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Relationship between perfluorooctanoate and perfluorooctane sulfonate blood concentrations in the general population and routine drinking water exposure

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ABSTRACT

In regions with heavily contaminated drinking water, a significant contribution of drinking water to overall human perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) exposure has been well documented. However, the relationship of PFOA/PFOS blood concentrations in the general population to routine drinking water exposure is not well characterized. This study determined the PFOA and PFOS concentrations in 166 drinking water samples across 28 cities in China. For 13 of the studied cities, PFOA and PFOS concentrations were analyzed in 847 human blood samples which were collected in parallel with the drinking water samples. The geometric mean PFOA and PFOS concentrations in drinking water were 2.5 ± 6.2 ng/L and 0.7 ± 11.7 ng/L, and population-weighted geometric mean blood concentrations were 2.1 ± 1.2 ng/mL and 2.6 ± 1.3 ng/mL, respectively. We found a significant correlation between the PFOA concentration in drinking water and blood ($r = 0.87$, $n = 13$, $p < 0.001$). The total daily intake of PFOA (0.24–2.13 ng/kg/day) and PFOS (0.19–1.87 ng/kg/day) were back-calculated from the blood concentrations with a one-compartment toxicokinetic model. We estimated relative source contributions (RSCs) of drinking water to total daily intake in China of 23 ± 3% for PFOA and 12.7 ± 5.8% for PFOS. Using the mean RSCs, we derived the health advisory values of 85 ng/L for PFOA and 47 ng/L for PFOS in China.

1. Introduction

Perfluoroalkyl acids (PFAAs), the subject of this study, are a subset of a much larger group of chemicals, *per-* and polyfluoroalkyl substances (PFAS), which are manufactured for numerous industrial and commercial applications because of their chemical stability, ability to lower surface tension, and hydrophobicity. Their widespread use, environmental persistence, and bioaccumulation have led to their ubiquity in environmental, wildlife, and human samples, including human blood, breast milk, and bone (Giesy and Kannan, 2001; Shoeib et al., 2006; Kärrman et al., 2007; Koskela et al., 2017; Zhang et al., 2018). Human exposure to PFAAs via drinking water, especially perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA), has attracted mounting attention due to their adverse effects on human health in development, metabolism, immune, and endocrine function (Barry et al., 2013; Braun et al., 2016). In 2016, the U.S. Environmental Protection Agency (U.S. EPA) established health advisory levels for PFOA and PFOS in drinking water of 70 ng/L (individual or combined) (U.S. EPA, 2016a, 2016b).

Identification of the exposure route is a critical step for risk management and effective exposure reduction strategies. It is anticipated that PFOS and PFOA are of concern in drinking water, due to their high water solubility and inefficient removal in a standard water treatment plant (Post et al., 2017). Indeed, significant relationships were observed between PFOA concentrations in drinking water, which had environmental contamination, and in serum samples of residents reliant on those sources as drinking water (Emmett et al., 2006; Hoffman et al., 2011; Post et al., 2009). Likewise, elevated PFOA levels were also found in the serum of residents of a German community, and attributed to consumption of drinking water contaminated with PFAAs (Hölzer et al.,

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2008). These studies well demonstrated that drinking water contributed significantly to human PFOA exposure in regions with highly contaminated drinking waters. On the other hand, it has been reported that the serum PFOA and PFOS concentrations were significantly higher in those participants who lived in a water district where PFOA had been found at above 20 ng/L or PFOS had been found above 40 ng/L (Hurley et al., 2016). To date, however, there are no reports on the relationship between PFOS/PFOA levels in blood and in drinking water for the general population.

The relative source contribution (RSC) is a critical factor required to develop a Health Based Value (HBV) for drinking water, to prevent that a total exposure exceeds a reference dose (RfD) or threshold level (U.S. EPA, 2000). While a subtraction method in which other sources of exposure except for drinking water are subtracted as background from an RfD has been recommended, such method may result in a maximum possible RSC value (U.S. EPA, 2000). Since human are exposed to PFOA and PFOS via various pathways beyond drinking water (e.g., air and diet) (Lorber and Egeghy, 2011), the percentage of total exposure typically accounted for by drinking water based on a comprehensive exposure assessment is more reasonable (U.S. EPA, 2016a, 2016b). However, due to limited available information on RSCs for PFOA/PFOS in drinking water, previous HBV development for drinking water used a default RSC factor of 20% (U.S. EPA, 2009a, 2016a, 2016b) while a higher RSC value results in higher the HBVs. Although RSCs could be estimated by direct measurement of all human exposure routes, such an approach would neglect the potential contribution from unclear exposure routes (e.g., intake via hand-to-mouth behaviors) (Lorber and Egeghy, 2011).

