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Review article

Exposure characteristics for congeners, isomers, and enantiomers of perfluoroalkyl substances in mothers and infants

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ABSTRACT

Per- and polyfluoroalkyl substances (PFASs) are ubiquitous in the environment, making it inevitable for humans to be exposed to these pollutants. The exposure begins while in utero and continues in infancy, during the potentially most sensitive early stages of life. This review summarizes the current knowledge on pre- and neonatal exposures based on more than 200 articles published from 2000 to date. All relevant biological matrices used in the cited studies were included, such as maternal blood, umbilical cord blood, breast milk, placenta, amniotic fluid, fetal organs, newborns' dried blood spots, and infant serum. We show that such exposures are geographically global with significant discrepancies among countries and continents, and that while the levels of major legacy PFASs (PFOS and PFOA) have declined since 2000, those of others may have not. We also show that levels of PFOS and PFOA exceed those of some major environmental toxins, such as *p,p′*-DDE, BDE-47, PCB-153, PBB-153, and OH-PBDEs in maternal blood. Given that the behavior and potential effects have an origin in molecular structure, biomonitoring and research at the levels of isomers and enantiomers are critically important. Through critical analysis of these works, we summarize the major achievements, consensus, and the deficiencies of existing research. To our knowledge, this is the first review on the overall internal exposure status of mothers and infants to PFASs during pregnancy and lactation.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are composed of a fully or partially fluorinated alkyl chain (C_nF_{2n+1}-) and one or more polar functional groups, such as carboxylate (PFCAs) or sulfonate (PFSAs) (Buck et al., 2011; de Voogt and Sáez, 2006). This distinctive structure makes PFASs amphiphilic and highly stable. As a result of their widespread use in a variety of consumer products since the 1940s (Prevedouros et al., 2006), humans are inevitably exposed to PFASs (Giesy and Kannan, 2002; Hansen et al., 2001; Codling et al., 2018). Evidence has been mounting that "legacy" PFASs such as perfluorooctane sulfonic acid (PFOS) can induce toxic effects in animals (UNEP, 2006) and adverse health effects on humans (Agier et al., 2019; UNEP, 2007; USDHHS, 2018). Their environmental persistence, bioaccumulation potential, and the proven and expected harms to the ecosystem and humans have prompted international communities to restrict the manufacturing and use of PFASs (USEPA, 2000). PFOS, perfluorooctanoic acid (PFOA), and perfluorohexane sulfonic acid (PFHxS), as well as their related compounds have been included in or are under consideration by the Stockholm Convention on Persistent Organic Pollutants (POPs) (UNEP, 2009, 2018a, 2018b). However, the impact and threats of PFASs on the ecosystem and human health will remain for decades or even centuries, given the continued production in some countries, the large quantities in existing consumer goods, and the long half-lives of such substances in the environment.

The number of PFASs with defined chemical structures exceeds 5000, based on the consolidated list by U.S. EPA (USEPA, 2018). Among these PFASs, PFOS and PFOA are the most frequently detected compounds. In recent years, other PFCAs ($C_{4\text{-}7,\ 9\text{-}18}$) and PFSAs ($C_{4,\ 6,\ 10}$) have also received increasing attention. Some emerging PFASs, including newly identified anions, cations, zwitterions, and neutral PFASs, have been frequently detected and may occupy a large fraction of the total organic fluorine in the environment (Xiao, 2017). However, these emerging PFASs have hardly been investigated in maternal and infant populations. In addition, the structural diversity of PFASs as well as the implication of such diversity on human health risks have not

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been sufficiently recognized. The molecular structures of selected linear PFACs and PFSAs are illustrated in Figures S1 and S2, respectively. Many PFASs share the same molecular formula and thus are isomers. Some PFASs are chiral and therefore have a number of enantiomers. For example, PFOA has linear (*n*-) or branched (*br*-) isomers and some of them have enantiomers (Figure S3). PFOS also has isomers some of which are chiral with enantiomers (Figure S4).

The general population and pregnant women are exposed to PFASs to varying degrees. According to data from the National Health and Nutrition Examination Survey (NHANES) of the United States, non-pregnant women have significantly higher levels of PFOS than pregnant women. PFOA concentrations showed no significant differences after adjustment for covariates (Woodruff et al., 2011). However, a study on French pregnant women reported a higher average freshwater fish consumption (11 g/day) than another study on French women from the general population (0.96 g/day). As freshwater fish was the food group most polluted by PFASs in that study, pregnant women may be exposed to PFASs more than the general population in France (Yamada et al., 2014). Although the difference between pregnant women and the general population is still controversial, the PFAS exposure of pregnant women and their infants has caused high concern because of their particular vulnerability to environmental toxins. For infants, the potential adverse health effects of PFASs include low birth weight (Johnson et al., 2014; Lee et al., 2013), obesity (Karlsen et al., 2017; Maria Mora et al., 2017), thyroid function disorders (Aimuzi et al., 2019; Ballesteros et al., 2017; de Cock et al., 2014a), hypotonic neurobehavior (Donauer et al., 2015), small for gestational age (Govarts et al., 2018), less gut microbiome diversity (Iszatt et al., 2019), among others. For women, exposure to PFASs is linked to reduced fecundity (Fei et al., 2009; Vélez et al., 2015), pregnancy-induced hypertension (Darrow et al., 2013), reduced ability to lactate (Fei et al., 2010; Konkel, 2017), among other adverse effects. These toxicological effects are expected to be compound-specific and may differ significantly among congeners, isomers, and enantiomers. Yet, most of the studies published to date have investigated PFOS and PFOA; only a fraction of them involved other PFCAs and PFSAs, few focused on isomers, and even fewer on enantiomers of chiral PFASs.

Most existing relevant reviews focus on the health risks (Bach et al., 2015; Johnson et al., 2014; Rappazzo et al., 2017), the distribution in breast milk (Lehmann et al., 2018; Macheka-Tendenguwo et al., 2018; VanNoy et al., 2018), or the general population (Miralles-Marco and Harrad, 2015; Post et al., 2012; Sungur, 2017; Sznajder-Katarzyńska et al., 2019). No previous reviews have presented the global spatio-temporal trends, the comprehensive exposure and transfer among matrices, and the overall internal exposure of PFASs in mothers and infants. No existing reviews distinguish isomers and enantiomers of PFASs in early life exposure. In this study, by summarizing the major achievements, consensus, and the deficiencies of existing research, we aim to gain insights on global and long-term scales that may not be possible from localized studies. We emphasize the distinctions among PFAS isomers and enantiomers, which will be valuable to a wide range of scientific communities working on identifying contamination sources, investigating cross-matrix transfer mechanisms, developing chemical analysis methods, building quantitative structure–activity relationship models, and synthesizing replacement chemicals. By focusing on the concentration levels, distribution characteristics, exposure factors, and mother-infant transfer of PFASs at the congener, isomer, and enantiomer levels, we intend to not only summarize the current knowledge but also provide insights that are valuable to future developments in this research field.

2. Methods

In this work, we identified more than 200 journal articles (some are cited in the Supplementary Material) published from 2000 to date by searching Web of Science on the topic of pre- and neo-natal exposure to PFASs. The search strings of "TOPIC" included but were not limited to ["perfluor*" AND ("infant" OR "maternal" OR "fetal" OR "newborn" OR "pregnant women" OR "breast milk" OR "human milk" OR "placenta" OR "amniotic fluid" OR "meconium" OR "prenatal" OR "postnatal" OR "gestation" OR "lactation")]. The search yielded 1871 records, including research articles and reviews as well as meeting abstracts, books, and other types of publications. The titles and/or abstracts were reviewed to include only those studies that reported data on measured levels of PFASs in maternal and infant samples. Studies were excluded if their primary purpose was health risk assessment or analytical method development or they did not report PFAS levels in pregnant women or infant (0–1 year old) samples. Data reported by government agencies, such as the U.S. Centers for Disease Control and Prevention (CDC) and the Arctic Monitoring and Assessment Programme (AMAP), were also collected and included in this review.

