Perfluorooctanesulfonate and Related Fluorochemicals in Human Blood Samples from China

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Perfluorooctanesulfonylfluoride (POSF)-based compounds have been manufactured and used in a variety of industrial applications. These compounds degrade to perfluorooctanesulfonate (PFOS) which is regarded as a persistent end-stage metabolite and is found to accumulate in tissues of humans and wildlife. PFOS, perfluorohexanesulfonate (PFHxS), perfluorooctanoate (PFOA), and perfluorooctanesulfonamide (PFOSA) have been found in human sera from the United States. In this study, concentrations of PFHxS, perfluorobutanesulfonate (PFBS), PFOS, perfluorohexanoic acid (PFHxA), PFOA, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), and PFOSA were measured in 85 samples of whole human blood collected from nine cities (eight provinces) in China, including Shenyang (Liaoning), Beijing (Hebei), Zhengzhou (Henan), Jintan (Jiangsu), Wuhan (Hubei), Zhoushan (Zhejiang), Guiyang (Guizhou), Xiamen (Fujian), and Fuzhou (Fujian). Among the 10 perfluorinated compounds (PFCs) measured, PFOS was the predominant compound. The mean concentration of PFOS was greatest in samples collected from Shenyang (79.2 ng/mL) and least in samples from Jintan (3.72 ng/mL). PFHxS was the next most abundant perfluorochemical in the samples. No age-related differences in the concentrations of PFOA, PFOS, PFOSA, and PFHxS were observed. Gender-related differences were found, with males higher for PFOS and PFHxS, and females higher in PFUnDA. Concentrations of PFHxS were positively correlated with those of PFOS, while concentrations of PFNA, PFDA, and PFUnDA were positively correlated with those of PFOA. There were differences in the concentration profiles (percentage composition) of various PFCs in the samples among the nine cities.

Introduction

Perfluorooctanesulfonylfluoride (POSF) is the precursor for the production of several perfluorinated compounds (PFCs), and perfluorooctanesulfonate (PFOS) is identified to be the end-stage metabolite of many PFCs (*1*). The strong carbon−fluorine (C−F) covalent bonds in PFCs account for the thermal and chemical stability of these compounds, which have been manufactured and used in a variety of industrial applications, such as surfactants and surface protectors, for over 50 years (*2−4*).

PFOS and perfluorooctanoate (PFOA) have been found to be the dominant PFCs in the environment and in biota (*5−9*). The first report of organic fluorinated compounds in human blood was as early as 1960s (*10*). Following the detection of PFOS and PFOA in blood sera of employees in the fluorochemical manufacturing industry (*1*), subsequent work has been conducted on general populations in several countries. Recent studies have reported the occurrence of PFOS, PFOA, and related fluorochemicals in human blood from the United States, Columbia, Brazil, Italy, Poland, Belgium, India, Malaysia, Korea, Japan, and Sri Lanka (*11−13*). These results indicated the widespread occurrence of PFCs in the general population (mainly PFOS, followed by PFOA in human blood). There were no age- or gender-related differences in the concentrations of PFOS and PFOA found in these studies.

In 2000, one of the fluorochemical manufacturing companies, the 3M Company, ceased the production of perfluorooctanyl-related materials because PFOS was found to be persistent in humans and wildlife. However, products made of perfluorooctanyl-related materials are still widely available in China. PFOS and PFOA have been found in the coastal seawaters of Hong Kong and the Pearl River Delta (*14*). A study on PFOS in blood serum samples collected in Shenyang (Liaoning Province), China, found concentrations ranging from 5.32 to 145 ng/mL (*15*). Besides this, there is virtually no other information on the distribution and the degree of contamination of PFCs in China, particularly in human tissues. The purpose of this study was to understand the geographical pattern of contamination of PFOS and related chemicals in China by measuring concentrations of PFCs in blood samples collected from nine cities (eight provinces). The influence of age and gender on blood PFC concentrations was also examined.

Materials and Methods

Sample Collection. Samples of whole human blood were collected from volunteer donors from local universities or hospitals in China in 2004 (Figure 1). The demographic information of the donors including age, sex, and sampling location are shown in Table 1. Whole blood samples were stored in polypropylene (PP) containers or vacutainers at −20 °C until analysis.

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FIGURE 1. Sampling locations of blood samples in China.

