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Review

A short review on human exposure to and tissue distribution of per- and polyfluoroalkyl substances (PFASs)

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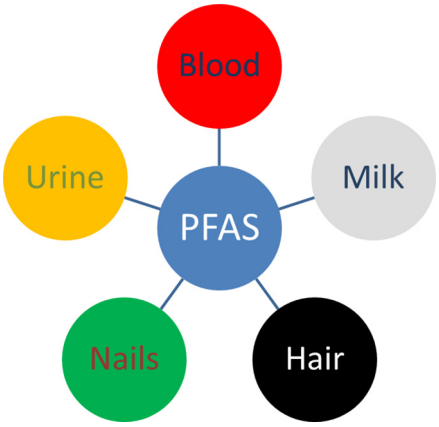
HIGHLIGHTS

- PFOS and PFOA were predominant in human blood and milk.
- Urine showed higher elimination of short-chain PFASs than other matrices.
- PFASs in blood and urine were found to be related to age and gender.
- PFASs in human milk were associated with mothers' age and parity.

GRAPHICAL ABSTRACT



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ABSTRACT

PFASs are widely distributed in natural and living environment and can enter human bodies via different routes. Many studies have reported that PFASs may be associated with human diseases, such as urine acid and thyroid diseases. In this study, we reviewed PFAS levels in human bodies reported in past seven years, including blood, urine, milk, and tissues (hair and nails). Most studies focused on human blood. Blood type, spatiality, human age, and gender were found to have a strong relationship with PFAS levels in blood samples. The PFAS distribution in urine samples was reported to be associated with the chain length of PFASs and human gender. Urinary excretion was found to be an important pathway of PFAS elimination. PFAS levels in human milk might be affected by various factors, such as mothers' age, dietary habit, parity of mothers and the interval of interpregnancy. Data in hair and nails remain very limited, but these matrices offer a non-invasive approach to evaluate human exposure to PFASs.

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Contents

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are one kind of chemicals with very unique properties (having both hydrophilic and hydrophobic functionalities). They are widely distributed in our daily-use products, including carpets, furniture, paper, cloth coatings, Teflon products, and fire-fighting foams (Ahrens and Bundschuh, 2014; Begley et al., 2005; Clara et al., 2008; Giesy and Kannan, 2002; Keawmanee et al., 2015; Lau et al., 2004; Z. Li et al., 2013; Paul et al., 2009; Prevedouros et al., 2006; Route et al., 2014; Y. Wang et al., 2010). The PFAS-containing products (e.g., furniture and carpets) usually have very long life spans. Thus, the release of PFASs from these products can last for many years, resulting in wide occurrence of PFASs in indoor dust and air (Fraser et al., 2013; Haug et al., 2011; Jogsten et al., 2012; Karaskova et al., 2016). Besides indoor dust ingestion, dietary intake and drinking are also important pathways for human exposure to PFASs (Clarke et al., 2010; Domingo, 2012; Domingo et al., 2012; Schwanz et al., 2016).

It was reported that >90% perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) could be assimilated by male rats within 24 h (Gibson and Johnson, 1979). Thus, oral uptake of PFASs can result in rapid and almost complete assimilation of these compounds, making their hazardous to humans. PFASs have been widely found in various food items (e.g., vegetables, dairy products, beverages, eggs, meat products, fish and shellfish) (Chu et al., 2016; Gebbink et al., 2015; Haug et al., 2010a; Hlouskova et al., 2013; J. Wang et al., 2010; Wu et al., 2012; Zhang et al., 2010a). Fish and shellfish consumption appeared to be the dominant PFAS exposure pathway (Haug et al., 2010b). Drinking water is another important pathway for human PFAS exposure. Among different types of drinking water, tap water showed higher PFAS levels than raw and bottled water (Boiteux et al., 2012; Heo et al., 2014; Schwanz et al., 2016).

Human biomonitoring (HBM) is an ideal instrument to estimate chemical substances and/or its biotransformation products in human biological fluids or tissues, which considers all sources and routes of uptake. HBM methods are sensitive, effective, and cost effective to elucidate human metabolism and toxic mechanism of chemicals, which makes it an ideal tool for risk assessment and risk management (Angerer et al., 2007). Blood (including whole blood, serum or plasma) is an important and excellent matrix to assess human internal dose of PFASs. PFOS was always the main chemical detected in blood samples. PFOS were detected in 100% of serum samples for Czech adult population, and the median concentration (2.43 ng/mL) was the highest in all PFASs (Sochorova et al., 2017). PFOS also accounted for the highest median concentration (4.15 ng/mL), followed by PFOA (1.3 ng/mL) in serum for population from various locations throughout Korea, and geographical differences were found in the concentrations of target PFASs (Cho et al., 2015). Serum PFOS concentrations in Chinese fishery employees were exceptionally high (10,400 ng/mL) compared to control group in the same city (18.7 ng/mL), the contaminated fish in Tangxun Lake was supposed to be the main exposure source (Zhou et al., 2014). Haug et al. (2010b) analyzed serum samples from 175 inhabitants in Norway, PFOS was detected with highest median concentration (25 ng/mL), followed by PFOA (3.6 ng/mL), and diet especially seafood were concluded to be major sources of PFASs. Among these studies, the concentrations of PFASs in human blood were related with geographical locations, diet habits and working habits.

Generally, most PFASs showed low elimination rate in human body (Stahl et al., 2011). For example, the geometric mean half-lives of serum elimination for PFOS and PFOA were 4.8 years (95% confidence intervals (CI), 4.0–5.8) and 3.5 years (95% CI, 3.0–4.1), respectively (Olsen et al., 2007). Therefore, the long half-life of PFASs in human body may potentially cause various health problems. A study in the United States (U.S.) adults reported that high PFOA and PFOS levels in blood were potentially related to chronic kidney disease (CKD) (Shankar et al., 2011). Occupational studies also observed a significant, positive relation between PFOA level and uric acid in workers subjected to elevated PFOA exposure (Costa et al., 2009; Sakr et al., 2007; Steenland et al., 2010). Two studies reported that statistically significant associations existed between serum PFOA concentrations in employees and the levels of thyroid stimulating hormone (TSH) or free thyroxine (FT_4) (Olsen et al., 1998; Olsen and Zobel, 2007). Furthermore, it was reported that PFAS exposure was positively associated with asthma and asthma related biomarkers in Taiwanese children (Dong et al., 2013). In addition, higher prevalence of attention deficit/hyperactivity disorder (ADHD) was found to be associated with higher exposure of all PFASs in U.S. children (Hoffman et al., 2010) (Stein and Savitz, 2011). Besides, PFAS exposure exhibited negative effects on human immunity. Serum PFAS levels in children aged 5 and 7 years were consistently found to be negatively correlated with immune response to routine childhood immunizations (Grandjean et al., 2012).