Our review is limited to perfluorinated carboxylates and sulfonates, including the congeners, isomers, and enantiomers of PFOS and PFOA, as studies on this topic for polyfluoroalkyl substances or PFASs with dual polar functional groups are scarce. Among selected references, about 140 articles are for congeners, 50 for isomers, and 10 for enantiomers. Approximately 76% were published since the year 2010, and 47% since 2015. These studies were screened based on their analytical methods and detection limits. As the internal standard method eliminates errors caused by changes in operating conditions to a certain extent, results obtained from using this method were considered more accurate than those using external standard methods. Therefore, only PFAS concentrations obtained by the internal standard method were used in our statistical analysis. Among these studies, the Limits of Detection (LOD), Limits of Quantification (LOQ), Method Detection Limits (MDL), or Method Quantification Limits (MQL) were examined to ensure that the sensitivity of instruments and methods are adequate. For most PFSAs and PFCAs, LOD should not exceed 1 ng/mL and LOQ should not exceed 2 ng/mL.

The concentrations of selected PFAS congeners in various sample matrices are summarized in Tables S1-S3 and Table 1. PFASs excluded from these Tables are those for which concentrations in maternal and infant populations have rarely been reported. In order to compare the differences among congeners of PFCAs or PFSAs, only studies that measured no less than three PFASs are included in Tables S1-S3. In Table 1, as much information as possible is summarized for all PFCAs and PFSAs, because the number of published studies on mother and infant sample matrices, including amniotic fluid, placentae, organs, dry blood spot, and fetal sera, is limited. In all Tables, the decimals and significant figures of the data are kept as those reported in the original papers. The data are similarly presented when they are cited and discussed in text.

The geographic patterns of PFAS concentrations in maternal whole blood, cord whole blood, and breast milk are illustrated in Figs. 1-3, respectively. Data in these Figures are from Tables S1-S3. To compare the differences in concentrations between geographic areas, the Independent Sample T-test was used with IBM SPSS Statistics software version 22. The significance level was set at $p = 0.05$. Studies (Needham et al., 2011; Roosens et al., 2010; Wang et al., 2019; Yao et al., 2019) that reported extremely high concentrations ($>$ mean + 3 $\times$ standard deviation) are excluded from the statistical analysis of geographic differences. PFAS concentrations in maternal and cord blood were available in three matrices: serum, plasma, and whole blood. Some of the data for concentrations in whole blood, as shown in Figs. 1 and 2, were converted from those reported in serum and plasma. Ratios of the conversions were chosen from three references (Ehresman et al., 2007; Eryasa et al., 2019; Hanssen et al., 2013) and are explained below.

Biomonitoring of PFASs using human serum or plasma is based on the assumption that PFASs primarily accumulate in the serum or plasma fraction of blood. However, this assumption was not proven true in some studies. Jin et al. used a mass fraction of PFASs in plasma (F_p) as

Table 1
Summary of PFCA and PFSA concentrations in other sample matrices.

Ref.	Location	Sampling years	Sample size		PFPeA	PFHxA	PFHpA	PFOA	PFNA	PFDA	PFUnDA	PFDoDA	PFHxS	PFOS
Amniotic fluid (ng/mL)														
(Stein et al., 2012)	New York, USA	2005–2008	≤28	Median				0.3	0.2	NA			0.4	0.4
(Jensen et al., 2012)	Denmark	1980–1996	300	Median										1.1
(Zhang et al., 2013a)	Tianjin, China	2010	29	Mean	0.032	0.191	0.013	0.044	0.025	< 0.01	< 0.02	< 0.02	< 0.03	0.02
				Median	< 0.03	< 0.05	< 0.01	0.043	< 0.01	< 0.01	< 0.02	< 0.02	< 0.03	< 0.03
(Long et al., 2019)	Copenhagen, Denmark	1995–1999	51	Median				0.32						1.44
Placenta (ng/g, wet weight)														
(Chen et al., 2017)	Wuhan, China	2015–2016	32	Mean				0.484					0.216	2.842
				Median				0.464					0.207	2.416
(Zhang et al., 2013a)	Tianjin, China	2010	29	Mean	< 0.05	0.04	0.11	1.58	0.99	0.7	1.27	0.49	0.41	8.18
				Median	< 0.05	0.03	0.1	1.41	0.96	0.67	1.17	0.46	0.36	7.32
(Mamsen et al., 2017)	Denmark	–	34	Mean				0.23	0.14	0.08	0.06			1.3
(Mamsen et al., 2019)	Denmark and Sweden	2014–2016	71	Mean				0.36	0.17	0.19	0.33			1.41
				Median				0.3	0.15	0.18	0.33			1.24
Fetal Organs (ng/g, wet weight)														
(Mamsen et al., 2017)	Denmark	–	108	Mean				0.17	0.09	0.08	0.06			0.6
(Mamsen et al., 2019)	Denmark and Sweden	2014–2016	53 (liver)	Mean				0.76	0.24	0.23	0.35		0.88	1.3
				Median				0.54	0.18	0.21	0.3		0.78	0.99
			57 (lung)	Mean				0.57	0.18	0.2	0.27		0.87	1.43
				Median				0.44	0.17	0.19	0.29		0.75	1.12
			44 (heart)	Mean				0.61	0.16	0.19	0.27			0.7
				Median				0.48	0.13	0.19	0.27			0.69
			46 (central nervous system)	Mean				0.29	0.11	0.13			0.7	0.43
				Median				0.19	0.11	0.13			0.7	0.39
			25 (adipose)	Mean				0.61	0.17	0.36			0.93	0.84
				Median				0.53	0.17	0.36			0.89	0.77
Dried Blood Spots (ng/mL)														
(Kato et al., 2009)	Texan, USA	2007	98	Mean				1	0.3				0.5	2.5
				Median				0.9	0.3				0.3	2.2
(Bell et al., 2018)	New York State, USA	2008–2010	2920,3111	Median				1.1						1.7
(Spliethoff et al., 2008)	New York State, USA	1999–2000	10	Mean				1.33	0.35				2.40	2.43
				Median				1.36	0.27				2.47	2.29
		2003–2004	20	Mean				0.8	0.38				1.84	1.74
				Median				0.73	0.35				1.64	1.59
Infant serum (ng/g)														
(Gyllenhammar et al., 2018)	Uppsala, Sweden	1996–1999	325 (2–4 months)	Mean			0.23	7.7	0.38	0.12	0.09		2.8	14
				Median		< 0.1	0.19	7.2	0.34	0.11	0.08	< 0.05	2	13
Infant serum (ng/mL)														
(Fromme et al., 2010)	Munich, Germany	2007–2009	40 (6 months)	Mean				8.0	1.1	< 0.4			0.7	3.3
				Median				6.9	1.0	< 0.4			0.6	3.0
(Toms et al., 2009)	Southeast Queensland, Australia	2006–2007	99 (0–6 months)	Mean				4.5					0.9	7.0
			120 (6–12 months)	Mean				7					1.9	9.7
(Haug et al., 2009)	Norwegian	2007	≥20 (0–12 months)	Median	< 0.050		0.069	1.6	0.55	0.075	0.072	< 0.050	0.31	4.0

NA: not available.

Fig. 1. Maternal whole blood median concentrations of PFASs in different countries and regions. Note: PFAS concentrations in serum were converted to those in plasma by dividing 1.0 (PFOS), 1.1 (PFHxS) and 1.0 (PFOA) (Ehresman et al., 2007); then concentrations in plasma were converted to those in whole blood by dividing 1.8 (PFOS), 1.8 (PFHxS) and 1.7 (PFOA) (Hanssen et al., 2013). [b] Mean values were used because median values were unavailable.

defined below:

$$F_p = C_p\ (1 - f_{cell})/C_{wb}$$

where C_p and C_{wb} are PFAS concentrations (ng/mL) in paired plasma and whole blood, respectively; and f_{cell} is the volume fraction of blood cells in whole blood. They found that F_p increased from 0.24 (C_6) to 0.87 (C_{11}) with the increasing length of the linear alkyl chain in the general population (Jin et al., 2016). Additionally, the plasma to whole blood concentration ratios (R_{PW}) of PFASs varies for different populations. For example, Hanssen et al. reported the mean R_{PW} ratios of 1.9 and 2.5 (calculated from the initial data) for linear PFOS in pregnant women and umbilical cord from Norilsk, Russia, respectively (Hanssen et al., 2013). However, Jin et al. reported the mean R_{PW} ratio of linear PFOS to be 1.57 (calculated from the initial data) in the general population from Shijiazhuang, Hebei Province, China (Jin et al., 2016), which was significantly ($p < 0.05$) different from that in cord blood

Fig. 2. Cord whole blood median concentrations of PFASs in different countries and regions. Note: PFAS concentrations in plasma were converted to those in whole blood by dividing 2.3 (PFOS), 2.2 (PFHxS) and 2.2 (PFOA) (Hanssen et al., 2013); PFAS concentrations in serum were converted to those in whole blood by dividing 1.93 (PFOS), 2.09 (PFHxS) and 1.88 (PFOA) (Eryasa et al., 2019). [b] Mean values were used because median values were unavailable. [c] Geomean values were used because median values were unavailable.