TABLE 1. Details of Human Blood Samples Analyzed from 2004

country	province	location	no. of samples (whole blood)	age (yrs): mean (min−max)	gender distribution M	gender distribution F
China	Jiangsu	Jintan	10	44 (30−66)	5	5
	Zhejiang	Zhoushan	10	23 (24−34)	0	10
	Liaoning	Shenyang	10	34 (21−46)	6	4
	Guizhou	Guiyang	11	33 (21−48)	6	5
	Hubei	Wuhan	7	25 (22−33)	6	1
	Hebei	Beijing	10	32 (25−40)	5	5
	Fujian	Fuzhou	10	43 (23−57)	5	5
	Fujian	Xiamen	7	36 (25−55)	4	3
	Henan	Zhengzhou	10	31 (7−45)	5	5

Reagents. Perfluorobutanesulfonate (PFBS), perfluorohexanesulfonate (PFHxS), PFOS, and perfluorooctanesulfonylamide (PFOSA) were provided by the 3M Company via Dr. K. Kannan at New York State University. Perfluorohexanoic acid (PFHxA), PFOA, and perfluorononanoic acid (PFNA) were purchased from Wako Pure Chemical Industries Ltd. Perfluoroheptanoic acid (PFHpA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), and perfluorododecanoic acid (PFDoDA) were purchased from Fluorochem Limited. HPLC grade water, methanol, tetra-*n*-butylammonium hydrogen sulfate (TBA), methyl-*tert*-butyl ether (MTBE), and sodium carbonate were purchased from Wako Pure Chemical Industries, Ltd.

Sample Preparation and Extraction. Samples of whole blood were thawed and allowed to return to room temperature before extraction. A total of 11 PFCs were identified and quantified by comparison to authentic standards. These include PFBS, PFHxS, PFOS, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, and PFOSA. Blood was extracted for PFCs by use of an ion-pairing method, the details of which are described elsewhere (*11*, *16*). In brief, 0.5 mL of whole blood was adjusted to 1 mL with 0.5 mL of distilled water. The solution was mixed with 1 mL of 0.5 M TBA solution and 2 mL of 0.25 M sodium carbonate buffer (pH 10) and then added to a 15 mL PP tube for extraction. After mixing, 5 mL of MTBE was added, and the mixture was shaken for 20 min

TABLE 2. Mass Determination of Analytes and Matrix Spike Recoveries

target analyte	primary and product ions (*m/z*)	matrix spike recovery (%) range	mean	SD	n
PFOSA	497.7 > 77.7	62.7−81.0	75.6	3.69	4
PFOS	498.6 > 79.7	88.4−121.3	96.4	8.10	4
PFHxS	398.7 > 79.7	52.2−110	78.6	2.69	4
PFBS	298.7 > 79.7	53.3−80.2	70.5	7.16	4
PFDoDA	612.7 > 568.8	78.8−101	86.9	2.78	4
PFUnDA	563 > 519	80−99.3	86.0	3.45	4
PFDA	512.8 > 468.8	80.4−106	94.6	2.79	4
PFNA	462.7 > 418.8	85.7−112	94.5	6.01	4
PFOA	413 > 368.7	76.1−103	92.5	2.17	4
PFHxA	312.8 > 268.8	43.1−65.1	55.1	5.60	4

at 250 rpm. The organic and the aqueous layers were separated by centrifugation at 3000 rpm for 15 min. Then, 4 mL of MTBE was removed and transferred to a second 15 mL PP tube. The extraction was repeated twice as described above, except that 5 mL of MTBE was removed each time, instead of 4 mL. All three extracts were combined in the second 15 mL PP tube. The final extract was concentrated under nitrogen gas after adding 1 mL of methanol. The extract was then passed through a 0.1 μm nylon filter before injection into the liquid chromatograph.

Instrumental Analysis. Analysis of the target analytes was performed by using a high-performance liquid chromatography−tandem mass spectrometer (HPLC−MS/MS), comprising an Agilent HP1100 liquid chromatography interfaced with a Micromass (Beverly, MA) Quattro Ultima Pt mass spectrometer operated in electrospray negative ionization (ESNI) mode. A 10 μL aliquot of the sample extract was injected onto a guard column (XDB-C8, 2.1 mm i.d. × 12.5 mm, 5μm; Agilent Technologies, Palo Alto, CA) connected sequentially to a Betasil C18 column (2.1 mm i.d. × 50 mm length; Termo Hypersil-Keystone, Bellefonte, PA) with 2 mM ammonium acetate−methanol as the mobile phase, starting at 10% methanol. MS/MS parameters were optimized so as to transmit the $[M - K]^-$ or $[M - H]^-$ ions (Table 2). Detailed instrumental parameters were reported elsewhere (*17*).