Due to the potential harmful effects on environment and human health, the production and regulation of PFASs have changed with time. In 2000, 3M first announced a global phase-out of its products containing C6, C8 and C10 PFASs and replaced them with shorter C4 PFASs (e.g., perfluorobutane sulfonic acid or PFBS) products. Eight major PFAS manufacturers joined the United States Environmental Protection Agency (USEPA) 2010/15 PFOA Stewardship Program in 2006 to work towards the elimination of long-chain perfluoroalkyl carboxylic acids (PFCAs) and their potential precursors by 2015. In addition, The EU Directive 2006/122/EC has restricted the use, and placement in the market of PFOS and its related substances in 2008. PFOS and

perfluorooctane sulfonyl fluoride (POSF) related compounds were listed under Annex B of the Stockholm Convention in 2009. As for PFOA, USA and Canada have devoted to eliminate PFOA, its salts, and precursors (Vierke et al., 2012). Although a Europe-wide regulation is absent for PFOA, some European countries have presented national regulatory activities. For example, in Norway, PFOA was banned from consumer products in 2013, and maximum PFOA concentration in drinking water was recommended in Germany. Some shorter chain PFASs, like PFBA and PFBS were produced as alternatives for C8-PFASs. In China, F-53B was one alternative products of PFOS, which has been used for many years. The different regulations of PFASs led to time or region-dependent production or environmental distributions of PFASs.

The physicochemical properties of PFASs, such as acid dissociation constant (pKa), air–water partition coefficient (K_{AW}), octanol–water partition coefficient (K_{OW}), and liquid vapour pressure (P_L), can be used to understand the global transport and fate of these compounds. Few studies investigated physicochemical properties of PFASs. K_{OW} was commonly used to indicate hydrophobicity, but it was difficult using experimental methods to measure K_{OW} of PFASs due to its low solubility in octanol (Du et al., 2014). Wang et al. (2011) estimated physicochemical properties of PFASs by using COSMOtherm. The results showed that K_{AW} and K_{OW} increased with the increase of perfluorinated chain length for linear PFASs with the same functional group; and the K_{AW} values were significantly affected by the functional groups for PFASs with the same perfluorinated chain length but different functional groups. The differences of physicochemical parameters for PFASs might affect their accumulation in human. For instance, shorter chain ($C \leq 8$) PFASs were dominant in urine samples (Zhang et al., 2013a) might be related with the low K_{OW} which means more water-soluble of these compounds.

Since PFASs were found to be related to human health problems, it is crucial to establish the data library of PFASs in human samples. In this study, we reviewed recent studies on PFASs in human blood, urine, milk, and human tissues (e.g. hair and nails). The potential distribution characteristics were also analyzed, which may benefit future human biomonitoring of PFASs.

2. Methods

Based on the online database search (Web of Science) of peer-reviewed articles, papers published between 2010 and 2017 were selected to analyze PFAS distributions in human blood, urine, milk, and human tissues. We summarized the articles published 2010–2017, but the data summarized was sampled between 1996 and 2016. There were 87, 11, 4, 5, and 2 papers were summarized for human blood, milk, urine, hair, and nail analysis, respectively. Since 2010 to 2017, the number of published articles for human blood showed a significantly increase (the numbers of articles in 2014–2017 were 15, 16, 21, and 22, respectively, and total number of articles in 2010–2013 was just 24), which indicated increasing attention for human biomonitoring on PFAS exposure.

The reported mean, median, and ranges of concentrations in human blood from different countries were compiled in Table S1 of Supporting Information. In addition, number of samples, the age and gender of reported populations were also added in Table S1. Occurrence of 7 PFASs with higher levels in blood samples (including serum, plasma, and whole blood) was plotted in Fig. 1 based on the median concentrations reported in related articles. Median concentrations of 18 kinds of PFASs in blood samples from population located in 22 countries were plotted in Fig. 2. People from nine different countries were analyzed respectively to figure out differences in PFAS concentrations between two genders, and the results were plotted in Fig. 3. To analyze PFAS concentrations in human milk, the mean, median values, and ranges of concentrations were summarized in Table S2 of Supporting Information. And 8 kinds of PFASs with higher levels in human milk samples collected from 8 different countries were potted in Fig. 4. The overall median (or mean) concentrations of one country shown in Figs. 2–4 were calculated with the reported median (or mean) concentrations from different articles in the same country. Values below the LOQ or LOD are considered as zero, and not considered into the calculation. Due to the limited data, all the available PFASs concentrations in urine, hair, and nail were all outlined in Table 1.

3. Human biomonitoring

3.1. Human blood

3.1.1. PFASs in whole blood, serum, and plasma

Fig. 1 shows PFAS concentrations in different kinds of blood samples (including: whole blood, serum, and plasma). PFAS concentrations in blood samples follow an overall order as: serum > plasma > whole blood. PFASs preferred to accumulate in body compartments with

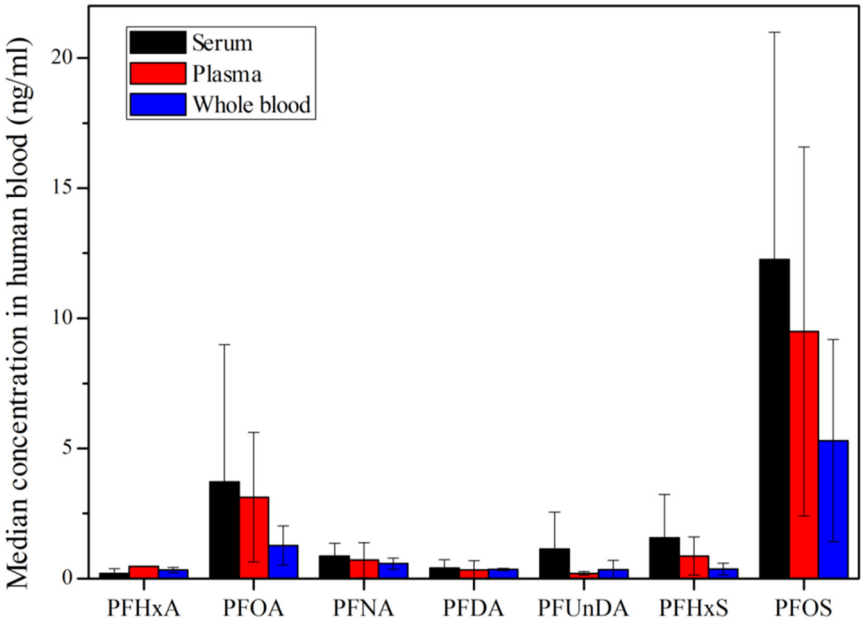

Fig. 1. The median concentrations of seven PFASs with higher levels in human whole blood, serum, and plasma.