To address this challenge, Lorber and Egeghy (2011) recommended back-calculation from the internal dose by using a reliable pharmacokinetics model to better reflect cumulative exposure via multiple pathways. For example, a simple toxicokinetic model was used to reconstruct daily intake based on serum samples collected from residents of southeast Queensland, Australia, with the average PFOA/PFOS contributions from drinking water of 2–3% (Thompson et al., 2011). However, the drinking water samples were collected from regions other than southeast Queensland, despite regional differences in PFOA/PFOS blood and drinking water concentrations, indicating that the water and blood concentrations were not appropriately paired. The same approach was applied to estimate RSCs for PFOS in four Chinese capital cities (Zhang et al., 2011) and for PFOA in one Chinese city (Bao et al., 2010; Bao et al., 2017). Although some attempts have been made to estimate RSCs, a nationwide RSC for drinking water is still needed to permit development of drinking water HBVs for PFOA and PFOS.

In the past two decades, the rapid urbanization and industrialization of China have placed enormous stress on the environment. Given increasing production of PFOA and PFOS in China (OECD, 2015), development of drinking water criteria for China is necessary. This study analyzed 12 PFAAs in 166 drinking water samples from 28 major cities in China to assess the contribution of drinking water to PFAA exposure. The PFAA concentrations were also determined in 847 blood samples collected from the general population in 13 cities in China to permit back-calculation of total daily intake. Finally, nationwide PFOA and PFOS drinking water RSCs of drinking water were estimated, providing informative data for establishing their drinking water criteria for China.

2. Materials and methods

2.1. Chemicals and reagents

Fourteen PFAA standards and eight isotopically-labeled internal standards were purchased from Wellington Laboratories Inc. (Guelph, Ontario, Canada). Details regarding standards and other reagents are provided in Supplementary Materials. Oasis WAX solid phase extraction cartridges (150 mg, 6 mL) were obtained from Waters (Milford, Massachusetts, USA).

2.2. Sample collection

In China, tap water is not commonly filtered further. Based on the assumption that all people drink tap water, 151 drinking water samples were collected during 2015–2017 from the final effluent of 93 drinking water treatment plants (DWTPs) across 24 cities (Heihe, Harbin, Baoding, Zhengzhou, Lanzhou, Shenyang, Zhuzhou, Tianjin, Dalian, Nanjing, Zibo, Binzhou, Beijing, Chaohu, Dongying, Jinan, Foshan, Changzhou, Shenzhen, Wuxi, Shanghai, Shijiazhuang, Dongguan, Lianyungang). In Mudanjiang, Hohhot, Xi'an, and Changsha, 15 drinking water samples were collected as tap water (without filtration) from individual home. These 28 cities are distributed along main drainage basins in China including Chaohu Lake, Haihe River, Heihe River, Huai River, Huangpu River, Liao River, Mudan River, Pearl River, Songhua River, Taihu Lake, Yangtze River, and Yellow River. The selected DWTPs are located in the key basins and regions as stated in “water pollution prevention action plan” promulgated in 2015 by the State Council of China. All of the investigated DWTPs are centralized drinking water supply units, serving a total population of about one hundred million urban consumers. The quantity and timing of drinking water samples collected from each DWTP are listed in Table S1. The samples were collected and stored in pre-washed, 500-mL narrow mouth polypropylene containers with screw tops. Procedural blank (n = 3 for each batch) were prepared by substitution of 500 mL of Milli-Q water. To confirm reproducibility of the monitoring method, duplicate sampling was conducted in Jinan and Xi'an. Samples were stored on dry ice during transport from sampling sites to the laboratory and extracted immediately upon arrival at the laboratory.

In 2015–2017, 847 whole-blood samples were collected from 410 female and 437 male healthy adults from the general population in 13 cities (Mudanjiang, Harbin, Shenyang, Hohhot, Xi'an, Zhengzhou, Zhuzhou, Changsha, Jinan, Nanjing, Wuxi, Shanghai, and Chaohu) where drinking water samples were simultaneously collected for PFOA and PFOS analyses (Fig. 1). All participants provided demographic information (e.g., age, gender, height, and residential history). Participants drank water from the DWTPs in their corresponding cities and were not occupationally exposed to the target analytes. Female and male participants were 18–45 and 18–43 years old, respectively. Human blood sample collection was approved by the Peking University Biomedical Ethics Committee (IRB00001052-14086).

2.3. Sample extraction and cleanup

Sample preparation was based on a previously reported method (Mak et al., 2009). All water samples and procedural blanks (500 mL) were spiked with 50 μL of isotopically labeled internal standards (10 μg/L) before extraction on preconditioned WAX cartridges. Extracts were dried under a gentle nitrogen stream and re-dissolved in 0.5 mL of methanol for UPLC–MS/MS analysis. Detailed sample extraction/cleanup and PFAA analytical instrument conditions are provided in Supplementary Materials.