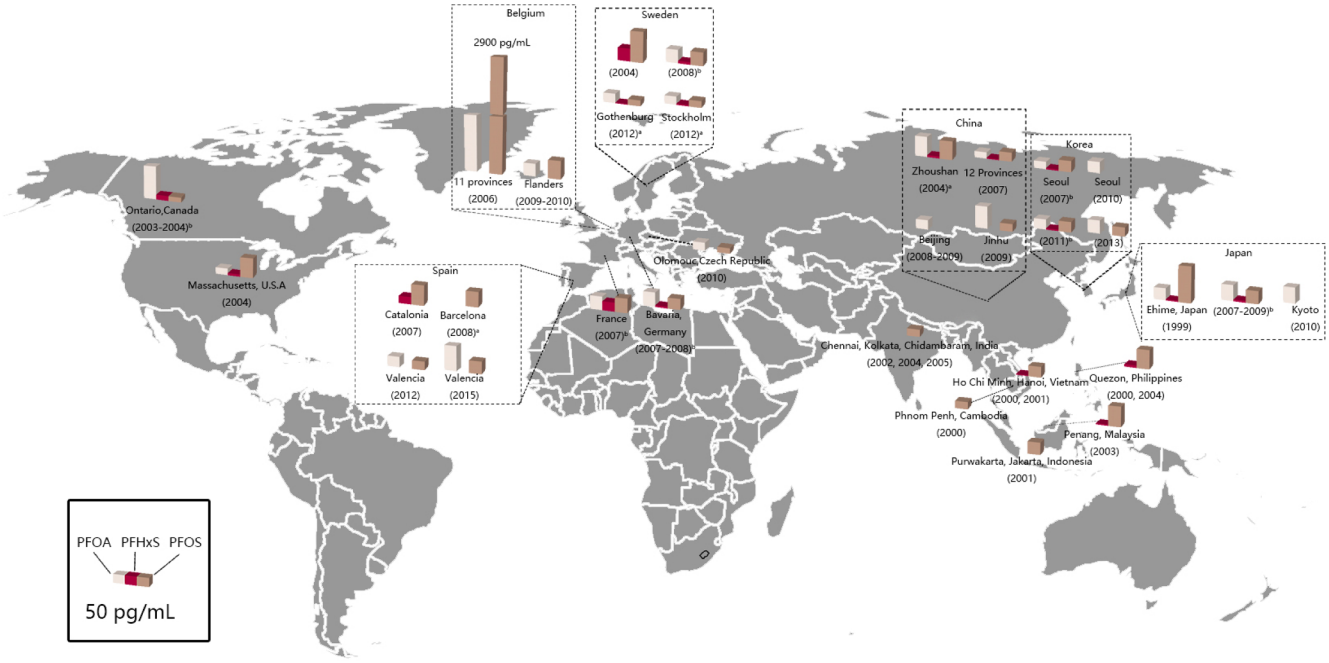

Fig. 3. The geographic distribution of PFOS, PFOA, and PFHxS concentrations in human breast milk. Note: [a] The median values were calculated from the original data. [b] Mean values were used because median values were unavailable.

from Norilsk, Russia. There have been no studies on the distribution of PFASs between serum and plasma in pregnant women. However, according to Ehresman's study on an occupational cohort, the mean serum/plasma ratios (R_{SP}) of PFHxS, PFOA, and PFOS concentrations were 1.1, 1.0, and 1.0, respectively (Ehresman et al., 2007). For the serum to whole blood concentration ratios (R_{SW}), a study on cord blood reported the median values for PFOS (1.93), PFOA (1.88), and PFHxS (2.09) (Eryasa et al., 2019). Based on these reports, we recommend the use of concentrations in whole blood to assess the exposure to PFASs, because those in either serum or plasma are not able to fully represent the internal exposure levels of mothers and their infants. For example, the mass of perfluorohexanoic acid (PFHxA) in plasma only represents 24% of that in whole blood (Jin et al., 2016); the plasma to whole blood concentration ratios of PFCAs in cord blood ranged from 0.67 (PFHxA) to 2.75 (PFUnDA) (Eryasa et al., 2019). Moreover, prenatal exposure to PFOS and perfluorodecanoic acid (PFDA) might influence the setting of leukocyte telomere length in female newborns' blood; therefore, PFASs in infant blood cells cannot be ignored (Liu et al., 2018).

3. Concentrations and distribution of congeners among biomatrices

3.1. Concentration levels and congener profiles

3.1.1. PFASs in comparison with other major pollutants

Humans are exposed to a variety of endocrine disrupting chemicals (EDCs). However, only a limited number of studies have analyzed PFASs and other pollutants in the same batch of maternal/infant samples. The results from such studies, in which the matrices were maternal plasma or serum (N = 7), cord plasma or serum (N = 6), breast milk (N = 3), amniotic fluid (N = 1), or newborn dried blood spots (N = 2), are summarized in Table S4. It is worth noting that most of these studies, including one from NHANES, had sufficiently large (> 100) numbers of samples and all of them implemented adequate quality control protocols. Classic POPs, such as organochlorine pesticides (OCPs), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), are lipophilic, so their concentrations are often reported as lipid-adjusted; while PFASs are oleophobic and their concentration units are often "ng/mL". For comparison, these units are unified as ng/mL based on the lipid content and density of blood and breast milk (Neville et al., 1988; Qiao et al., 2018).

Among organic pollutants in Table S4, PFOS and PFOA were the dominant PFASs; *p,p′*-DDE, BDE-47, and PCB-153 were usually the most abundant OCP, PBDE, and PCB, respectively. In maternal blood, (DEHP or MEHP) > (PFOS and PFOA) > *p,p′*-DDE > BDE-47 > PCB-153 > (PBB-153 and OH-PBDEs) (Braun et al., 2014; Hjermitslev et al., 2019; Long et al., 2015; Louis et al., 2018; Maekawa et al., 2017; Woodruff et al., 2011; Zota et al., 2018). In cord blood, (DEHP and MEHP) > (PFOS and PFOA) > (MECPP, MEHHP, and MEOHP) > *p,p′*-DDE > PCB-153 (de Cock et al., 2014a; de Cock et al., 2014b, 2016; Govarts et al., 2018; Maekawa et al., 2017; Remy et al., 2016). These rank orders in blood noticeably differ from that in breast milk, where *p,p′*-DDE > PCB-153 > (Dieldrin, Cis-heptachlor-epoxide, HCB, and β-HCH) > PFOS > (BDE-209 and BDE-47) (Croes et al., 2012; de Cock et al., 2017). In newborn dried blood spots, only "BPA > (PFOS and PFOA)" was reported (Bell et al., 2018). These indicate that PFAS concentrations were relatively high in blood but relatively low in breast milk when compared with those of lipophilic EDCs. Breast milk has much higher lipid content (58.5 g/L) (Croes et al., 2012; Neville et al., 1988; USIM, 1991) than serum (7.13 g/L) (Qiao et al., 2018). Therefore, breast milk may preferentially accumulate more lipophilic POPs over PFASs that are amphiphilic. As for heavy metals, it was reported that the concentrations of PFASs were comparable with those of manganese, cobalt, nickel, molybdenum, antimony, mercury and lead in maternal serum (Maekawa et al., 2017), and those of chromium, manganese, lead in amniotic fluid (Long et al., 2019).