Quality Assurance/Quality Control. To achieve lower detection limits, all accessible polytetrafluoroethylene (PTFE) materials were removed from the instruments and apparatus to minimize background signal due to contamination. PP tubes and septa were selected after a thorough checking for blanks (*18*). Impurities of each standard chemical were tested at nanogram per milliliter level, and no contamination from chemical reagents was confirmed. Our test results showed that the widely used surrogate ^{13}C-PFOA (^{13}C-PFOA from Perkin-Elmer) contained significant amounts of PFBA and PFPeA. Hence, ^{13}C-PFOA was used only for checking the overall recovery of target chemicals during the analytical procedure. Due to the problem of contaminants in the standards, recoveries of native chemicals were tested in a series of preliminary experiments instead of using internal standards. All target chemicals were spiked into test samples of blood, and the samples were extracted and analyzed following the same procedures as described above. Recoveries were evaluated by subtracting background levels from detected concentrations. Resultant recoveries of PFBS, PFHxS, PFOS, PFHxA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, and PFOSA were 70.5, 78.6, 96.4, 55.1, 92.5, 94.5, 94.6, 86.0, 86.9, and 75.6% (*n* = 4 each), respectively (Table 2). PFC concentrations were not corrected for recoveries.

Procedural blanks associated with every 10 samples were tested to check for possible laboratory contamination and interferences, and they were below 8.1 pg/mL. The only exception was PFHpA which exhibited a significant blank. Consequently, results concerning PFHpA were not discussed
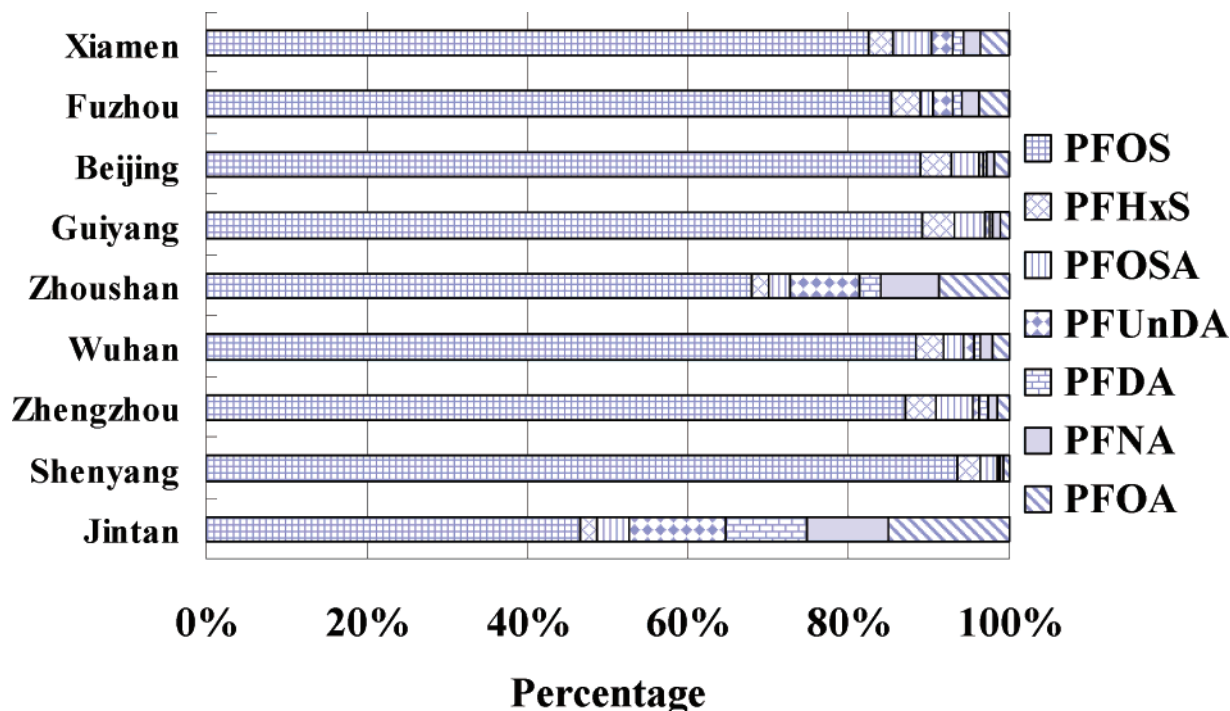
FIGURE 2. Composition profile of perfluorochemicals found in human blood samples in China.