An aliquot of blood (0.2 mL) was spiked with 20 μL of isotopically labeled internal standards (10 μg/L) and extracted via ion-pair liquid–liquid extraction (Yeung et al., 2006). The extracts were dried by nitrogen and re-dissolved in methanol (0.2 mL) prior to UPLC–MS/MS analysis. PFAAs were not detected in procedural blanks. Recoveries of target compounds in spiked water and blood samples ranged from 75 ± 3% to 120 ± 8% and from 61 ± 4% to 91 ± 17%, and the limits of quantitation (LOQs) were 0.05–0.2 ng/L and 0.02–0.18 ng/L, respectively (Table S3).

2.4. Data treatment and statistical analysis

Statistical analyses were performed in SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA). Concentrations below limit of quantitation (LOD) were assigned to the LOD divided by the square root of 2 for data

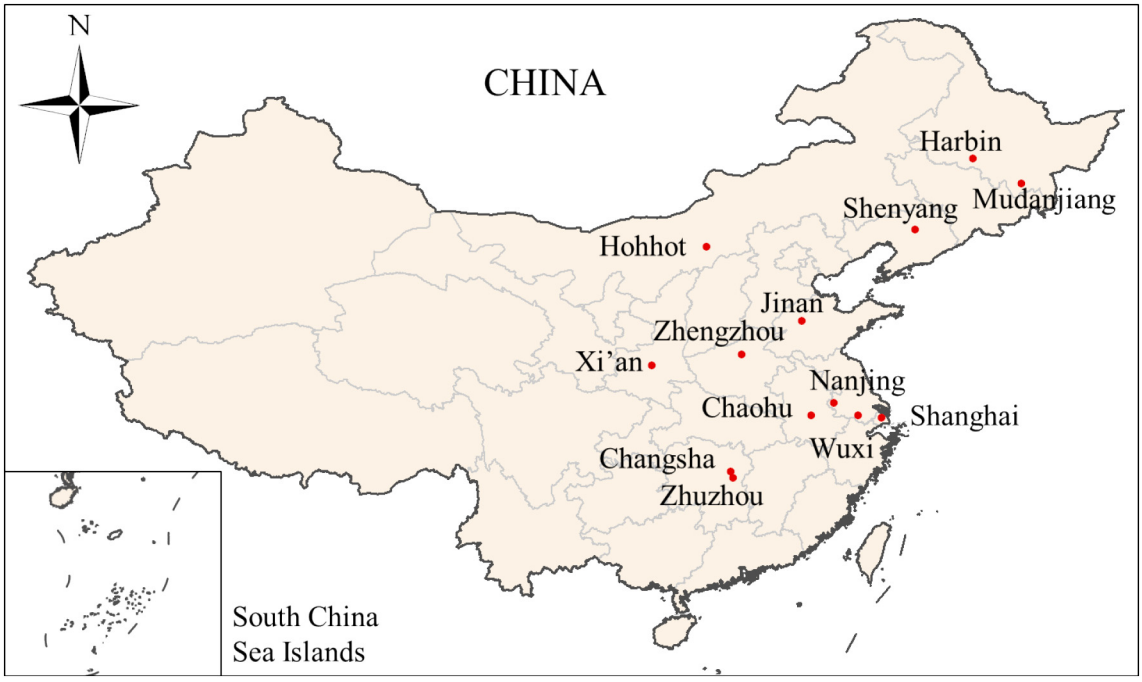

Fig. 1. Map of China, showing the cities where human blood samples were collected from 2015 to 2017.

analysis, although concentrations below LOD were assigned to 0 for histogram development. The significance of relationships between target compound concentrations were regressed using a least square method, with the statistical level of significance set to $p < 0.05$. Spatial distributions of compounds were visualized with ArcMap (ESRI® ArcGIS 10.0).

3. Results and discussion

3.1. Occurrence of PFAAs in drinking water

Among eight perfluoroalkylcarboxylic acids (PFCAs, including C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, and C_{12}) and four perfluoroalkylsulfonates (PFSAs, including C_4, C_6, C_7, and C_8), four PFAS including PFOA, PFNA, PFDA, and PFOS was detected in 165 of 166 drinking water samples. The average total level of PFAAs was 34.4 ± 4.7 ng/L (mean ± standard error), with a maximum concentration of 410.4 ng/L detected in a sample from Lianyungang City. Among 12 target PFAAs, the detection frequency of PFOA in drinking water samples was highest (92%), followed by PFNA (90%), PFHxA (87%), PFHpA (80%), PFOS (79%), PFDA (71%), PFBS (64%), PFPeA (62%), PFHxS (59%), PFUnDA (46%), PFHpS (20%), and PFDoDA (14%). PFOA was found with the highest concentration of 9.9 ± 1.7 ng/L (mean ± standard error), followed by PFOS (7.7 ± 2.1 ng/L), PFHxS (6.3 ± 1.3 ng/L), and PFHxA (4.1 ± 1.0 ng/L). With undetected observations simulated by ProUCL 5.1 software (U.S. EPA, 2009b), concentration data were found to fit a log-normal distribution. As shown in the cumulative probability curves, PFOA was higher than PFOS in drinking water (Fig. 2), with the geometric mean concentrations in drinking water of 2.5 ± 6.2 ng/L for PFOA and 0.7 ± 11.7 ng/L for PFOS. Due to the ubiquity in drinking water, environmental persistence, and toxicity of PFOA and PFOS, the U.S. Agency for Toxic Substances and Disease Registry (ATSDR, 2018) and several U.S. states including Minnesota, New Jersey, and Vermont (ITRC, 2018) have developed drinking water criterion values for PFOA and PFOS that are lower than the U.S. EPA lifetime health advisories (LHAs, 70 ng/L for PFOA, PFOS or combined). Given that the animal studies are usually sub-chronic, the U.S. EPA established the LHAs by a human equivalent dose (HED) approach (U.S. EPA, 2016a, 2016b),