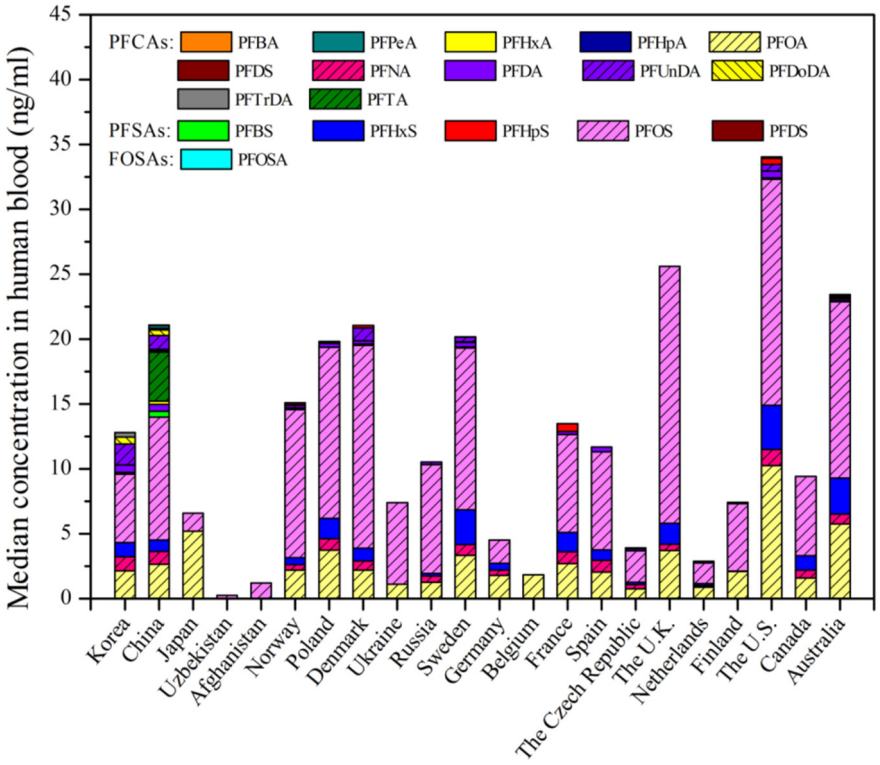

Fig. 2. The median concentrations of PFASs in human blood from different countries.

protein-rich contents, such as kidney, liver and blood (Verreault et al., 2005), the ability of PFASs bind to serum proteins may explain bioaccumulation behavior of these compounds (Han et al., 2003; Luebker et al., 2002) and serum albumin was the main bonding target for PFASs (Bischel et al., 2010; Chen and Guo, 2009; Jones et al., 2003; MacManus-Spencer et al., 2010). PFOA and perfluorononanoic acid (PFNA) were reported to be >90.0% and 99.9% bound to human serum albumin (HSA), respectively (Bischel et al., 2010; Han et al., 2003). Jones et al. (2003) found all PFOS was bound to bovine serum albumin (BSA) when the concentration was in excess of 1 mg/mL. Chen and Guo (2009) investigated binding ability of five perfluoroalkyl acids (PFAAs) to HSA, the bonding constants of PFOS and PFOA on specific site (tryptophan residue) to HSA were 2.2×10^4 M^{-1} and 2.7×10^5 M^{-1}, respectively. Perfluorododecanoic acid (PFDoDA) had a weaker binding affinity to tryptophan residue (Trp^{214}) than PFOS and the binding constant was not obtained, and two four-carbon PFAAs (PFBA and

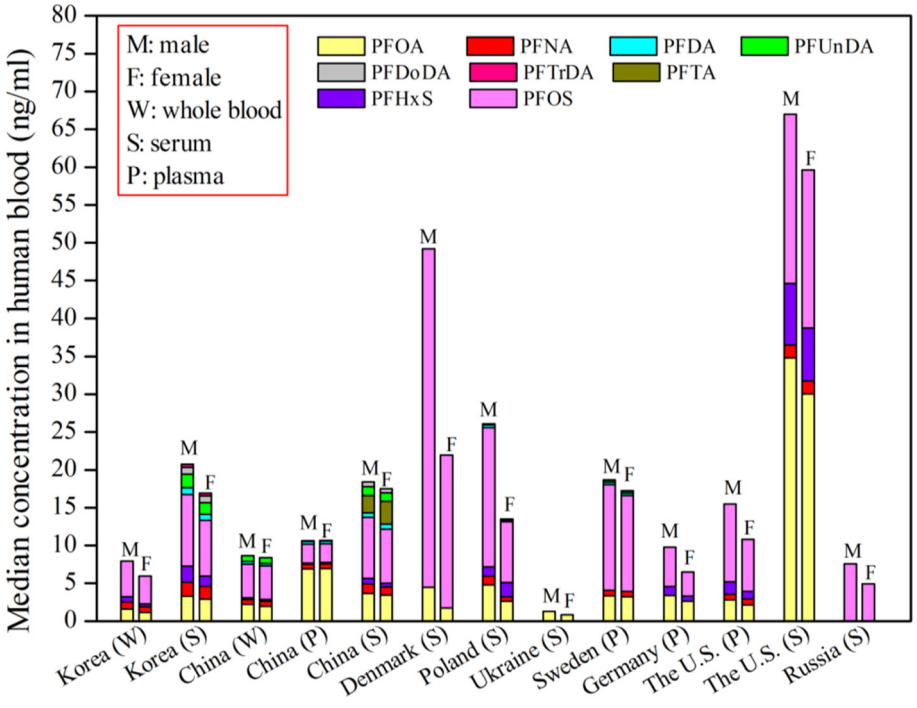

Fig. 3. The median concentrations of several common PFASs in human blood with different genders.

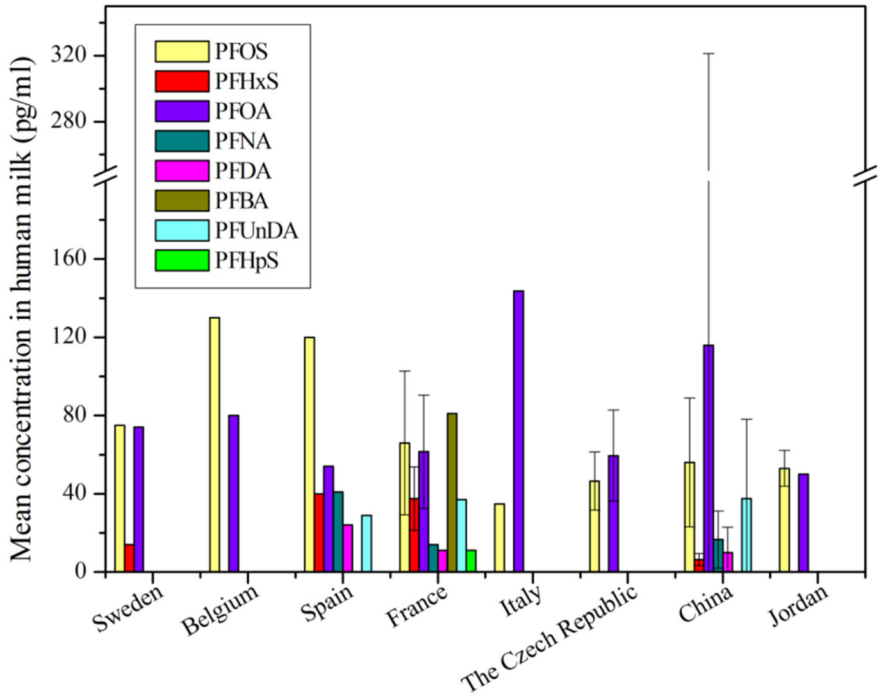

Fig. 4. The mean concentrations of common PFASs in human milk from different countries.