3.1.2. Differences and correlations among PFASs

In maternal and infant samples, PFOS and PFOA were usually the most abundant PFASs with either PFOS or PFOA dominating (Tables S1-S3 and Table 1). Exceptions include: PFHxA are the highest in the amniotic fluid from Tianjin, China (Zhang et al., 2013a); and in some places, PFHxS are the highest in cord serum (Li et al., 2017; Needham et al., 2011; Zhang et al., 2017), infant central nervous system and adipose tissue (Mamsen et al., 2019), and the newborn dried blood spots (Spliethoff et al., 2008). In maternal blood, PFHxS concentrations

were lower than PFOS concentrations in all studies but higher than PFOA concentrations in some studies, including those from Uppsala, Sweden (Kärrman et al., 2007a) and Faroe Islands, Denmark (Needham et al., 2011). These special cases might imply the existence of specific local pollution sources. There were clear temporal trends of increasing PFHxS concentrations and decreasing PFOA concentrations in pregnant women from Uppsala, Sweden from 1996 to 2010; globally, however, the time trends of these PFASs in human appear to be more complex (Glynn et al., 2012).

The concentrations of congeners were ranked and compared, but the rank orders were not always consistent among studies. In blood, breast milk, and amniotic fluid, most studies reported the concentration rank orders of PFOA > PFNA > PFDA and PFOS > PFHxS > perfluoroheptyl sulfonate (PFHpS), as can be seen from the data in Tables S1-S3 and Table 1. Concentrations of PFNA and PFUnDA were also relatively high among PFCAs, but which of these two compounds had a higher concentration varied from case to case.

Correlations among PFAS congeners or between PFASs and their precursors have been found in maternal and infant samples. For example, the concentrations of PFOS, PFDA, perfluorododecanoic acid (PFDoDA), and PFNA showed positive correlations with each other in cord serum from Shanghai (Wang et al., 2016). PFOS was found to be significantly associated with PFHxS and PFOA in breast milk from Zhoushan (Kim et al., 2011a), and with PFUnDA, PFDA, and PFNA in breast milk from Seoul (So et al., 2006). These associations implied a common exposure source of these compounds in the specified localities. However, there was no or little association between PFOS and PFCAs detected in maternal serum in Korea, most likely implying different sources (Kim et al., 2011a). Some PFASs and their precursors showed significant correlations. For instance, a strong correlation was found between PFOS in cord serum and perfluorooctane sulfonamide (PFOSA, the precursor of PFOS) in maternal serum, implying that the latter might be a source of the former (Yang et al., 2016).

3.1.3. Concentration and distribution of PFASs in various matrices

In different matrices, PFAS concentrations showed different ranges or characteristics. In maternal blood (Table S1), the highest median or mean concentrations of the frequently reported PFASs, including PFOA, PFNA, PFDA, PFUnDA, PFHxS, and PFOS, are greater than 1 ng/mL, whether in whole blood, plasma, or serum. For PFOS and PFOA, the highest median or mean serum levels all surpassed 10 ng/mL. In cord blood, except for PFOS, PFOA, and PFHxS, all PFASs had median or mean concentrations lower than 1 ng/mL (Table S2). In most cases, concentrations of PFCAs ($C_{8\text{-}12}$) and PFSAs ($C_{6\text{-}8}$) in cord whole blood/plasma/serum are lower than the concentrations in corresponding maternal whole blood/plasma/serum, which suggests that placenta may retard or partially prevent the crossing of PFASs, but does not form an impenetrable barrier for fetal protection.

In breast milk (Table S3), the median or mean concentrations of all PFASs were less than 0.3 ng/mL, except in two studies (Kuklenyik et al., 2004; Roosens et al., 2010). Most whole volume-based concentrations in breast milk were much lower than those in maternal blood and cord blood. Kärrman et al. reported that the concentration of PFOS in breast milk was approximately 1% of the paired maternal serum level (Kärrman et al., 2007a). Cariou et al. reported levels of PFASs in breast milk that were 20–150-fold lower than those in serum (Cariou et al., 2015). Kärrman et al. suggested that the strong binding affinity to protein in blood obstructed PFASs from entering breast milk (Kärrman et al., 2010). Despite relatively low concentrations, PFAS congeners are still widely detected. For example, the detection rates of perfluoropentanoic acid (PFPeA), PFHxA, and PFHpA in breast milk ranged from 67.4% to 81.8% in the investigation of 264 Korean mothers (Kang et al., 2016). In Belgian breast milk, PFHxA and PFNA were detected even more frequently than PFOS and PFOA (Roosens et al., 2010). Some less reported short-chain PFASs and long-chain PFASs, such as perfluorobutanoic acid (PFBA), perfluorobutyl sulfonate (PFBS), perfluorotetradecanoic acid (PFTeDA), PFHxDA, PFODA, and perfluorodecyl sulfonate (PFDS) were also detected in breast milk (Lee et al., 2018; Lorenzo et al., 2016).

The concentration ranges of PFASs in amniotic fluid were comparable to those in breast milk, based on a few studies (Jensen et al., 2012; Long et al., 2019; Stein et al., 2012; Zhang et al., 2013a). Amniotic fluid plays a key role in protecting fetuses and mothers during gestation, with its volume and composition changing with gestational age. It is usually available by amniocentesis in the second trimester (gestational weeks 13–28) (Jensen et al., 2012). Before 20 weeks of gestation, amniotic fluid is mainly derived from fetal blood and fluids thus can be regarded as a useful biomarker of intrauterine exposure (Beall et al., 2007). Compared with maternal and cord blood, amniotic fluid has irreplaceable advantages in the assessment of prenatal exposure risks because the concentrations of contaminants in maternal blood does not adequately reflect those in fetal compartments, and cord blood reflects the situation only at birth but not during organogenesis. Although the PFAS concentrations in amniotic fluid are relatively low compared with blood, it was reported that PFOS levels in amniotic fluid influenced fetal adrenal and testicular steroidogenesis during the sensitive gestational weeks (weeks 11–22) (Anand-Ivell et al., 2018).

In placentae, the mean or median concentrations of all PFASs, except PFOS, PFOA, and PFUnDA, were less than 1 ng/g. Most PFASs had their highest mean or median concentrations of more than 0.3 ng/g. The relatively high concentration of PFUnDA in placentae should be noted (Zhang et al., 2013a). PFAS concentrations in infant organs were comparable to those in the placenta (Mamsen et al., 2019; Mamsen et al., 2017). The concentrations ratios of PFOS, PFOA, PFNA, and PFUnDA ranged from 0.11 to 0.15 for placenta: maternal plasma and from 0.05 to 0.13 for fetal organs: maternal plasma in a study in Denmark (Mamsen et al., 2017). Among fetal liver, lung, heart, central nervous system, and adipose tissue, the total PFAS burden was highest in lung tissue in first trimester samples and liver in second and third trimester samples (Mamsen et al., 2019).

PFAS concentrations in newborn dried blood spots were comparable to those in cord whole blood. In infant serum, median and mean concentrations of PFASs were comparable to but not always less than those in maternal serum. In a study in Munich, Fromme et al. found that the body burden of PFOS and PFOA increased during the first six months but decreased after the 19th month of life. Additionally, in the sixth month of life, PFOA concentration in infant serum was much greater than that in maternal serum. Although concentrations of PFASs in breast milk were low, these observations implied that breastfeeding might lead to high body burden in infants because most infants were exclusively breastfed during the first six months and breast milk always had more PFASs than infant formula in that study (Fromme et al., 2010).

Meconium is the first fecal excretion of neonates, which is comprised primarily of water (70–80%), lipid, protein, bile acid, and salts (Jeong et al., 2016). It has been shown to reflect the long-term accumulation of pollutant residues from gestational week 12 in utero (Veyhe et al., 2013). Compared with other maternal and infant matrices, meconium has some advantages. The non-invasive sampling method of the meconium minimizes the risks to participants and facilitates sample collection. Meconium reflects the body burden of toxins in the fetus more accurately than maternal samples (e.g. maternal blood and breast milk) and more directly than cord blood. Plenty of studies have proved that meconium is a useful tool to evaluate newborns' prenatal exposure to heavy metals, pesticides (Ostrea et al., 2002), and PCBs (Zhao et al., 2007), but no levels of PFASs in meconium were available in the literature.