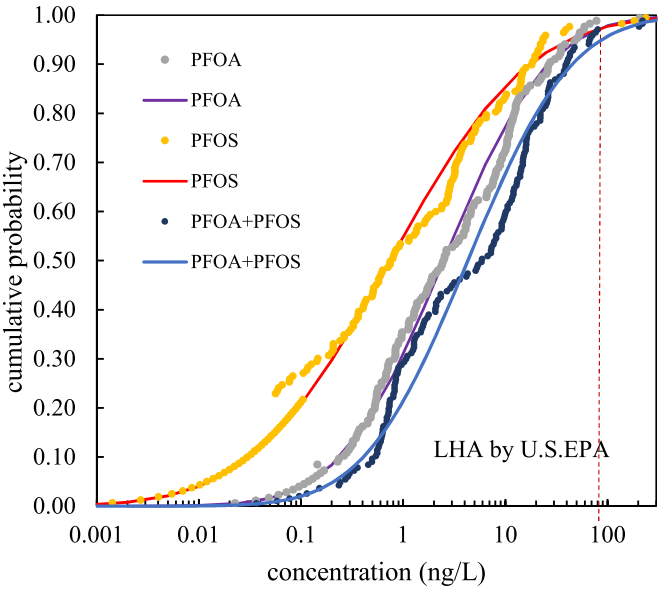

Fig. 2. Cumulative probability curves for the concentrations of PFOA, PFOS and the sum of PFOA and PFOS in drinking water in China. The estimates were based on individual samples. LHA: lifetime health advisory for drinking water from the U.S. EPA (70 ng/L for PFOA, PFOS or combined).

which integrates both interindividual toxicokinetic and exposure duration differences in humans relative to animals (Dong et al., 2017). Thus, we compared the PFOA and PFOS levels in drinking water with the LHAs recommended by U.S. EPA in 2016. Based on cumulative probability distributions (Fig. 2) and lifetime health advisory recommended by U.S. EPA (LHA, 70 ng/L for PFOA, PFOS or combined), the over-LHA rates were estimated to be 3.4% for PFOA, 3.2% for PFOS, and 6.4% for combined. According to previous reports on the U.S. EPA's third Unregulated Contaminant Monitoring Rule (UCMR3), where the minimum reporting level for PFOA and PFOS were 20 ng/L and 40 ng/L, respectively, detection frequencies for PFOA and PFOS across 4864 public water supplies in the U.S. were 2.0% and 2.2%, respectively

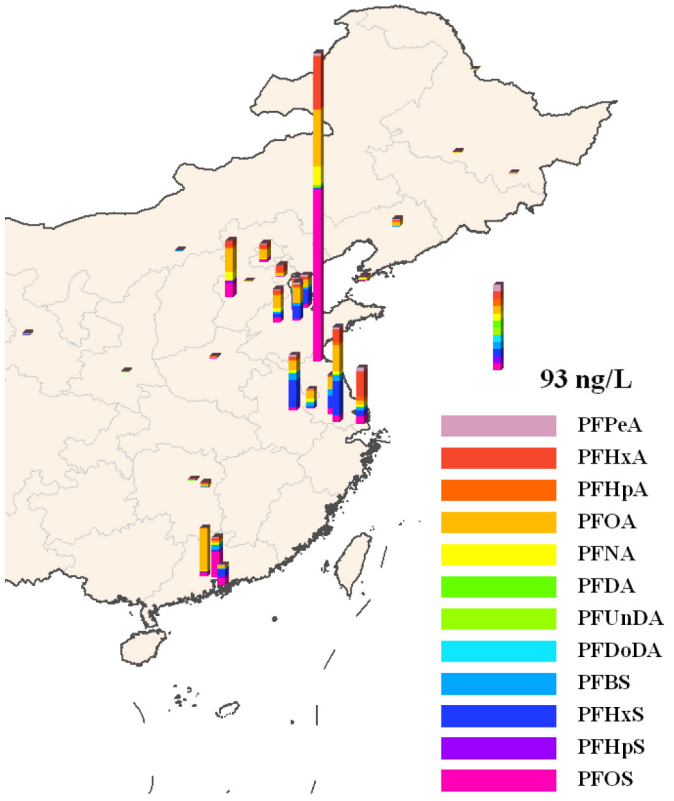

Fig. 3. Spatial distributions of PFAAs in drinking water in China.