in this report. The blank levels in the tube used for sample collection was checked and found to be less than 7 pg/mL in washed methanol for all analytes. The limits of quantification (LOQs) were defined as the smallest mass of standard injected which resulted in a reproducible measurement of peak areas consistent with the calibration curve, maximum blank concentration, concentration factors, and a signal-to-noise ratio equals to or greater than 3. LOQs for the samples used in this study were 100 pg/mL for PFBS, PFHxS, PFHxA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, and PFOSA, whereas that for PFOS was 200 pg/mL.

Concentrations of target analytes were quantified using calibration curves constructed using individual standards of six different concentrations (50, 200, 1000, 10 000, 20 000, 50 000 pg/mL). The linearity and the repeatability of these calibration curves were confirmed prior to each set of determinations (*17*). Reliability of the above method was further verified through participation in the First International Laboratory Calibration Study coordinated by ASG-RIVO and Örebro University (*19*). Our laboratory reported acceptable results for the blood plasma sample with one of the least coefficients of variation. Thus, our results were judged to be accurate and precise.

Statistical Analysis. A Mann–Whitney *U* test was used to assess if there is a significant difference in PFC concentrations in the blood samples between the sexes. A Spearman rank correlation analysis was used to examine possible correlations among various PFCs in the samples.

Results and Discussion

Concentrations of PFCs in Blood Samples from China. Because the recovery of PFHxA was poor and the concentrations of PFBS and PFDoDA were found to be less than the LOQs in all the samples, results are given for only seven PFCs (= total PFCs) in the present study. Among the target analytes, PFOS occurred at the greatest concentrations. The greatest concentrations of PFOS, PFHxS, and PFOSA were found in whole human blood from Shenyang (Liaoning), whereas the lowest concentrations were found in samples from Jintan (Jiangsu). It should be noted that all blood samples from Zhoushan (Zhejiang) were obtained from female donors only.

Zhejiang exhibited the greatest mean concentration of PFDA. Jintan exhibited the greatest mean concentrations of PFUnDA, PFNA, and PFOA. Among the nine cities investigated in this study, the greatest total PFC concentrations were observed in whole blood from Shenyang, which is well-known for its heavy industries.

The mean concentration of PFOS in blood samples from Shenyang detected in this study was greater than that reported in a previous study from the same city (*15*). Concentrations of PFCs in whole blood samples measured in the present study were converted to concentrations in blood sera by multiplying by a factor of 2 to allow comparison across different studies (*12, 16*). After conversion to serum concentration basis, mean PFOS concentrations from Shenyang were 142 ng/mL (31.7–225 ng/mL) for males and 170 ng/mL (80.4–310 ng/mL) for females in the present study. Concentrations of PFOS in the previous study were 40 ng/mL (5.32–145 ng/mL) for males and 45.5 ng/mL (10.6–142 ng/mL) for females. On this basis, concentrations of PFOS from the present study were 3–4 times greater than those reported in the previous study. The reason for such large differences is unknown. A detailed comparison of concentrations of other PFCs between the two studies is not possible since only PFOS concentrations were reported in the previous study.

The profiles of relative concentrations (percentage composition) of the seven PFCs measured among the nine cities are shown (Figure 2). Xiamen and Fuzhou (Fujian), Zhoushan, Shenyang, and Jintan exhibited different patterns of relative concentrations of the seven PFCs, while Beijing (Hebei), Guiyang (Guizhou), Wuhan (Hubei), and Zhengzhou (Henan) exhibited similar composition patterns. The different composition profiles of PFCs suggested that there might be different exposure sources of and/or pathways to PFCs in the general population. However, further research is needed to better understand these aspects.