In summary, PFAS concentrations approximately followed this distribution in most cases: (maternal, cord, and infant blood) > (placenta and infant organs) > (breast milk and amniotic fluid). In making this comparison, the density of the human body (around 1 g/cm^3) was used to convert the mass based concentration units in placentae and infant

organs to volume based units.

3.1.4. Associations and transfer of PFASs among matrices

Significant correlations have been reported in paired maternal and cord serum for PFOA, PFNA, PFDA, PFUnDA, PFDoDA, perfluorotridecanoic acid (PFTrDA), PFOS, and PFHxS, suggesting transplacental transfer of PFASs (Gützkow et al., 2012; Inoue et al., 2004; Kato et al., 2014; Manzano-Salgado et al., 2015; Zhang et al., 2013a; Zhao et al., 2017). Meanwhile, significant associations or linear regressions have been reported between breast milk and matched maternal serum for PFOS, PFOA, PFNA, PFDA, and PFUnDA, suggesting the transfer of PFASs from maternal blood to breast milk (Kärrman et al., 2007a; Liu et al., 2011). In amniotic fluid, the PFOA level showed a significant correlation with that in paired maternal blood and cord blood (Stein et al., 2012; Zhang et al., 2013a). If the concentration in maternal serum exceeded 1.5 ng/mL, PFOA could generally be detected in amniotic fluid (Stein et al., 2012). In placentae, the concentrations of PFHxS, PFOS, PFHpA, PFOA, PFNA, PFDA, PFUnDA, and PFDoDA were found to be significantly correlated with those in maternal blood and cord blood ($p < 0.05$) (Zhang et al., 2013a). Between infant serum 2–4 months after delivery and maternal serum three weeks after delivery, significant correlations were found for PFHpA, PFOA, PFNA, PFDA, PFHxS, and PFOS ($p < 0.05$) (Gyllenhammar et al., 2018).

The maternal-fetal/infant transfer of PFASs was influenced by the gestational age and the structures and properties of PFASs. For PFASs in cord serum, the strongest correlations with PFASs in maternal serum were for maternal serum samples collected during the third-trimester rather than the first or second trimesters (Zhao et al., 2017). In amniotic fluid, PFOS concentration increased with increasing gestational time at amniocentesis during pregnancy weeks 12–22 (Jensen et al., 2012). In fetal organs, it was reported that the fetal to maternal plasma concentration ratios of PFOS, PFOA, PFNA, PFDA, and PFUnDA increased with the fetal age ($p < 0.05$) (Mamsen et al., 2017). The concentrations of PFOA, PFNA, and PFOS in infant serum were also positively related to gestational age ($p < 0.05$) (Gyllenhammar et al., 2018). The transfer efficiencies of PFASs from maternal blood to amniotic fluid were dependent on carbon chain length and functional groups in PFAS molecules. Shorter-chain PFCA congeners transferred more readily into amniotic fluid (Zhang et al., 2013a), probably because longer-chain PFCAs bind to blood protein more strongly (Jones et al., 2003). Moreover, PFOA transferred more readily into amniotic fluid than PFOS, which might be explained by the difference in solubility between these two compounds (PFOA > PFOS) (Giesy et al., 2010; Zhang et al., 2013a). For infant serum and maternal serum, the infant/maternal ratios declined with increasing carbon chain length of the PFCAs ($C_{8\text{-}14}$) and PFSAs (C_6 and C_8) (Gyllenhammar et al., 2018).

Overall, the associations of PFAS levels in mothers and infants were strong. The amount transferred tends to increase gradually with the gestational age, and the transfer efficiencies differ among individual PFASs. The strong correlations or linear regressions among various matrices can help predict fetal or infant exposure levels based on blood concentrations of PFASs in pregnant women, leading to better pregnancy care and infant nursing plans, especially when they are built upon data from a large number of samples.

3.2. Geographic distribution

PFOS, PFOA, and PFHxS are the most concerning PFASs, and have been included in the list or the candidate list of POPs in the Stockholm Convention. With the data summarized in this review for these major PFASs, we have plotted their global distributions in maternal blood, cord blood, and breast milk (Figs. 1–3). The data in blood maps were unified to the concentrations in whole blood, based on the approach explained in Section 2 above. It can be seen that PFASs have been detected in maternal and infant populations in Asia, Europe, North America, Africa, and Oceania. Although there are no specific reports on maternal or infant exposure levels in South America, studies have found PFASs in female blood in Colombia and Brazil (Kannan et al., 2004). This indicates that exposure to PFASs in the maternal and infant population is a global problem.

3.2.1. Variation of PFAS exposures among countries and continents

In maternal blood (Fig. 1), the highest median concentrations of PFOS, PFHxS, and PFOA in whole blood were 12.40 ng/mL in Tianjin, China (Zhang et al., 2013a), 6.21 ng/mL in the Faroe Islands (Chan et al., 2011), and 25.19 ng/mL in Shandong, China (Wang et al., 2019), respectively. Tianjin is located near the western coast of the Bohai Sea. It is an industrial city with manufacturing facilities for electronics, petrochemicals, metallurgy, and textile industries. PFOS and other PFASs might be acceptable or specifically exempted for use in some of these industries (NDRCC, 2019; UNEP, 2009). In most places, the median whole blood concentrations of PFOS and PFOA were more than 1 and 0.5 ng/mL, respectively (Kim et al., 2011b; Papadopoulou et al., 2016). Median concentrations of PFHxS in whole blood were lower than 1 ng/mL in most locations, except in Sweden (2.02 ng/mL) (Kärrman et al., 2007a) and the Faroe Islands (6.21 ng/mL) (Needham et al., 2011).

In cord blood (Fig. 2), the PFOA levels from Shanghai (Aimuzi et al., 2019; Huang et al., 2019; Liu et al., 2018; Wang et al., 2016) and Shandong (Wang et al., 2019; Yao et al., 2019) in China were higher than those from other places. Shanghai is home to numerous fluorochemical manufacturers. The use and discharge of PFOA in these industries might contribute to the relatively high levels of PFOA in water from the Yangtze River (So et al., 2007), tap water (Mak et al., 2009), and cord plasma in Shanghai. The highest PFOS and PFHxS median levels in cord whole blood were reported in the Faroe Islands (3.42 and 4.35 ng/mL, respectively). Except for the Faroe Islands and Guangzhou populations, median PFHxS concentrations in cord whole blood were usually below 0.3 ng/mL; while for PFOS and PFOA, the median concentrations in most places were greater than 0.3 ng/mL.

There was great geographical variation of PFASs in breast milk (Fig. 3). The highest reported median level of PFOS, 2900 pg/mL, was from Belgium (Roosens et al., 2010), and the highest concentration of PFOA, 814 pg/mL, was from a rural area of Shanghai, China (Liu et al., 2010). Among Asian countries investigated in the same study, Japan generally had higher levels of PFOS and PFOA in breast milk than other countries, including China, Korea, India, Indonesia, Malaysia, Philippines, Vietnam, and Cambodia (Fujii et al., 2012; Tao et al., 2008b). In China, Korea, and Japan, long-chain PFCA congeners with an odd number of carbons had a higher detection frequency than those with an even number of carbons, except for PFDA in Japan (Fujii et al., 2012). Industrial applications of odd-numbered PFCAs produced via oxidation of fluorotelomer olefins might contribute to this distribution in breast milk (Prevedouros et al., 2006).