(U.S. EPA, 2016a, 2016b). In the present investigation, detection frequencies > 20 ng/L for PFOA and > 40 ng/L for PFOS among 166 drinking water samples were 13.9% and 2.4%, respectively. We noted that UCMR3 included all U.S. public water systems serving > 10,000 people and 800 representative smaller public water systems, while our study targeted Chinese DWTPs that serve a total population of about one hundred million urban consumers. Although differences in sampling design preclude a direct comparison with previously reported data in the U.S., the data reported herein indicate more widespread and higher levels of PFOA contamination in China relative to the United States.

The spatial distribution of PFAAs in drinking water revealed relatively high total concentrations in China's east coastal region and the Pearl River Delta (Fig. 3), which may be related to the relatively developed economy in these regions. The highest concentrations of PFOA and PFOS were detected in the Lianyungang City drinking water, with mean concentrations of 61.4 ng/L (range: 38.32–78.56 ng/L) and 168.2 ng/L (range: 137.8–237.0 ng/L), respectively. The mean concentration of PFOA in Foshan City drinking water (45.5 ng/L; range: 0.32–205.6 ng/L) was the second highest, followed by that from Wuxi City (27.8 ng/L; range: 11.1–54.1 ng/L). For PFOS, Dongguan City drinking water had the second highest mean concentration (26.7 ng/L; range: 14.4–42.5 ng/L), followed by Shijiazhuang City (14.7 ng/L; range: 8.7–20.7 ng/L). The concentrations of PFOA and PFOS in drinking water were also reported in eight of the 28 cities investigated in this study in 2002–2006, including Shenyang, Beijing, Xi'an, Dalian, Harbin, Shenzhen, Shanghai, and Nanjing (Jin et al., 2009; Mak et al., 2009). The mean concentrations for PFOA in Shenyang, Beijing, Xi'an, Dalian, Harbin, and Nanjing and those for PFOS in Beijing, Xi'an, Dalian, Harbin, Shanghai, and Nanjing were higher in this report than those in the drinking water collected in 2002–2006 (Table S4), suggesting of an increasing trend in concentration in most cities.

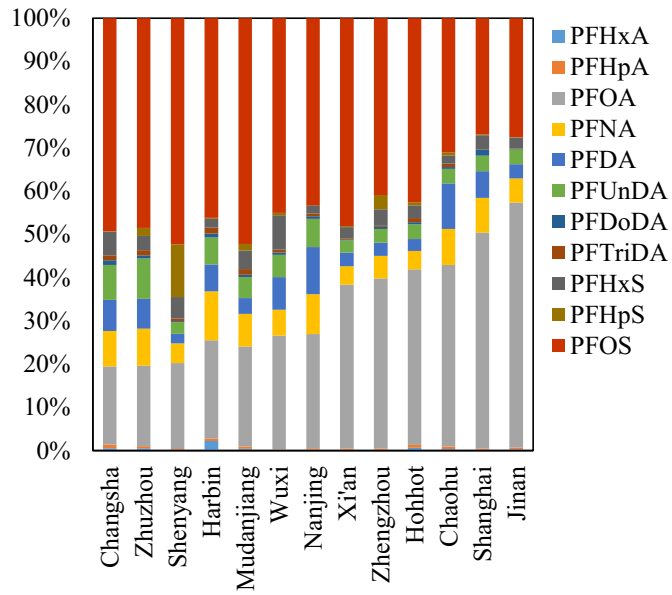

Fig. 4. Profiles of PFAAs in blood samples in the studied Chinese cities.

3.2. Human exposure to PFOA and PFOS and relationship with routine drinking water exposure

Among eight PFCAs (C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, and C_{13}) and three PFSAs (C_6, C_7, and C_8), PFOA and PFOS were detected in almost all blood samples (846/847), and PFNA, PFDA, PFUnDA, and PFHxS were detected in 99% (840/847), 98% (832/847), 97% (822/847), and 86% (729/847), respectively. The results for all eleven PFAAs (including frequencies of detection, mean, geometric mean and maximum concentration) are provided in Table S5. The highest and lowest total PFAA concentrations were found in Wuxi City (32.9 ng/mL; range: 10.0–96.0 ng/mL) and Xi'an City (3.45 ng/mL; range: 0.98–13.8 ng/mL), respectively. In general, PFOA and PFOS were the predominant PFAAs in blood (Fig. 4). Notably, PFOA in blood from Jinan, Chaohu, and Shanghai accounted for 42–57% of the total concentration of PFAAs, even higher than the contribution of PFOS (27–31%). PFOS is typically considered the major congener in human blood samples (Chen et al., 2009; Wang et al., 2015) due to its longer half-life in humans (1971 days) relative to PFOA (840 days) (Olsen et al., 2007; Bartell et al., 2010) and its relatively high daily intake (Chen et al., 2018). The high proportion of PFOA in the blood samples suggested that humans in these three cities were exposed to high PFOA compared to PFOS.

