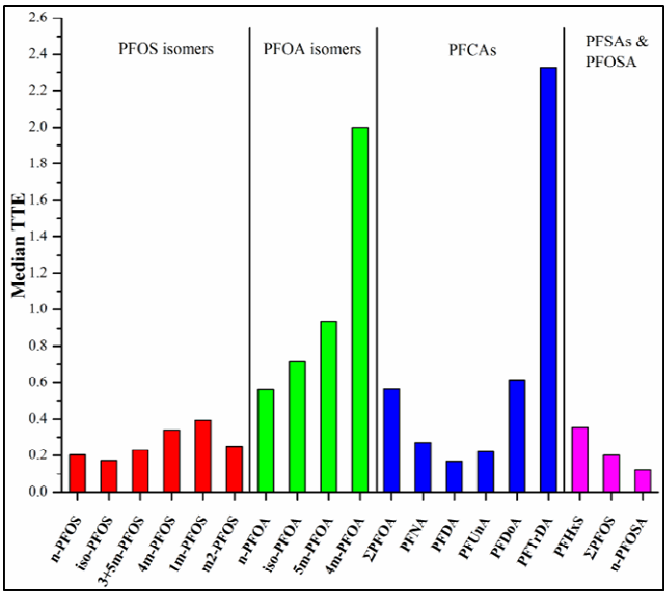
(45) Monroy, R.; Morrison, K.; Teo, K.; Atkinson, S.; Kubwabo, C.; Stewart, B.; Foster, W. Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. *Environ. Res.* **2008**, *108*, 56-62.

(46) Midasch, O.; Drexler, H.; Hart, N.; Beckmann, M.W.; Angerer, J. Transplacental exposure of neonates to perfluorooctanesulfonate and perfluorooctanoate: A pilot study. *Int Arch Occ Env Hea*. **2007**, *80*, 643-648.

(47) Inoue, K.; Okada, F.; Ito, R.; Kato, S.; Sasaki, S.; Nakajima, S.; Uno, A.; Saijo, Y.; Sata, F.; Yoshimura, Y. Perfluorooctane sulfonate (PFOS) and related perfluorinated compounds in human maternal and cord blood samples: Assessment of PFOS exposure in a susceptible population during pregnancy. *Environ. Health Perspect.* **2004**, *112*, 1204-1207.

TOC Artwork


Newborn
Cord blood collected


Median TTE
PFOS isomers
PFOA isomers
PFCAs
PFSAs & PFOSA
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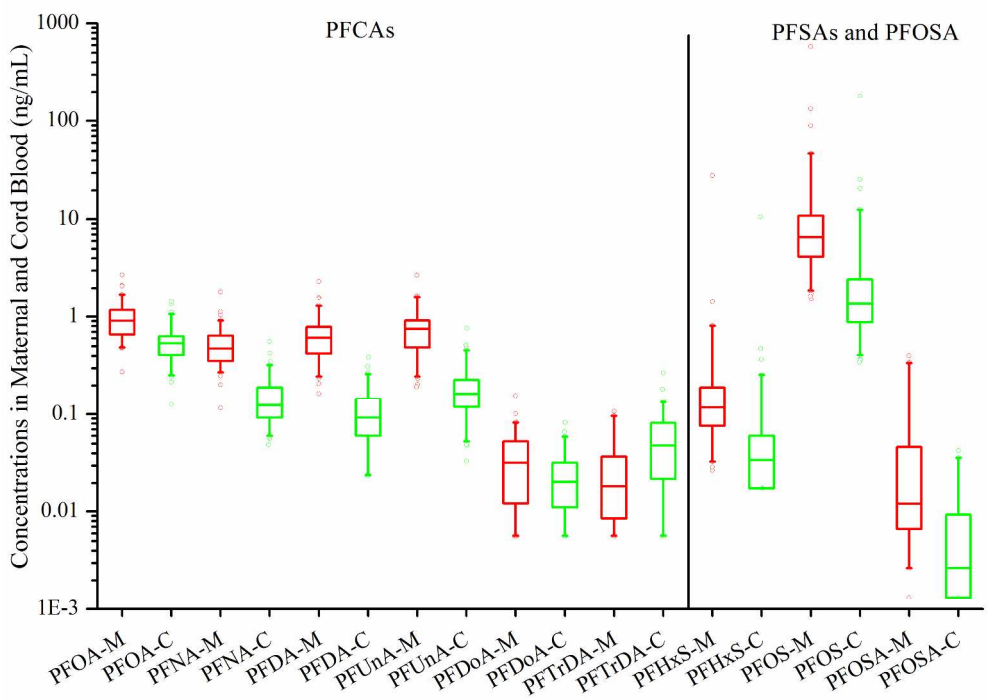
iso-PFOS
3+5m-PFOS
4m-PFOS
1m-PFOS
m2-PFOS
n-PFOA
iso-PFOA
5m-PFOA
4m-PFOA
ΣPFOA
PFNA
PFDA
PFUnA
PFDoA
PFTrDA
PFHxS
ΣPFOS
n-PFOSA

Figure Captions

Figure 1. Concentrations of PFASs in paired maternal-cord blood. PFASs in maternal blood was shown in red, and in cord blood was shown in green. The upper and lower bounds of the boxes indicate the 75th and 25th percentiles, respectively. The horizontal lines within the boxes indicate median values. The upper and lower limits of the whiskers indicate 95% and 5% values, respectively, and circles above or below the whiskers indicate outlier values.