We furthered our analysis by grouping the countries and used two-tailed t-tests to examine the differences among continents and to compare developed and developing countries. The classification of countries was based on the statistical appendix of the *World Economic Outlook (WEO) 2020* published by the International Monetary Fund (IMF, 2020). Countries listed as advanced economics in WEO were classified as developed countries, and countries listed as emerging market and developing economies in WEO were classified as developing countries. Results of the t-tests for PFOA, PFHxS, and PFOS in breast milk and cord whole blood are summarized in Table S5. Concentrations reported from a number of studies were much higher than those in most other places, which may be due to proximity to pollution sources or occupational exposure. These include the following cases: maternal and cord blood from Shandong, China (Wang et al., 2019; Yao et al., 2019) and the Faroe Islands, Denmark (Needham et al., 2011), and breast milk from Belgium (Roosens et al., 2010). These are considered as special cases and were excluded from our calculations of the descriptive statistics. The limited number of datasets in some cases could have

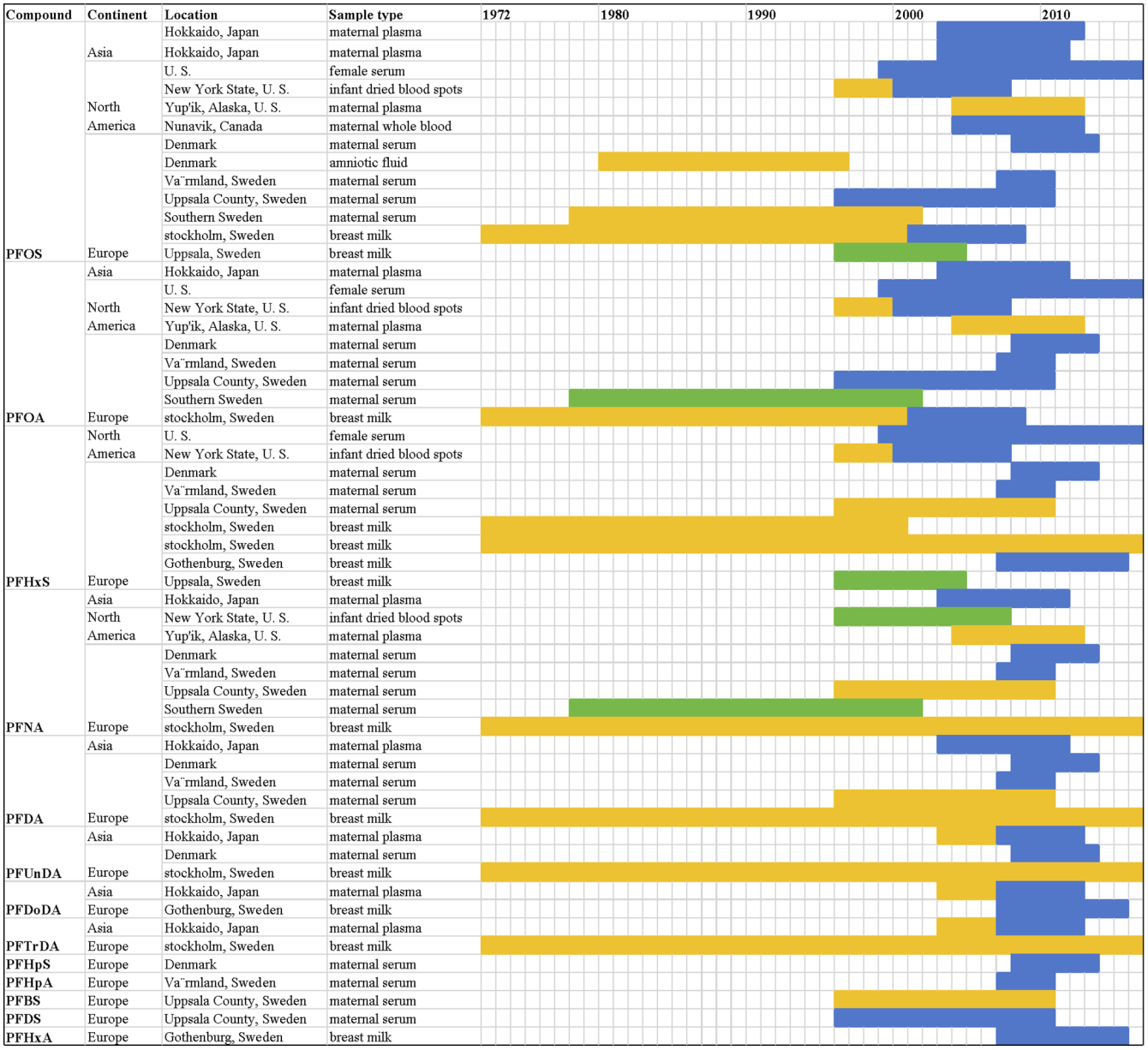

Fig. 4. Temporal trend of PFASs in maternal and infant samples in Asia, North America, and Europe from 1972 to 2016. Yellow represents an upward trend, blue represents a downward trend, and green represents roughly leveled trend (Abass et al., 2018; Bjerregaard-Olesen et al., 2016; CDC, 2019; Glynn et al., 2012; Jensen et al., 2012; Kärrman et al., 2007a; Nyberg et al., 2018; Ode et al., 2013; Okada et al., 2013; Shu et al., 2018; Spliethoff et al., 2008; Sundström et al., 2012; Tsai et al., 2018). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

weakened the statistical power of the comparisons; therefore, the discussions below should be considered as preliminary and interpreted with caution.

We found that PFOA concentrations in cord blood in developing countries were significantly higher than those in developed countries ($p < 0.05$). Geographically, Asian countries had significantly higher levels of PFOA in cord blood than European and North American countries. PFOA was included in the list for elimination of the Stockholm Convention in 2019. It has been regulated in some developed countries earlier and also restricted in some developing countries (IPEN, 2019; USEPA, 2006). As opposed to PFOA, we found that PFHxS concentrations in breast milk were generally lower in developing countries than in developed countries ($p < 0.05$). Compared with European and North American countries, Asian countries appear to have lower levels of PFHxS in breast milk. PFHxS has been used as a substitute for PFOS in the past (Zhou et al., 2019); it is likely that developed countries may have started the use of PFHxS earlier than developing countries. For PFOS, we did not find statistically significant differences in concentrations of maternal and infant samples among continents or regions ($p > 0.05$). PFOS has been industrially synthesized since before 1950, and it has been globally restricted under the Stockholm Convention for more than a decade (UNEP, 2009).

3.2.2. Factors that cause differences in PFAS exposure levels

Proximity to some major pollution sources may lead to extremely high exposures. These sources included fluorochemical manufacturing plants, airports, military fire training areas, wastewater treatment plants, landfills, and other industrial sites that manufacture or use PFASs (Sunderland et al., 2019). The geometric mean concentrations of PFOS (1386 ng/mL), PFOA (371 ng/mL), and PFHxS (863 ng/mL) in the serum of workers in the fluorochemical manufacturing plant in Hubei, China (Gao et al., 2015), were 98, 118, and 744 times that of

pregnant women in the first trimester in Wuhan, Hubei, China (Pan et al., 2017), respectively. PFAS-based aqueous film-forming foams used for firefighting in airports and military bases have caused severe PFAS contamination in drinking water (Gyllenhammar et al., 2015; Hu et al., 2016), groundwater, lakes, soil (Filipovic et al., 2015), and fish (Bhavsar et al., 2016; Gewurtz et al., 2014; Hansen et al., 2016) in many countries around the world, which has indirectly led to high PFAS levels in human serum (Gyllenhammar et al., 2015; Hansen et al., 2016). PFAS pollution from firefighting training areas can last for more than 20 years (Bhavsar et al., 2016).

Production and emission policies will affect the general exposure levels of PFASs. Globally, the phase-out of PFOS manufacturing by 3 M in 2002 (USEPA, 2000), the 2010/2015 PFOA Global Stewardship Program launched in 2006 (USEPA, 2006), and the Stockholm Convention on POPs since 2009 (UNEP, 2009) were extremely important to alleviate the global pollution of PFASs. In some countries, such as China, government regulatory frameworks for PFOS and PFOA also mitigated human exposure to these pollutants. For example, PFOS was added to the China Strictly Restricted Toxic Chemicals List in 2018 (MEEC, 2018), and nonstick fluororesin paint in kitchenware produced with PFOA was designated as a high pollution and high environmental risk product in 2017 by the Chinese government (MEEC, 2017). However, in some other countries, such as Malaysia, Bangladesh, and India, no PFASs are regulated (IPEN, 2019).