National PFOA and PFOS serum or blood levels have also been reported in the general populations of many other countries. Several papers investigated the ratio between serum and whole blood in adults, with the ratios of 1.93–2.3 in a study in Norway's study (Poothong et al., 2017) and ~ 2 in a U.S. study (Ehresman et al., 2007). To allow comparison, the PFOA and PFOS concentrations in whole blood in this study were translated to serum concentrations by multiplying by a factor of 2, based on a previous report (Kannan et al., 2004). The population- weighted geometric mean concentrations (across the 13 cities) of PFOA and PFOS in serum were 4.1 ± 1.2 ng/mL and 5.2 ± 1.3 ng/mL, respectively. The median levels of PFOA and PFOS in plasma or serum from Singapore, Japan, and the Czech Republic were 0.76–2.1 ng/mL and 2.4–8.3 ng/mL, respectively (Liu et al., 2017; Yamaguchi et al., 2013; Sochorová et al., 2016); the geometric means in plasma or serum in the general populations of Canada, South Korea, and the U.S. were 2.56, 2.85, and 1.94 ng/mL for PFOA and 9.10, 10.23, and 4.99 ng/mL for PFOS, respectively (Haines and Murray, 2012; Lee et al., 2017; U.S. CDC, 2018); and the mean concentrations in serum samples from Spain were 0.45 ng/mL for PFOA and 0.77 ng/mL for PFOS (Gómez-Canela et al., 2015). Thus, the PFOS level in human

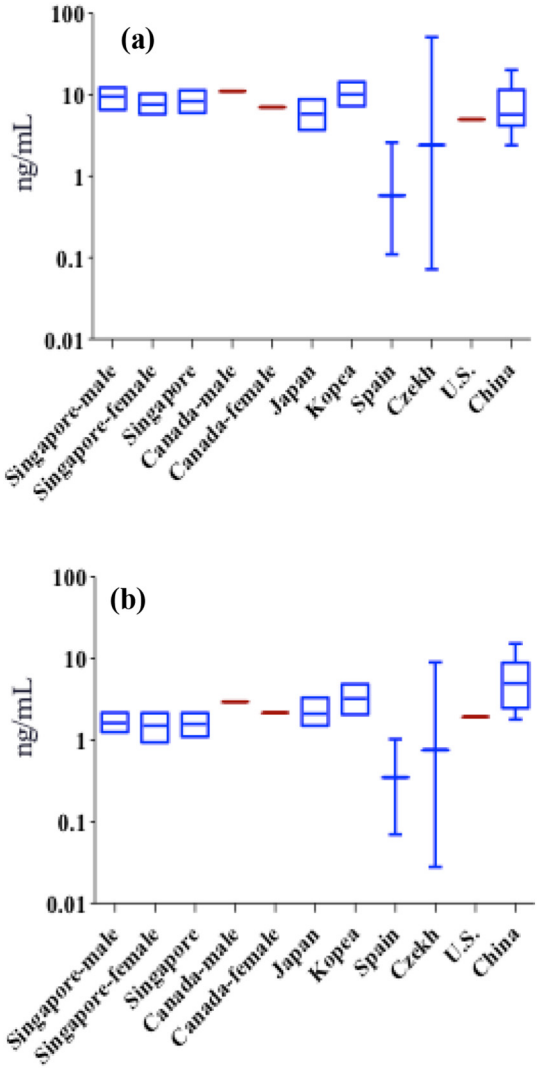

Fig. 5. Comparison of (a) PFOS and (b) PFOA concentrations detected in human blood in China (this study) with those detected in other countries (other studies of which references see the text). Box plots show 25th -75th percentile (box), minimum – maximum (whiskers), median values (blue lines), and geometric means (red lines). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

plasma in China was higher than that in the U.S., the Czech Republic, and Spain, but lower than that in Japan, South Korea, Singapore, and Canada (Fig. 5a). Notably, the PFOA concentrations in human plasma in China were higher than those in all other countries (Fig. 5b).