PFBA) showed no significant interaction with protein at Trp^{214} site. These results indicated the binding affinity of PFASs to HSA was related to carbon chain length and acid head group of PFAA. Longer chain PFAAs were more toxic than shorter ones (Chen and Guo, 2009), and similar results were reported in the study of Qin et al. (2010). Qin et al. (2010) reported that PFOA and perfluorodecanoic acid (PFDA) exhibited remarkable influence on BSA. The dominant intermolecular forces in the binding of PFASs to BSA and HSA were attributed to van der Waals forces and hydrogen bonds (Chen et al., 2015; Qin et al., 2010). Karrman et al. (2006) found that higher levels of PFOS and PFOA were measured in human serum and plasma than whole blood, as PFOS and PFOA can bind to serum and/or plasma proteins (Han et al., 2003; Jones et al., 2003; Luebker et al., 2002). In addition, PFOS and PFOA were found to be the dominant compounds in human blood samples (H.Y. Kim et al., 2014; Roosens et al., 2010; Wan et al., 2013; Zhang et al., 2010b). Cho et al. (2015) detected PFAS levels in serum of general populations from three different geographical areas in Korea (Seoul, Busan and Yeosu). PFOS showed the highest median concentration (4.15 ng/mL) followed by PFOA (1.30 ng/mL), which was relatively lower than the results reported by Ji et al. (2012a) with the median concentration of PFOS and PFOA at 8.21 and 3.50 ng/mL (Table S1). Such observation was also similar to previous findings that PFOS was found at the highest concentration in human serum followed by PFOA in the world, and their concentrations were generally an order of magnitude higher than the other PFASs. Other PFASs (e.g., PFNA, perfluorobutanoic acid (PFBA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluoroheptane sulfonate (PFHpS), PFDoDA, perfluorotridecanoic acid (PFTrDA), and perfluoroundecanoic acid (PFUnDA)) were detected with much lower concentrations than those of PFOS and PFOA, generally <2 ng/mL (Eriksson et al., 2017; Fromme et al., 2017; Fu et al., 2014; D.H. Kim et al., 2014; Wan et al., 2013).

Several studies have evaluated temporal trends of PFASs in human blood. PFOS and PFOA concentrations in human blood appeared to decrease from 2000 to 2012 in the U.S. populations (Gebbink et al., 2015; Olsen et al., 2017). The declining trend of PFOS was also supported by Kato et al. (2011), but PFOA concentration was found to remain unchanged from 2003 to 2008 in the same study. In Germany, PFOS and PFOA concentrations in plasma showed a sharp increase from 1982 to 1986, and then a strong decrease was observed in PFOS concentration between 2001 and 2010, the concentration of PFOS in plasma dropped to 4 ng/mL (about one tenth in 1980s). But PFOA concentration fluctuated between 4.8 and 6.3 ng/mL after 1986, a decreasing trend appeared until 2008 (Schroter-Kermani et al., 2013). Similar trends for PFOS concentrations changes were observed in Norwegian males, PFOS concentrations in serum increased about five-fold from 1979 to 2001 and decreased by 26% from 2001 to 2007. PFOA and PFHxS concentrations also increased between 1979 and 2001, but PFOA concentration decreased by 23%; PFHxS showed no decrease trend, but other PFASs (PFNA, PFDA and PFUnDA) increased continuously throughout the entire study period (1979 to 2007) (Nost et al., 2014). Increased temporal trend of PFOS was consistent with the increase and levelling off trend of global production and releases amounts of PFOS and its precursors until the mid-1990s, and voluntary emission reduction measures was implemented until 1997, and stronger decline of PFOS would be contributed to phase-out of PFOS and its precursors by the main producer (Paul et al., 2009). Glynn et al. (2012) investigated 13 PFAAs and perfluorooctane sulfonamide (FOSA) in serum from Swedish primiparous women, the concentrations of PFNA, PFDA, PFBA, and PFHxS were increased by 4.3%, 3.8%, 11%, and 8.3% from 1996 to 2010, respectively. Whereas, FOSA, PFOS, PFDA, and PFOA concentrations decreased by 22%, 8.4%, 10% and 3.3%, respectively. The decrease trend implied reduce and elimination of the exposure sources to latter compounds, whereas the sources of exposure to former compounds displayed increase. Serum PFOS concentrations remained unchanged for Korean populations during the period of 1994–2008, whereas PFOA concentrations increased (Harada et al., 2010). Serum PFOS levels also increased over time in Japanese populations from 1983 to 1999 (Harada et al., 2007), PFOA concentrations declined obviously in high-exposed area (Osaka) but not in low-exposed areas (Sendai and Takayama) from 2003 to 2008 (Harada et al., 2010).

3.1.2. Geographical distribution and exposure pathways

Fig. 2 shows spatial distribution characteristics of different PFASs in human blood. In recent Korean studies, significant geographical differences were found. The population of Busan (H.Y. Kim et al., 2014)

Table 1
The mean (median) or range of PFAS levels in human urine, hair and nail.