Specific to individuals, certain socio-demographic characteristics and living habits will also cause differences in PFAS exposure levels. Primiparae had greater concentrations of PFOA, PFOS, PFNA, PFDA, PFUnDA, PFDoDA, and total PFASs in breast milk compared to multiparae (Croes et al., 2012; Guzmàn et al., 2016; Tao et al., 2008a). Other sociodemographic characteristics, such as maternal body mass index, age, annual income, education level, and smoking status were also significantly associated with maternal exposure levels of PFASs (Lee et al., 2018; Tsai et al., 2018). Mothers' eating habits, including consumptions of fish, snacks, and milk, and the frequency of dining-out had significant influences on increasing PFASs in breast milk (Guzmàn et al., 2016; Lee et al., 2018). The use of cosmetics (for PFOA, PFHpA, and PFHxA) and the use of nonstick frying pans (for PFHpA and PFOA) were significant determinant factors in breast milk (Kang et al., 2016). For infants, the serum PFAS concentrations were related to gestational age at birth, drinking water, and whether the infant was bottle-fed or breast-fed (Gyllenhammar et al., 2018).

3.3. Temporal trend

The literature data available to this review on the time trend of PFAS exposure involved the sampling years from 1972 to 2016. The relevant samples included maternal blood, breast milk, amniotic fluid, and newborn dried blood spots. These studies were mainly from Europe (Bjerregaard-Olesen et al., 2016; Glynn et al., 2012; Jensen et al., 2012; Kärrman et al., 2007a; Nyberg et al., 2018; Ode et al., 2013; Shu et al., 2018; Sundström et al., 2012) and North America (Macheka-Tendenguwo et al., 2018; Spliethoff et al., 2008), and there were also studies on pregnant women in Hokkaido, Japan (Okada et al., 2013; Tsai et al., 2018). We summarized these studies in Fig. 4 where an upward trend was highlighted with yellow if the PFAS concentrations increased over time, a downward trend was highlighted with blue if the PFAS concentrations decreased over time, and a roughly leveled trend was highlighted with green if PFAS concentrations showed no marked changes over time. PFAS concentrations in general female serum in the U.S., from NHANES (CDC, 2019), are also included in Fig. 4.

Based on the data from NHANES, the geomean of PFOS concentrations in the serum of women in the U.S. decreased from 28 ng/L in 1999–2000 to 2.53 ng/L in 2015–2016; we found that the decline followed a first-order kinetics pattern with a "half-time" (time for levels to decrease by half - $t_{1/2}$) of 5 years. During the same period, PFOA concentrations decreased from 4.80 ng/L to 1.36 ng/L with $t_{1/2}$ of 8.8 years, and PFHxS decreased from 1.79 ng/L to 0.88 ng/L with $t_{1/2}$ of 14.6 years (CDC, 2019). While in the dried blood spots of New York State infants during 2000–2007, PFOS, PFOA, and PFHxS decreased with $t_{1/2}$ of 4.4, 4.1, and 8.2 years, respectively (Spliethoff et al., 2008), which were close to the average half-times of PFOS (5.4 years), PFOA (3.8 years), and PFHxS (8.5 years) in the serum of retired fluorochemical production workers (Olsen et al., 2007). In primiparous women from Sweden, the half-times of PFOS and PFOA in serum were 8.2 and 22 years, respectively, which are longer than those in the U.S. (Glynn et al., 2012).

As shown in Fig. 4, most PFASs in maternal and infant samples had an increasing trend before 2000, except in Uppsala, Sweden (Glynn et al., 2012; Kärrman et al., 2007a) and Southern Sweden (Ode et al., 2013). After 2000, both PFOS and PFOA showed downward trends in most places except Yup'ik, Alaska, U.S.; (Macheka-Tendenguwo et al., 2018) PFHxS also deceased in the U.S. (CDC, 2019; Spliethoff et al., 2008), Denmark (Bjerregaard-Olesen et al., 2016), Värmland (Shu et al., 2018), and Gothenburg (Nyberg et al., 2018), but increased in Uppsala County (Glynn et al., 2012) and Stockholm (Nyberg et al., 2018). While in Hokkaido, Japan (2003–2012), Denmark (2008–2013), and Värmland, Sweden (2007–2010), PFNA and PFDA showed increase trends. For PFUnDA, PFDoDA, and PFTrDA, the maternal plasma concentrations rose significantly from 2003 to 2006 but then dropped significantly from 2007 to 2012 in Hokkaido, Japan (Tsai et al., 2018). The temporal trends of PFHpS, PFHpA, PFDS, and PFHxA were downward in Denmark (Bjerregaard-Olesen et al., 2016) or Sweden (Glynn et al., 2012; Nyberg et al., 2018; Shu et al., 2018).

Overall, in the mother and infant populations, the exposure to most PFASs increased before 2000; after 2000, PFOS and PFOA declined in most places, while other PFASs showed regional differences or had unclear temporal trends.

4. Concentrations and distribution of isomers among biomatrices

4.1. Importance of Isomer-specific investigation

The structures of PFOA and PFOS isomers are shown in Figures S3 and S4, respectively. PFOA and PFOS have been frequently quantified in most studies, but their isomers have rarely been reported in studies on pregnant women and their infants, mainly because of the lack of analytical instruments for isomer separation and detection in many laboratories. Starting in 2013, the U.S. NHANES data collection began to measure and report linear and branched isomers separately for both PFOS and PFOA for various populations in the country (CDC, 2019), but pregnant women and infants are not reported separately. Among other PFCAs and PFSAs, concentrations of linear and branched isomers were reported separately for only PFHxS, PFDS, and PFNA in a few studies (Chen et al., 2017; Llorca et al., 2010; Nyberg et al., 2018).

The production histories of some PFASs are isomer-specific; thus the relative abundance of isomers found in environmental and human samples can be valuable in tracing the pollution sources and evaluating their contributions (Benskin et al., 2010a). There have been two historical manufacturing methods of PFASs: electrochemical fluorination (ECF) and telomerization. ECF was used by the 3 M Company, the largest manufacturer of PFASs worldwide. This process could yield PFOS and PFOA with approximately constant ratios of the linear isomer to branched isomers: 7:3 for PFOS and 8:2 for PFOA (Reagen et al., 2007). The use of ECF by 3 M ceased between 2000 and 2002 (Giesy and Kannan, 2001; USEPA, 2000), and telomerization became the predominant manufacturing technology, which yielded linear PFOA (Parsons et al., 2008). However, in some developing countries, the production of PFOS and its derivatives using ECF has continued (Benskin et al., 2010b; Xie et al., 2013). The detection of branched isomers of PFOA may be indicative of a source of ECF-produced PFOA (Jiang et al., 2014). For PFOS, if the proportion of branched isomers in environmental samples is higher than that in the technical ECF

products, it may suggest the presence of PFOS precursors (PreFOS) that transform to PFOS (Martin et al., 2010). The total historic emissions of PreFOS probably surpass those of PFOS (Armitage et al., 2009; Paul et al., 2009), and PreFOS could account for up to 60–80% of the exposure in the population with high concentrations of PFOS in serum (Vestergren et al., 2008). In addition, a large number of unidentified organic fluorine compounds were found in diverse environmental and human samples (Miyake et al., 2007; Yeung et al., 2008; Yeung et al., 2009). These unidentified organic fluorine compounds might include perfluorooctane sulfonamidoacetate, N-methyl perfluorooctane sulfonamidoacetate, N-ethyl perfluorooctane sulfonamidoacetate, among numerous fluorochemicals (Yeung et al., 2008). The unidentified compounds accounted for more than 60% of extractable organic fluorine in human whole blood from Jintan, China (Yeung et al., 2008). This aggravated the concerns of the potential risks of exposure to PreFOS.