Global Comparison of PFC Concentrations in Human Blood. The mean concentrations of PFCs from other related studies are summarized in Table 3. The mean concentration of PFOS in whole blood samples from China, when converted to a serum basis, was slightly greater than concentrations in

TABLE 3. Perfluorochemical Concentrations in Human Blood Sera (ng/mL) from Various Countries[a]

country	PFOS	PFHxS	PFOA	PFOSA
United States[b]	43.2	4.00	19.1	4.14
Colombia[b]	8.28	0.20	6.16	1.57
Brazil[b]	11.7	3.77	<20	1.00
Italy[b]	4.32	1.64	<3	1.78
Poland[b]	42.1	1.30	21.3	2.06
Belgium[b]	15.7	1.04	4.82	<3
India[b]	1.85	1.60	2.64	<3
Sri Lanka[c]	5.03	0.57	6.38	N.A.[d]
Malaysia[b]	12.7	1.98	<10	4.57
Korea[b]	21.1	3.95	61.8	1.30
Japan[e]	24.6	5.92	6.40	7.92
China[f]	52.7	1.88	1.59	1.82

[a] Samples with values below the limits of quantification were treated as zero in the calculation of mean. [b] Values are from ref 12. [c] Values are from ref 13. [d] N.A. = not analyzed. [e] Values are from refs 16 and 26. [f] Whole blood data were converted to a serum basis by multiplying by a factor of 2.

samples from the United States and Poland. Concentrations of PFCs in human blood from China were 2−5 times greater than those from Japan, Korea, Malaysia, Belgium, and Brazil (12), and Sri Lanka (13). Excluding data from the employees of a fluorochemical production plant (1.75 μg/mL) (1), blood samples from China contained the greatest mean concentrations of PFOS. The greater concentrations of PFOS in the Chinese samples may be related to the frequent (daily) uses of PFC-containing products. Furthermore, the increased industrial and economic activities in China have led to the rapid development of various industries such as textiles, electronics, and packing products, and this could also result in an increased exposure to PFCs.

Previous studies have reported that PFOA is the PFC that occurred at the second greatest concentrations in human blood (serum and whole blood) samples (12, 13, 20). However, in the present study, concentrations of PFOA were fourth highest among the PFCs measured. Indeed, concentrations of PFOA in the Chinese blood samples were the smallest compared with those of other countries. The greatest concentrations of PFOA were found in serum samples from Korea (61.8 ng/mL), which were approximately 40-fold greater than those measured in the present study. The least concentrations of PFOA reported for human blood samples from previous studies were from Belgium. However, these concentrations were still almost 3 times greater than those found in the present study (12).

Concentrations of PFHxS were approximately 20- to 30-fold smaller than those of PFOS in the present study. Concentrations of PFHxS were 2 times smaller than those of the United States, Korea, and Japan but were about 9 times greater than that of Colombia and 3 times greater than that of Sri Lanka. Concentrations of PFHxS in the Chinese samples were similar to those of Poland and Belgium. PFHxS is the sulfonate form of perfluorohexanesulfonyl fluoride (PHSF), which is a component of fire-fighting foams and is also used for postmarket carpet treatment applications (21).

In the present study, PFOSA was detected in all blood samples from China. Concentrations of PFOSA measured in human blood were smaller than those of the United States and Poland but slightly greater than that of Colombia (12). PFOSA is a metabolite of N-methyl- and N-ethyl-perfluorooctanesulfonamidoethanol. All these compounds are used primarily for surface treatment of textiles and paper. As well, sulfuramid (N-ethyl-perfluorooctanesulfonamide) is used as an insecticide to control cockroaches and ants, and this compound can be transformed into PFOSA in rats, dogs, and rabbit renal mitochondria (22). PFOSA would be expected to

be converted to PFOS and would not undergo further transformation (22). Therefore, the occurrence of PFOSA in human blood may indicate recent exposure of N-methyl- and N-ethyl-perfluorooctanesulfonamidoethanol.

There is, to date, little information on longer-chain PFCs in human fluids and biotic samples (7, 13). Indeed, reports of concentrations of PFCs such as PFDA, PFNA, and PFUnDA in human body fluids were generally scarce (13). Concentrations of PFDA, PFNA, and PFUnDA measured in human blood samples in the present study were 8.4, 6.2, and 9.8 times greater than the concentrations of the respective compounds in samples from Sri Lanka (13). In comparison with the results of the United States, concentrations of PFDA and PFUnDA from China were 1.2 and 1.5 times greater. In contrast, concentrations of PFNA in U.S. samples were 2.3 times greater than those of China. Fluorotelomer alcohols (FTOHs) have been reported to yield even- and odd-chain-length perfluoroalkyl carboxylates (PFCAs) such as PFNA, PFDA, PFOA, and PFUnDA (21). The observation that PFOA, PFNA, and PFUnDA had similar concentrations in the Chinese blood samples suggests that these PFCs may have originated from the degradation of fluorotelomer alcohol from common sources.