Sample	n	Region	Mean (median) or range of PFAS concentrations												Ref.
Urine (ng/L)			PFBA	PFPeA	PFHxA	PFHpA	PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFBS	PFHxS	PFOS	
	30	Barcelona, Spain	483,545 (336966)	<740	30,068 (39422)	2567 (2182)	824 (664)	<40	743 (696)	3558 (3558)	<290	1050 (1041)	11,889 (2484)	<370	(Perez et al., 2012)
	86	Hebei, China				1.9 (0.82)	81 (19)	2.2 (1.7)	0.46 (0.22)	0.42 (0.30)			2.4 (1.1)	37 (25)	(Zhang et al., 2013a)
	63	Shanxi, China					12.9							49.6	(J. Li et al., 2013)
(Children)		Dae-gu, Korea		2340	731	1350						492			(D.H. Kim et al., 2014)
(Adult)		Dae-gu, Korea		2390	1380	495			495		442				(D.H. Kim et al., 2014)
(Adult)	54	Tianjin, China					11							23	(Zhang et al., 2015)
(Mother)	27	Tianjin, China					6							15	(Zhang et al., 2015)
Hair (ng/g)			PFBA	PFPeA	PFHxA	PFHpA	PFOA	PFNA	PFDA	PFBS	PFHxS	PFOS	PFDS	PFDoS	
	24	Barcelona, Spain	<0.18–39.3				<0.10–6.1	<0.01–1.3	<0.02–45.9	<0.09–10.7		<0.08–6.5			(Perez et al., 2012)
	53	Shanxi, China					0.69					1.06			(J. Li et al., 2013)
		Antwerp, Belgium	0.214	0.077	0.047	<0.017	0.046	<0.14–4			0.057	<0.097	0.03	0.046	(Alves et al., 2015)
	6	Seville city, Spain		<0.9–13	<0.2–8.9	<0.2–10	<0.6–1.6					<0.2–2.5			(Martin et al., 2016)
	6	Granada, Spain			<2–5.5	<2–7.1	<4–23.9					<2–9.9			(Rodríguez-Gómez et al., 2017)
Nail (ng/g)			PFOA	PFNA	PFDA	PFDoDA	PFTA	PFOS							
	63	Shanxi, China	0.24					1.04							(J. Li et al., 2013)
(Fingernail)		Dalian, China	1.75 (0.19)	28.7 (20.4)	7.41 (5.84)	11.8 (8.94)	9.82 (8042)	44.7 (33.5)							(Liu et al., 2011)
(Toenail)		Dalian, China	0.60 (0.19)	22.7 (16.8)	7.41 (5.87)	7.97 (6.02)	6.66 (5.72)	33.5 (26.1)							(Liu et al., 2011)

showed relatively higher PFAS levels than other cities in Korea, such as Yeosu (Cho et al., 2015), Seoul (Cho et al., 2015; Harada et al., 2010), Dae-gu (D.H. Kim et al., 2014) and Siheung (Ji et al., 2012a). Significant spatial variation in blood PFAS concentration also occurred in China (Fu et al., 2014; Li et al., 2011; Wan et al., 2013; Zeng et al., 2015; Zhang et al., 2011; Zhang et al., 2010b; Zhang et al., 2013b; Zhang et al., 2014). The median PFOS concentrations in blood samples collected from Shijiazhuang and Handan (22.6 ng/mL) (Zhang et al., 2013b) were almost 2–3 times higher than Hong Kong (7.65 ng/mL) (Wan et al., 2013) and Tianjin (12.2 ng/mL) (Zhang et al., 2014), and 5–15 times higher than Yuanyang (1.47 ng/mL) (Fu et al., 2014), Sinkiang-Uighur Autonomous Region (1.92 ng/mL) (Zeng et al., 2015), Nanchang (4.41 ng/mL) (Zhang et al., 2010b), Shenzhen (2.07 ng/mL) (Li et al., 2011), Shanghai (2.48 ng/mL) (Wang et al., 2016), and Beijing (0.97 ng/mL) (Shi et al., 2017) (Table S1). PFOS was the dominant compound in human blood samples in most regions, but PFOA was predominant in serum collected from Shenzhen with a median concentration of 6.72 ng/mL followed by PFOS (2.07 ng/mL). The median concentrations of PFOS in serum collected from Shijiazhuang and Handan (22.6 ng/mL) (Zhang et al., 2013b) were higher than that in Taiwan (8.52 ng/mL) (Hsu et al., 2013), The U.S. (8.6 ng/mL) (Olsen et al., 2012), France (2.96 ng/mL) (Dereumeaux et al., 2016), and Denmark (Bjerregaard-Olesen et al., 2016).

A positive and significant correlation between PFOS and perfluorohexane sulfonate (PFHxS) in human blood was found in previous studies (Cho et al., 2015; Ji et al., 2012a; Zhang et al., 2010b), and a positive association between PFOA and PFOS was also reported by Fu et al. (2014). Positive relationships between these compounds indicated that they might come from similar exposure sources. Geographical variations in blood PFAS concentrations could result from dietary intake, drinking water, and industrialization level of the study area (Falandysz et al., 2006; Guo et al., 2011; Post et al., 2012; Rylander et al., 2010; Weihe et al., 2008; Zeng et al., 2015). A number of studies have reported that dietary intake, especially fish and seafood consumption, is the predominant pathway for human exposure (Falandysz et al., 2006; Gulkowska et al., 2006; Guo et al., 2011; Haug et al., 2010b). Considering bioaccumulation and bio-magnification effects, species at high trophic levels of food chain could accumulate more PFASs (Yamada et al., 2014). High levels of perfluorotetradecanoic acid (PFTA) were detected in serum of Taiwanese aged 12–15 years old, with a mean concentration of 30.7 and 27.4 ng/g in boys and girls respectively (Table S1), which were attributed to a high fish consumption rate (Cho et al., 2015; Pan et al., 2010). Rylander et al. (2010) assessed plasma PFAS levels in middle-aged Norwegian women and found 'fish eaters' were detected with higher PFOS, PFHxS and PFNA levels than women in 'western' diet (more pizza, rice, meat, chocolate, bakery products, snacks dominated), but PFOA level showed no association with dietary consumption cluster. Zhang et al. (2011) and Zhang et al. (2010a) reported that fish and seafood consumption contributed most to PFOS exposure in Chinese adult while drinking water was just a minor exposure source. For residents living in coastal areas, seafood consumption is considered as a main dietary source of PFASs (Gulkowska et al., 2006). Weihe et al. (2008) reported whale meat consumption was dominant in human PFAS exposure from Faroe Islands. In recent study, fish consumption was reported to be positively correlated with levels of PFOS, PFNA, PFDA, and PFUnDA in cord blood in Shanghai, China (Wang et al., 2016). Meat consumption was reported to be positively related with serum PFNA and PFDA in Norwegian (Haug et al., 2010b), but serum PFOS, PFHxS, and PFNA in Norwegian middle-aged women were negatively correlated with meat consumption. It was reported that meat had no significant influence on human blood PFAS levels in Korea (Ji et al., 2012a). Instead, consumption of potato was proposed as an important determinant factor of several PFAS levels in Korean serums (Ji et al., 2012a). The contribution of other vegetables and dairy products to human PFAS exposure is not very clear and requires additional studies. Drinking water is recognized as one

of the most major exposure pathways of PFASs (Post et al., 2012). Significant relation between water source and serum PFOA level was reported (Emmett et al., 2006). Their results showed plasma PFAS concentrations of people exposure to PFAS contaminated drinking water were 4.5–8.3 times higher than the references. Nakdong River in Korea supplied the vast majority of drinking water to Busan and higher PFAS concentrations were detected in this river than other major rivers in Korea (Hong et al., 2013; Kim et al., 2012), which may result in higher human blood PFASs concentrations in Busan than other Korean cities. Similarly, contaminated drinking water in Uppsala, Sweden (Gyllenhammar et al., 2015) resulted in significant increase of PFHxS concentration in serum collected between 2001–2004 and 2006–2009 (Stubleski et al., 2016). Concentration of PFHxS in the same region showed 20% decrease in serum between 2006–2009 and 2011–2014, after the contaminated water was diluted with water from other sources (Stubleski et al., 2016).