As described above, only PFOA, PFNA, PFDA, and PFOS were detected in both > 70% blood samples and water samples, and a correlation analysis was applied to explore their relationship of concentrations between the geometric mean blood concentrations in the general population of 13 cities and the corresponding mean drinking water concentrations. Although individual differences exist both in exposure (water consumption rate) and toxicokinetics (rate of excretion, i.e. half-life), the correlation between concentration in drinking water and in human blood for PFOA was significant ($r = 0.87$, $n = 13$, $p < 0.001$) (Fig. 6), indicating that drinking water was an important contributor to human exposure to PFOA. The concentrations of PFOS, PFNA, or PFDA in drinking water did not significantly correlated with those in blood, possibly due to their relatively high bioaccumulations in food such as aquatic organisms (Liu et al., 2011) and therefore having relatively low contribution from drinking water to total intake. Although previous studies determined that drinking water was a primary contributor to

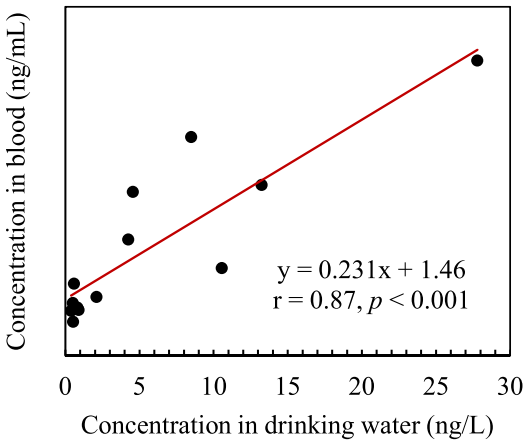

Fig. 6. Correlation of PFOA concentrations in drinking water and human blood.

total PFOA intake, based on correlation between PFOA concentrations in drinking water and in blood, those studies focused on regions where drinking water was heavily contaminated with PFAAs (Emmett et al., 2006; Hölzer et al., 2008) or the concentrations in drinking water widely ranged from 6 or 60 ng/L to several μg/L (Post et al., 2009; Hoffman et al., 2011). And a significant difference was also observed between the serum concentrations of PFOS or PFOA and detection in drinking water (Hurley et al., 2016). To the best of our knowledge, this is the first report of a correlation between PFOA concentrations in drinking water and in human blood for routine exposure of the general population. The ratio between serum and drinking water concentrations for PFOA was estimated to be 231 (slope × 1000), higher than those reported in previous papers (Emmett et al., 2006; Hoffman et al., 2011; Post et al., 2009).

3.3. RSCs and HBVs of PFOA and PFOS in drinking water

To develop drinking water criteria for PFOA and PFOS, the RSCs of drinking water were estimated by Eq. (1), where DI_{water} is the daily intake via drinking water (ng/kg/day), C_w is the PFOA or PFOS concentration in drinking water (the mean concentration in drinking water from each city was used, Table 1), D_w is the daily drinking water consumption, BW is body weight, and EDI was the estimated daily intake (calculated using the geometric mean blood concentrations of PFOA and PFOS via a one-compartment toxicokinetic model; Supplementary Materials).

$$\%RSC = \frac{DI_{water}}{EDI} * 100\% = \frac{C_w D_w}{BW * EDI} * 100\% \quad (1)$$

For the general population in this study, the average water intake (1.7 L) and the average body weight of adults (65 kg) were set to those reported by the Major Science and Technology Program for Water Pollution Control and Treatment of China (2014–2017) (RCEES-CAS, 2018). The EDI in 13 cities was 0.24–2.13 ng/kg/day for PFOA and 0.19–1.87 ng/kg/day for PFOS (Table 1). The slope of the linear regression of DI_{water} vs. EDI for PFOA was 0.23 ± 0.03 (90%CI: 0.17–0.29, $p < 0.01$; Fig. S1), indicating that the PFOA RSC for drinking water was 23 ± 3% (90%CI: 17–29%). This value was similar to the default RSC (20%) used to set a drinking water health advisory for PFOA (U.S. EPA, 2016a). Based on the mean RSC, we calculated an HBV for PFOA in drinking water in China of 85 ng/L (Eq. 2). In Eq. 2, RfD is the reference dose of PFOA (20 ng/kg/day) and was derived from a study on developmental toxicity in mice, and D_w/BW was set to 0.054 L/kg/day to represent the 90th percentile water ingestion for women according to the U.S. EPA's 2016 LHA for PFOA (U.S. EPA, 2016a). Thus, the observed over-HBV rate in drinking water was 2.7%.

Table 1
Estimated Daily Intake, Daily Intakes from drinking water, and RSCs of drinking water for PFOA and PFOS from 13 cities in China.