Gender- and Age-Related Accumulation. To investigate possible gender- and age-related accumulation of PFCs, data of blood samples from the nine cities were pooled and then analyzed for possible gender- and age-related patterns. The perfluoroalkylsulfonates (PFOS, PFHxS, etc.) were found to be significantly different ($P < 0.05$) between males and females. Concentrations of perfluoroalkylsulfonates were greater in males. For the perfluoroalkylcarboxylates, there was generally no significant difference between the sexes except for PFUnDA, which showed significantly greater concentrations in females than males ($P < 0.05$). Differences in concentrations of PFCs between the sexes had also been observed in blood samples from Poland and Japan. However, the overall results of this study did not indicate any consistent gender-related patterns (12). Similarly, no gender-related differences in the concentrations of PFOS or PFOA were reported in a study of PFOS concentrations in human blood in the United States. (23). It is conceivable that the differences in PFC concentrations between the sexes observed in the present study may be attributable to confounding factors, e.g., occupation and lifestyle of the donors, not considered in this study. No association between age and the concentrations of PFOA, PFOS, PFOSA, or PFHxS was observed in the present study. Similar results have also been observed in other countries (12).

Relationships among PFCs. A significant positive correlation between PFOS and PFHxS concentrations was observed in the present study ($R^2 = 0.65$, $P < 0.05$). PFOS is a major end-stage metabolite of POSF-based compounds, and PFHxS is an impurity in POSF-based products. Since POSF is a precursor, the correlation between PFOS and PFHxS suggests that (1) PFHxS might have occurred with the POSF-based products as an impurity and (2) the sources for human exposure of PFOS and PFHxS may be common or related in China.

There were statistically significant positive correlations between PFNA, PFDA, and PFUnDA with PFOA ($R^2 > 0.42$, $P < 0.05$). FTOHs can be degraded to fluoroalkyl carboxylic acids such as PFOA, PFNA, PFDA, and PFUnDA. Therefore, the significant positive relationships suggest that there might be a common exposure pathway for the fluoroalkyl carboxylates to human.

Global Comparison of PFC Composition. The profiles of relative concentrations of PFOS, PFHxS, PFOA, and PFOSA were compared among different countries (Figure 3). The percentage compositions of the four PFCs were quite different, and the percentage composition in China was
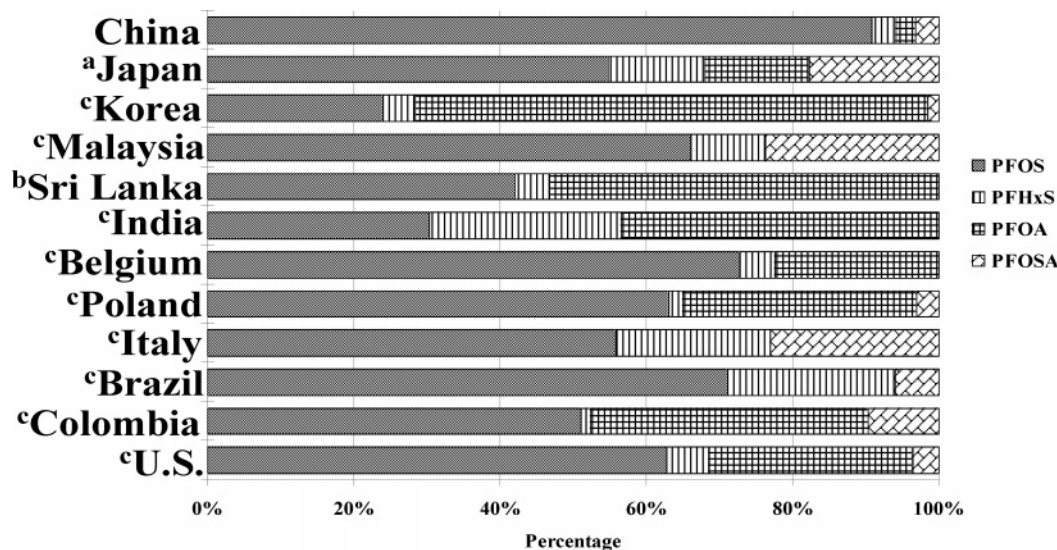
FIGURE 3. Composition profile of perfluorochemicals found in human blood samples from various countries: a, data from refs *16, 26*; b, data from ref *13*; c, data from ref *12*.
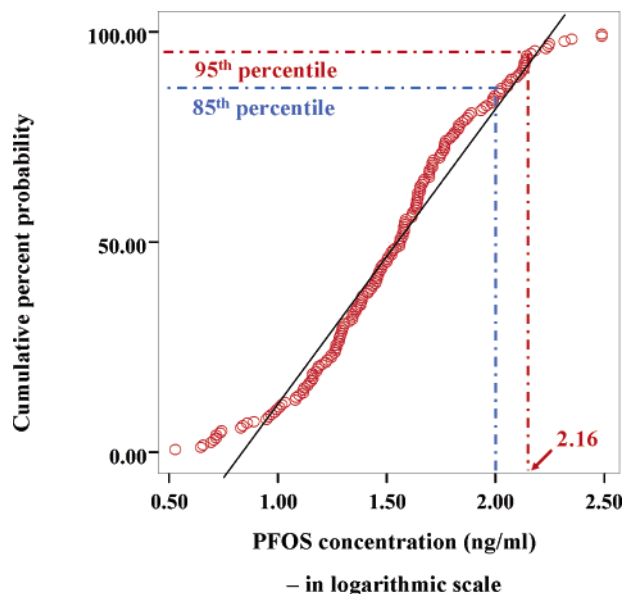