In addition to significant geographical differences between countries, urban-rural gradients in blood PFAS concentrations were also reported. Donors living in urban Yuanyang contained higher serum PFOA concentrations than those in its rural district, this was attributed to significantly higher meat consumption frequency for urban residents, and the meat consumption was found positively related with PFOA concentration (Fu et al., 2014). Except for different dietary habits between urban and rural populations, different industrial and commercial level should also be responsible for the different PFAS levels in urban and rural areas. Furthermore, higher concentrations of total perfluoroalkyl acids (ΣPFAAs) were detected in urban population than rural population in Shijiazhuang (Zhang et al., 2013b). And people in agricultural and pastoral regions (low degree of industrialization) showed lower PFASs levels in blood samples. For example, the median concentrations of PFOS in Henan (Fu et al., 2014) and Sinkiang-Uighur Autonomous Region (1.47 and 1.92 ng/mL, respectively) (Zeng et al., 2015) were much lower than four cities around the Bohai Sea (5.02 ng/mL) (Guo et al., 2011) (Table S1). In addition, samples from underdeveloped countries, such as India (Kannan et al., 2004), Africa (Hanssen et al., 2010), and Afghanistan (Hemat et al., 2010), were always detected with low human PFAS concentrations.

3.1.3. Age and gender

Many researchers investigated the relationship between PFAS concentrations in human blood and age. PFAS concentrations in blood of Korean showed an increasing trend with age in several studies, such as donors in Busan (H.Y. Kim et al., 2014), Siheung (Ji et al., 2012a), Daegu (Ji et al., 2012b), Yeosu (Cho et al., 2015), and Busan and Seoul (Harada et al., 2010). Significant increases of PFAS levels with age were also reported in other countries including Norway (Haug et al., 2010b), China (Fu et al., 2014; Liu et al., 2009) and Japan (Harada et al., 2010). Higher PFAS levels in older age group were contributed by dietary intake (especially fish consumption) (Gulkowska et al., 2006), long biological half-lives of PFASs (Bartell et al., 2010), and longer exposure time (Calafat et al., 2007). However, Hsu et al. (2013) reported blood PFOS concentrations in Taiwanese increased with age, but the same trend was not found for PFOA. The similar findings were also reported in human blood in some other countries (Nilsson et al., 2010; Roosens et al., 2010). PFOS and PFOA concentrations in Chinese donors exhibited a significant increase and decrease with age, respectively (Zhang et al., 2011; Zhang et al., 2010b). The decrease of PFOA concentration in human blood over age was explained by a relatively higher exposure rate in infant and toddlers than adults. PFOA showed the highest concentrations among PFASs in Chinese indoor dust (Zhang et al., 2010a), and inhalation and ingestion of dust is one of the major PFOA pathways in young children (Zhang et al., 2010b). As PFAS levels in mothers and infants have shown a high positive relationship in several studies (Monroy et al., 2008; Roosens et al., 2010), breast milk is the other major exposure source of PFOA. In addition, PFOA was reported to be the most primary compound in drinking water (Haug et al., 2010a), and children generally drink more water in order to build their body weight (D.H. Kim et al., 2014). However, different results were also reported that PFAS levels in human blood of general populations in China (Wan et al., 2013; Yeung et al., 2006; Zeng et al., 2015) had no significant correlation with age. In an Australian study, PFHpA and 8:2 fluorotelomer sulfonic acid (8:2 FTSA) concentrations in serum tended to decrease with age, while PFHpS and PFOS showed an increase with age and PFHxS remained at the same level (Eriksson et al., 2017). Increasing PFAS levels in cord blood were found with the growth of maternal age in several studies (Shi et al., 2017; Wang et al., 2016), although a contradictory result was reported in an Odense study (Dalsager et al., 2016). PFOA level in cord plasma tended to increase with increasing gestational age, the same tendency reported for PFOS and PFHxS concentrations (Wang et al., 2016). Thus, there lacks a consistent conclusion on the relationship between PFAS concentrations in human blood and age.

Previous studies have reported significant difference in blood PFAS levels between sexes. A Korean study showed most PFAS concentrations in human blood were higher in males than females (H.Y. Kim et al., 2014), consistent with the findings of another Korean study with the exception of PFOS (Cho et al., 2015). Donors from Hong Kong also contained significant higher plasma PFASs (such as PFOS, PFOA, PFHxS and PFHxA) in males, except for PFUnDA which showed higher concentrations in females (Wan et al., 2013). PFOS and PFOA in Taiwanese serum were also detected with significant higher concentrations in males (Hsu et al., 2013). Gender-specific pattern was also seen for PFOS in populations living in most regions of China (e.g., Sinkiang-Uighur Autonomous Region (Zeng et al., 2015), Tianjin (Zhang et al., 2014), Henan (Fu et al., 2014)), where higher levels occurred in males, while no statistically significant differences between two genders were observed in cord serum and plasma of Beijing and Shanghai, China, respectively (Shi et al., 2017; Wang et al., 2016). People in Sweden were measured with higher PFHpA levels in males but higher PFHxS levels in females, whereas other compounds did not differ significantly between two genders (Salihovic et al., 2015). D.H. Kim et al. (2014) reported there was no significant difference in serum PFAS levels between Korean girls and boys aged 5–13 years old. Furthermore, Zeng et al. (2015) found that gender difference in serum PFOS was ordinarily observed at the ages of 13–50 years. Higher levels of PFHpA and PFOS were observed in males during an Australian research, where PFHpA, 8:2 FTSA and polyfluoroalkyl phosphate diesters (diPAPs) showed no gender differences (Eriksson et al., 2017). Lower concentrations of various PFASs in females than males might be correlated with menstruation and lactational transfer to infants during pregnancy and breastfeeding. Menstruation was reported to contribute 30% of the discrepancy in PFOS elimination among two genders (Wong et al., 2014). Higher concentrations of PFUnDA in primi- and multiparous mothers than nulliparous women were observed in Sweden donors (Salihovic et al., 2015), whereas an opposite result was found in pregnant women of Odense, Denmark (Dalsager et al., 2016). In the latter study, PFOA and PFHxS concentrations were higher in nulliparous compared to primi- and multiparous women in Faroe Islands, while PFNA and PFDA were higher in primi- and multiparous women (Oulhote et al., 2016). Furthermore, higher consumption of food and occupational exposure could also contribute to higher blood PFAS levels in males than females (Wan et al., 2013). Extremely high levels of PFOS and PFHxS in serum of fishery employees (10,400 and 542 ng/mL, respectively) and their family members (3540 and 150 ng/mL, respectively) from Tangxun Lake were observed than populations in other areas all over the world (Zhou et al., 2014). However, the gender-dependent PFAS contamination was generally not found in several Chinese studies (Liu et al., 2009; Zhang et al., 2011; Zhang et al., 2010b). Thus, there is no clear conclusion on the relation of PFAS concentrations with two genders.