Figure 2. Isomer compositions of (A) PFOS and (B) PFOA in the paired maternal-cord blood (%, mean), and commercial products. The isomer compositions data on commercials products were cited from Jiang et al.[18] Data on China PFOS are the average value of PFOS products from 3 products in Wuhan, Dongguan and Qinhuangdao. Data on China PFOA are the average value of PFOA products from 5 products in Beijing, Shanghai and Guangzhou.

Figure 3. TTE distributions for different-chain-length PFCAs, PFSAs and PFOSA. The upper and lower bounds of the boxes indicate the 75th and 25th percentiles, respectively. The horizontal lines within the boxes indicate median values. The upper and lower limits of the whiskers indicate 95% and 5% values, respectively, and circles above or below the whiskers indicate outlier values.



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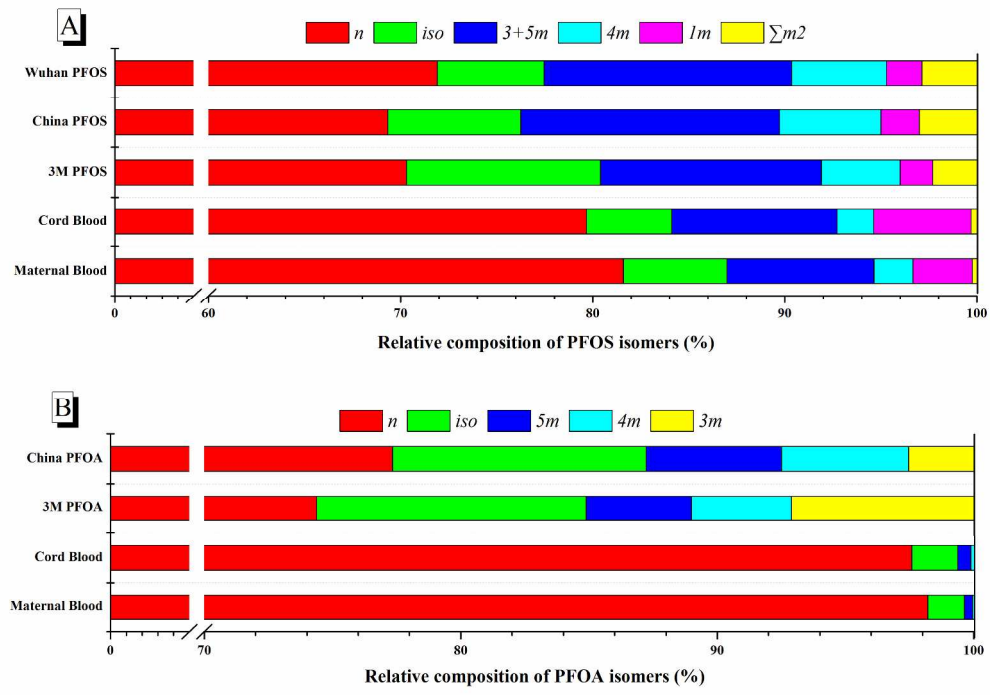

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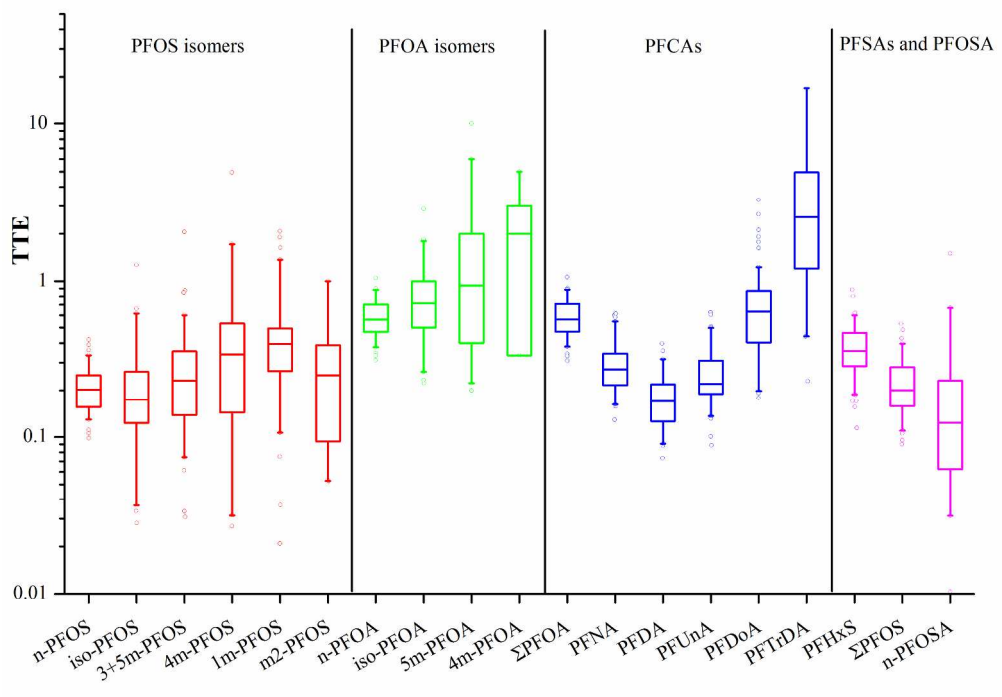

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