FIGURE 4. Plot of percent cumulative probability (probabilistic scale) against concentrations of PFOS (logarithmic scale) in human blood samples from China.

unique, with about 90% contribution from PFOS and around 3% from PFOA, PFHxS, and PFOSA each. Among the southeast Asian countries, the relative proportions of PFCs detected are quite different. For example, Korea had the greatest proportion of PFOA (70%) and the least for PFOS (24%). The large variabilities in both composition profiles and concentrations of PFCs in human body fluids among different countries suggest that there may be specific exposure sources and pathways of PFCs to humans in different countries. Further research is required to clarify these aspects.

Risk Assessment of PFOS in Blood. The risk of exposure to PFOS was estimated by comparing the probability of exceedance to several points of departure, or toxicity reference values (TRVs). The probability associated with a particular point of departure was estimated from a plot of percent cumulative probability (probabilistic scale) as a function of PFOS concentration (logarithmic scale) in human blood samples (Figure 4). Protective values, the benchmark internal concentrations (BMICs), were chosen as "points of departure" for risk characterization (*24*). Three values, (1) 33

μg/mL, derived from the lower 95% confidence limit of the BMIC based on rat pup weight gain during lactation (*24*), (2) 44 μg/mL, the NOAEL of the rat liver toxicity (*24, 25*), and (3) 62 μg/mL, the lower 95% confidence limit of the BMIC (10% response) for liver tumor formation in rats (*25*), were used in the risk evaluation of serum PFOS concentrations in the Chinese population. A similar approach has also been adopted in another study (*23*).

Concentrations of PFOS were less than 100 ng/mL in blood serum of 95% of the U.S. population (*23*). In the present study, serum PFOS concentrations were less than 100 ng/mL in 85% of the Chinese population. The 95th percentile of the serum PFOS concentrations in the Chinese population was 146 ng/mL. It is noteworthy that all the samples with serum PFOS concentrations greater than 146 ng/mL were from Shenyang.

With the use of the above three points of departure, a human serum concentration of 146 ng/mL (95th percentile of PFOS concentrations from China observed in the present study) resulted in margins of exposure of 202, 287, and 404, respectively. These margins of exposure suggest that PFOS posed little or no intermediate risk to the Chinese population. Given that sources and pathways of PFOS exposure to the Chinese population are still unknown, and that PFOS is moderately bioaccumulative, future risk could increase if releases are not controlled. Furthermore, at this time the relationship of PFOS exposure and potential risks posed by PFOS in the presence of mixtures of PFCs has not been evaluated. While future monitoring to determine possible sources of PFCs is warranted, it is unlikely that concentrations of PFOS in the general Chinese population would exceed presently known thresholds for adverse effects to humans.

Supporting Information Available

Table showing mean, standard deviation, median, minimum, and maximum perfluorochemical concentrations (ng/mL) in whole human blood from different cities in China stratified by donor gender. This material is available free of charge via the Internet at http://pubs.acs.org.

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