3.1.4. Others

Other factors such as dietary habits, lifestyles, family income, education level, social status and body mass index (BMI) could also affect

PFAS levels in human blood. The positive association between family income and serum PFAS levels was reported in a Chinese study (Nelson et al., 2012), where higher family income was associated with increasing PFDA and PFNA levels in cord plasma and mother's education level was also positively associated with higher PFUnDA and PFHxS levels but negatively with PFBS levels (Wang et al., 2016). Another Danish study also reported statistical, negative association between mother's education level and PFOS or PFOA concentrations (Dalsager et al., 2016). A significant increasing trend of blood PFAS concentrations was found in Norwegian middle-aged women as BMI increased (Rylander et al., 2010), similar to the trend observed in a Korean study, although the trend in the latter study disappeared when BMI was over 30 (Ji et al., 2012a). However, some other studies showed that PFASs decreased with pre-pregnant BMI increase (Dalsager et al., 2016; Oulhote et al., 2016), while other studies revealed no association between PFAS and pre-pregnant BMI (Shi et al., 2017). For example, a Chinese study observed PFUnDA and PFDoDA concentrations decreased with the increasing of pre-pregnant BMI, but inverse results for PFHxS and PFBS (Wang et al., 2016).

3.2. Human urine

In addition to human blood, urine has been used as a less invasive approach for the evaluation of human PFASs exposure. Urinary excretion is an important pathway of elimination of PFASs which could be accumulated in human blood and liver (Zhang et al., 2015). Zhang et al. (2015) and J. Li et al. (2013) analyzed PFOA and PFOS concentrations in urine from general populations located in Tianjin City and Shanxi Province in China, respectively. Comparable PFOA levels in urine were observed in Tianjin and Shanxi with mean concentrations of 11 and 12.9 ng/L, but the mean urinary PFOS concentration in Shanxi were over two times of that in Tianjin (23 and 49.6 ng/L, respectively). It was noticed that the PFOA levels in Hebei (China) were remarkably higher (81 ng/L) than two mentioned Chinese provinces (Zhang et al., 2013a). Compared with the studies in China, much higher PFAS levels in urine were observed in Barcelona, Spain (Perez et al., 2012). In this study, PFBA was found with the highest mean concentration (483,545 ng/L) and detection frequency (100%), while PFOA and PFHxS were found in relatively higher detection frequency than other compounds with mean concentrations of 824 and 11,889 ng/L, respectively (Table 1). As PFBA might be an end-product of some long-chain PFASs (Perez et al., 2012), high PFBA levels in urine could be contributed by biodegradation of some PFASs and elimination through urine. High PFOA levels could be contributed by the main process for PFOA elimination, while the PFHxS concentrations for blood in previous studies (Ericson et al., 2007; Karrman et al., 2007; Olsen et al., 2007) were more than the high concentrations found in this study for urine, which indicated its higher blood protein affinity compared to urine. Specially, mean PFOS concentration (<370 ng/L) in this study was very low, which could be explained by longer elimination half-life of this compound (Perez et al., 2012). D.H. Kim et al. (2014) analyzed urine samples of children and adults in Korea, where PFPeA was found to be predominant with mean concentrations of 2340 and 2490 ng/L. Thus, PFAS levels in urine samples from different countries showed some spatial variations due to different pollution levels in each place.

The chain length is also a critical factor affecting urine PFAS distribution. Urine was reported to be the major excretion pathway for short chain-length PFASs ($C \leq 8$) (Zhang et al., 2013a), whereas fecal excretion contributed more to the elimination of longer PFASs ($C > 10$) (Beesoon et al., 2012). Zhang et al. (2013a) reported urinary elimination of long-chain PFASs (C7–C10) was negatively associated with the chain-length. In the urine samples from Korea and Spain, shorter chain PFASs were found with higher detection frequencies and levels, but PFSAs were rarely observed (D.H. Kim et al., 2014; Perez et al., 2012). The higher elimination of short-chain PFASs from urine may be attributed to their shorter half-lives in human body (U.S. EPA, 2009) Furthermore, they are more water-soluble (low affinity towards body tissues) and excreted more efficiently than long-chain PFASs (Bhhatarai and Gramatica, 2011; Inoue et al., 2012). The absence of PFOS in Spanish urine samples (Perez et al., 2012) may result from its longer serum elimination half-life (5.4 years) (Olsen et al., 2007). Similarly, PFHxS (with a shorter chain-length than PFOS) levels in urine were even lower than PFOS (Zhang et al., 2013a), which could be also due to its longer serum elimination half-life (8.5 years) (Olsen et al., 2007). Significant interaction between long-chain PFASs and organic anion transport polypeptide (OATP) could contribute to less efficient elimination of these compounds (Yang et al., 2009). The renal clearance efficiencies of PFOA in Japanese and Chinese population were found higher than those of PFOS, which indicated urinary elimination rate of PFOA (GM: 25%) was faster than PFOS (GM: 16%) (Harada et al., 2005; Zhang et al., 2015). Previous study showed that excretion was the main pathway for PFOA elimination in rats and rabbits (Hundley et al., 2006). In addition, PFASs (e.g., PFHxS) can bind strongly with blood proteins, and this could affect the transfer efficiency of these chemicals to urine (J. Li et al., 2013; Perez et al., 2012).

Significant gender differences of PFOA or PFOS levels in urine were observed in Chinese populations (J. Li et al., 2013; Zhang et al., 2015). However, no significant gender and age differences were found for urinary elimination of PFASs in Korea (D.H. Kim et al., 2014). Zhang et al. (2013a) showed that the urinary elimination of PFOS was negatively related with age, and positive relationships were found between PFAA concentrations in human urine and blood in Hebei (China). However, a weak positive and no relation between urine and serum were observed for PFOS and PFOA in Shanxi (China), respectively (J. Li et al., 2013). Generally, the association of gender, age, and blood PFAS levels with urine PFAS levels is not clear, and more investigations on these factors are needed. PFAA concentrations in paired human blood (ng PFAA/mL) and urine (ng PFAA/L) samples were significant related in the study of Zhang et al. (2013a). Such finding implies that urine may be considered as an alternative matrix for HBM, which was less invasive and easier to collect than blood. Nevertheless, the relatively low PFAS concentrations, absence of a standard method, and influence by sampling time could limit the accuracy of urine measurements, though creatinine concentration adjustment has been used to overcome the limitation of different sampling time (Barr et al., 2005).

Limited information about PFAS concentrations in human stool were reported. Beesoon et al. (2012) collected urine and stool samples in a Canadian family, the result indicated that urine was the primary extraction pathway for PFASs, none of the PFASs were detected in stool samples except for PFTA and PFTrDA were detected in one and three children in the studied family, respectively.