City	PFOA				PFOS			
	EDI (GM ± GSD) ng/day/kg	Mean con. in water ng/L	DI_{water} ng/kg/day	RSC %	EDI (GM ± GSD) ng/day/kg	Mean con. in water ng/L	DI_{water} ng/kg/day	RSC %
Changsha	0.25 ± 1.82	0.53	0.01	6	0.38 ± 1.92	0.14	0.004	1
Chaohu	0.63 ± 1.72	10.56	0.28	44	0.25 ± 1.83	3.33	0.087	35
Harbin	0.52 ± 1.75	0.58	0.02	3	0.55 ± 2.19	0.05	0.001	0.2
Hohhot	0.38 ± 2.30	0.50	0.01	3	0.36 ± 2.14	0.07	0.002	1
Jinan	1.23 ± 1.81	13.24	0.35	28	0.32 ± 2.15	5.01	0.131	41
Mudanjiang	0.35 ± 1.76	0.82	0.02	6	0.40 ± 2.14	< LOD	0.0003[a]	0.07
Nanjing	1.58 ± 1.52	8.50	0.22	14	1.35 ± 1.86	1.09	0.029	2
Shanghai	1.18 ± 2.73	4.24	0.11	9	0.36 ± 2.78	9.09	0.238	65
Shenyang	0.84 ± 1.74	4.56	0.12	14	1.10 ± 2.29	0.25	0.007	1
Wuxi	2.14 ± 1.65	27.79	0.73	34	1.87 ± 2.01	7.52	0.197	11
Xi'an	0.32 ± 1.70	0.39	0.01	3	0.19 ± 2.35	0.44	0.012	6
Zhengzhou	0.33 ± 1.87	0.89	0.02	7	0.19 ± 1.89	0.11	0.003	1
Zhuzhou	0.42 ± 1.61	2.11	0.06	13	0.58 ± 1.83	0.33	0.009	1

[a] PFOS was not detected in drinking water, and the concentration in drinking water was replaced with LOD/sqrt(2)(0.0106 ng/L). GM: geometric mean; GSD: geometric standard deviation.

$$HBV = \frac{RfD * BW * RSC}{D_w} \quad (2)$$

As for PFOS, no correlation of concentrations between blood and drinking water was observed, and thus the mean RSC (12.7 ± 5.8%) was calculated based on the RSCs of 13 cities in Table 1. This was less than the default RSC (20%) adopted as a drinking water health advisory (U.S. EPA, 2016b). However, Zhang et al. (2010) estimated a RSC for PFOS in drinking water of ~8% based on a nationwide total diary study, similar to the mean RSC proposed in this study. Using the mean RSC of 12.7% estimated in the present paper, we calculated a PFOS HBV of 47 ng/L by Eq. 2, where an RfD was 20 ng/kg/day PFOS, based on a study on developmental toxicity in rats (U.S. EPA, 2016b). Thus, the observed over-HBV rate was 4.6%, indicative of a relatively high human risk exposure from drinking water compared with PFOA. Considering that the U.S. EPA proposed a RSC range of 20–80% to avoid an extremely low limit for a single source that might represent a nominal fraction of the total exposure (U.S. EPA, 2000), the RSC of 20% was also used in estimation of a PFOS HBV. Thus, the PFOS HBV was 70 ng/L, same as U.S. EPA HBV (U.S. EPA, 2016a, 2016b).

While the RfDs based on the sensitive developmental toxicity in mice were used to estimate the PFOS and PFOA HBVs in this study, epidemiological studies have reported a variety of responses associated with exposure to PFOA or PFOS. The 5% lower benchmark dose ($BMDL_5$) values of PFOS that resulted in increased cholesterol, impaired vaccination response in children, and decreased birth weight were 21–29, 10.5, and 21 ng/mL, respectively, and those of PFOA linked to increased cholesterol, increased serum level of alanine transferase, and decreased birth weight were 9.2–9.4, 21, and 4–11 ng/mL, respectively (EFSA, 2018). These threshold PFOA values for increased cholesterol and decreased birth weight are both lower than the potential increases in serum concentrations (14.7 ng/mL for PFOA) caused by consuming drinking water at the HBV (predicted based on one-compartment toxicokinetic model by excluding other exposure allocations), suggesting that the PFOA HBV estimated here would not be sufficiently protective. The PFOA HBV may be required revision when the uncertainties associated with the epidemiological studies are better understood through future studies. For PFOS, we estimated serum values of 14.5 and 21.6 ng/mL, based on consumption of drinking water with PFOS concentrations at the HBVs of 47 and 70 ng/L corresponding to RSCs of 12.7% and 20%, respectively. The PFOS serum concentrations estimated in both cases were higher than $BMDL_5$ for decreased vaccination response in children.

4. Conclusion

Overall, this study reports a large-scale investigation of PFAA contamination in drinking water and human blood samples across several major cities in China. For the first time, significant correlation was reported between PFOA concentrations in drinking water and in the blood of the general population. The mean RSCs for PFOA and PFOS in drinking water were 23% and 12.7%, respectively, and the proposed HBVs for China's drinking water were 85 ng/L and 47 ng/L, respectively. These results are anticipated to support improved drinking water quality management.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.02.009.

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