3.3. Human milk

As human milk is an important food source to infants, breastfeeding is another important PFASs exposure pathway for newborns besides trans-placental transfer. Investigations on PFAS levels in human milk from different studies are reviewed in the present study (Fig. 4). In a study for population in Sweden, few kinds of PFASs were quantified above the limits of detection in human milk, and PFOS and PFOA were still the predominant compounds with higher concentrations and detection frequencies than other PFASs (Sundstrom et al., 2011). Similar results were reported in other countries (e.g., Belgium (Roosens et al., 2010), Spain (Karrman et al., 2010), France (Antignac et al., 2013; Kadar et al., 2011), Jordan (Al-sheyab et al., 2015), Italy (Barbarossa et al., 2013), and China (Liu et al., 2010)). PFOS and PFOA concentrations were generally within the ranges of 6–288 pg/mL and 18–241 pg/mL in human milk from different countries, respectively (Al-sheyab et al., 2015; Barbarossa et al., 2013; Kadar et al., 2011; Karrman et al., 2010).

PFAS levels in human milk were overall much lower than those in human blood from the same subjects (Cariou et al., 2015), which is possibly related to low transfer rate of these chemicals from mother' blood

to breast milk. No significant correlation was observed between mothers' age and PFAS concentrations in breast milk in most countries, such as Belgium (Roosens et al., 2010), Spain (Karrman et al., 2010; Motas Guzman et al., 2016) and France (Antignac et al., 2013; Kadar et al., 2011). However, increase of PFOS and PFOA concentrations with mothers' age were observed in Jordan (Al-sheyab et al., 2015), although the reason remains unclear. Moreover, other factors (e.g. the weight at birth and the gender of the infant) were found to have no relations with measured exposure levels (Antignac et al., 2013; Kadar et al., 2011). The parity of mothers was reported to have a significant correlation with PFAS concentrations in human milk. For example, it was found that primiparas showed higher PFAS levels than multiparas in France, Italy, and Belgium (Barbarossa et al., 2013; Croes et al., 2012; Kadar et al., 2011; Motas Guzman et al., 2016). The relatively higher concentration of PFAS in the first child also suggested higher PFAS contamination in breast milk for the first child (Motas Guzman et al., 2016). However, Antignac et al. (2013) reported that no significant correlations were found between the number of maternal pregnancies and PFAS concentrations in breast milk in France. Since PFAS levels in breast milk could be affected by the interval of interpregnancy, similar levels of PFASs could be observed in breast milk between the first and latter lactation when the interpregnancy interval is long enough (Whitworth et al., 2012). It is noted that breast milk in the beginning of the lactation is of greater viscosity (higher protein) and the PFAS concentrations are higher in this period (Al-sheyab et al., 2015). This was supported by recent findings that protein showed higher affinity towards PFASs in human body (Karrman et al., 2010), which indicated the reason for limited possibility for PFASs to enter human milk at the same time. In human milk collected from 12 provinces of China, geographical variations in PFAS levels were observed in breast milk, and the exposure levels showed positive correlation with the degree of industrialization and economic development (Liu et al., 2010). The exposure to PFASs for newborns through breastfeeding is related to the mothers' exposure level, the length of lactation and the baby's ingested volume.

Overall, PFASs levels in human milk might be affected by various factors, such as mothers' age, parity of mothers and the interval of interpregnancy. Minimizing maternal dietary exposure especially fish consumption and the use of Teflon products in kitchen could reduce the contamination levels in breast milk.

3.4. Hair and nails

The mean (median) or range of PFAS concentrations in hair and nails are summarized in Table 1. Compared to urine sample, long-chain PFASs were efficiently detected in hair samples from Belgian people due to their low excretion rates (Alves et al., 2015). It was proposed that contaminants could migrate into hair via blood, sweat or sebum secretions, and deposition from the external environment (such as air and dust) (Henderson, 1993), but the most possible vehicle for PFASs in hair remains unknown. PFOS and PFOA were reported as the most frequently detected PFASs in hair samples in Spain (Perez et al., 2012). J. Li et al. (2013) found significantly higher PFOA/sum of PFOA and PFOS ratio in hair (42.2%) than other matrices (17%, 21.1%, and 13.4% for urine, nail, and serum), which indicated a tendency of PFOA accumulation. Hair samples are non-invasive and easily collected, stored and transported (Liu et al., 2011). while it is also a complex matrix and many factors (including color, type, melanin content and multiple sites) should be taken into consideration (Pragst and Balikova, 2006). However, in the study of Alves et al. (2015), no discrepancy of PFASs extraction was found in different types of hair. And the limitation of using hair in biomonitoring was that both internal and external exposure contributed to the incorporation of PFASs in hair (J. Li et al., 2013; Zhang et al., 2007). To date there is no standard method to identify which source dominates.

Nail is another alternative and non-invasive matrix used in the assessment of PFAS exposure. Similar to hair, nail is easier in collection, transportation and storage than urine samples. Liu et al. (2011) reported that nail showed more advantages than urine and hair in human PFAS biomonitoring, after calculating the Spearman correlation coefficients between serum and these three matrixes for PFOA and PFOS. Their results showed that the highest correlation coefficient for PFOS was observed between serum and nail, and no correlations were found for PFOA between serum and hair or urine. Significant correlations between PFOS and PFOA were found in both serum ($r = 0.608$, $p < 0.001$) and nail ($r = 0.605$, $p < 0.001$) samples and the correlation coefficients of were remarkably similar. Furthermore, similar proportion profiles of PFOA and PFOS were found in nail and serum samples in the studied populations. Different from hair, a washing method was successfully used to remove endogenous contamination, which can avoid the interference by endogenous contamination (Liu et al., 2011). Liu et al. (2011) also investigated whether fingernails or toenails were more appropriate for PFAS exposure assessment. The similar PFAS level and positive correlation analyzed in fingernails and toenails showed both of them are suitable to use. However, it should be noted that fingernails can provide more raw samples but shorter exposure integration due to their higher growth rate, while toenails are on the contrary. In summary, nails are promising matrix for human biomonitoring of PFASs, but relevant data are extremely limited and further in-depth investigations are needed.

4. Conclusions

Overall, the biomonitoring of PFASs mainly focused on human blood and urine. PFAS concentrations in blood samples follow an overall order as: serum > plasma > whole blood. Geographical variations in blood PFAS concentrations could result from dietary intake, drinking water, dust, and industrialization level of the study area. Concentrations of PFAS in human blood appeared to be associated with age, gender, and other factors, including dietary habits, lifestyles, family income, education level, social status and BMI. PFAS levels also showed spatial differences in human urine and were affected by chain length of PFAS and human gender. Furthermore, urinary excretion is found to be an important pathway for the elimination of PFASs. PFAS levels in human milk were overall much lower than those in human blood, likely due to low transfer rate of these chemicals from mother's blood to breast milk. To date, studies remain limited in the use of human hair or nails as a promising non-invasive approach for PFAS biomonitoring.

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Appendix A. Supplementary data

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