Isomers of some PFASs showed obvious discrepancies in bioaccumulation, biomagnification, tissue distribution, and toxicity. Existing animal experiments indicated that linear PFOS (*n*-PFOS) accumulates more than branched PFOS (*br*-PFOS), except in Arctic cod (50% *br*-PFOS) (Jiang et al., 2014; O'Brien et al., 2011b; Powley et al., 2008; Sharpe et al., 2010). In *diporeia*, a sculpin, the biomagnification factor of monomethylated isomers of PFOS (15) was much higher than that of *n*-PFOS (9.0) (Houde et al., 2008; Langlois and Oehme, 2006; Peng et al., 2014). The linear PFOS was found to contribute 46.3–96.5% of total PFOS in most tissues, such as muscle, kidney, gill, and liver in aquatic organisms (Fang et al., 2014). Compared to monomethyl and diperfluoromethyl isomers, *n*-PFOS preferentially distributes to the eggs rather than the liver (Fang et al., 2014). The toxicity discrepancy of PFAS isomers was demonstrated in rats, mice, and chicken embryonic hepatocyte cultures. The results showed that linear ammonium salt of PFOA was more toxic than branched isomers, and technical-grade PFOS elicited a greater response of functional categories and pathways than linear PFOS (Loveless et al., 2006; O'Brien et al., 2011a).

Within humans, the distribution, transport, and health risks may differ significantly among isomers. It has been reported that *br*-PFOS preferentially accumulated in human blood rather than *n*-PFOS (Haug et al., 2009; Kärrman et al., 2007b; Riddell et al., 2009; Zhang et al., 2013c). At the same time, *br*-PFOS was also preferentially eliminated through the urinary system compared with *n*-PFOS (Zhang et al., 2013b). The distribution of isomers in humans may differ by sex; it was reported that females might possess a higher proportion of *br*-PFOS than males in the United States (Liu et al., 2015). For pregnant women, both branched PFOS and PFOA showed greater transplacental transfer efficiency than the corresponding linear isomers (Chen et al., 2017), which may be attributable to the stronger binding of linear PFOS and PFOA to serum proteins which are less able to cross the placental barrier (Beesoon and Martin, 2015). Very few data are available on the toxicities of PFAS isomers in pregnant women and their infants. Regarding the potential health risks, Jiang et al. found that the percentages of PFOA and PFOS isomers were significantly associated with certain medical parameters (Jiang et al., 2014). For example, the total white blood cell counts significantly increased with the increasing proportion of *br*-PFOS in maternal serum (Jiang et al., 2014). Li et al. found a positive correlation between perfluoro-1-methylheptane sulfonate (1*m*-PFOS) and gestational age, as well as a negative correlation between isomers of PFOS and birth weight. Additionally, total *br*-PFOS could cause a greater adverse influence on infant birth weight than *n*-PFOS (Li et al., 2017).

The laboratory analysis of PFAS isomers can be achieved via liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Chen et al., 2017) and gas chromatography-mass spectrometer (GC-MS) (Shafique et al., 2017). Traditional quantification method of PFOS using MS/MS transitions 499 → 80 and/or 499 → 99 may underestimate or overestimate the total PFOS concentrations in real samples, because the proportions of isomers in standards and environmental samples are different, and isomers have different relative response factors in detectors (Riddell et al., 2009). With the advancement in analytical technologies, the structure identification (Langlois and Oehme, 2006) and quantification (Riddell et al. 2009) of many PFOS isomers have become feasible on LC-MS/MS. However, some PFOS isomers, such as 3*m*-PFOS, 5*m*-PFOS, and diperfluoromethyl PFOS isomers, could not be well separated by currently available liquid chromatographic columns (Chen et al., 2017; Salihovic et al., 2013). Gas chromatography may be more effective in isomer separation, although a derivatization process is usually required. Derivatization reagents of PFAS isomers include 2,4-difluoroaniline (de Silva and Mabury, 2006), *iso*-propanol (Langlois et al., 2007), tetrabutylammonium hydroxide (Chu and Letcher, 2009), and diaryl iodonium salts (Harada et al., 2020). GC-MS approach was used to identify 11 PFOS isomers in environmental samples with high sensitivities (Chu and Letcher, 2009; Harada et al., 2020). The quantification of individual isomers avoids the problem of overestimation or underestimation to some extent.

4.2. PFAS isomers in pregnant women and infants

The timeline of studies on PFAS isomers in pregnant women and their infants is shown in Fig. 5. As early as 2007, Benskin et al. reported

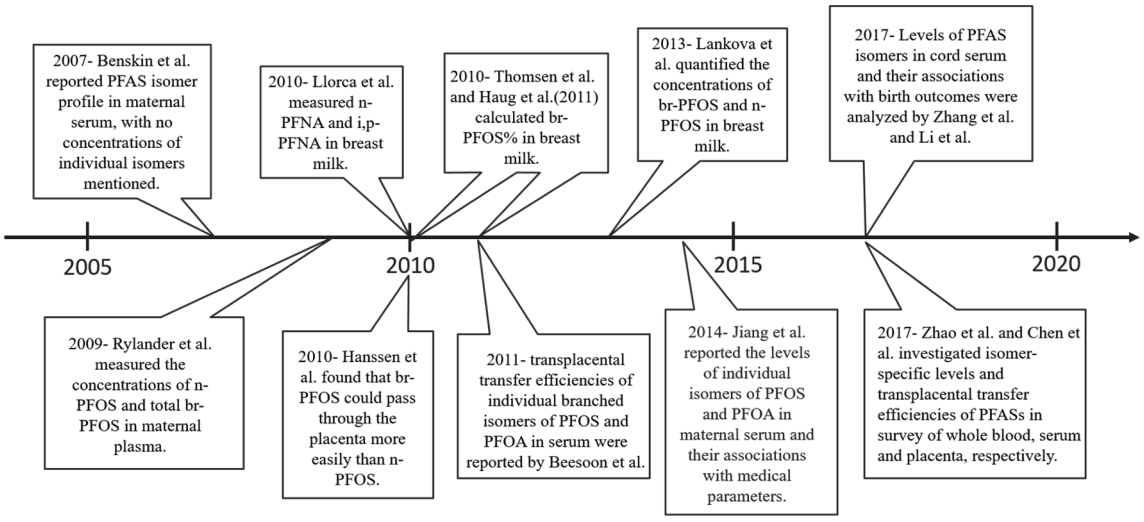

Fig. 5. Timeline of studies on PFAS isomers in pregnant women and infants.

the isomer profile of PFASs in human serum samples collected from pregnant women in Edmonton, Canada, without providing the concentration data of individual isomers (Benskin et al., 2007). In 2009, Rylander et al. measured the concentrations of *n*-PFOS and total *br*-PFOS in maternal plasma samples from south central Vietnam, which averaged 2.9 and 0.79 ng/mL, respectively; and found that *br*-PFOS constituted 19% of the total PFOS on average (Rylander et al., 2009). This percentage was similar to that in Oslo, Norway, where *br*-PFOS in maternal milk was found to be about 18% of the total PFOS (Haug et al., 2011; Thomsen et al., 2010). Additionally, the isomer pattern was similar among the mothers and remained relatively stable during the whole lactation period (Thomsen et al., 2010). A study from South Africa reported that *n*-PFOS constituted 58% and 52% of the total PFOS in maternal serum and cord blood, respectively. It may be that *br*-PFOS passes through the placenta more easily than *n*-PFOS (Hanssen et al., 2010). Transplacental transfer efficiency of individual isomers of PFOS and PFOA were reported by Beesoon et al. without presenting the data of concentrations in maternal serum and cord serum (Beesoon et al., 2011). In 2013, Lankova et al. used the PFOS standard (78.8% *n*-PFOS and 21.2% *br*-PFOS) to quantify the concentrations of *br*-PFOS and *n*-PFOS in breast milk. The average *n*-PFOS concentration (33 pg/mL) was higher than the average *br*-PFOS concentration (20 pg/mL) in breast milk samples from Czech women (Lankova et al., 2013). Concentrations of individual isomers of PFOS and PFOA in pregnant women in Asia were first reported in 2014 (Jiang et al., 2014). Subsequent relevant studies on individual isomers were mainly conducted in Chinese cities, including Wuhan (Chen et al., 2017), Guangzhou (Li et al., 2017; Zeng et al., 2019; Zhang et al., 2017), and Beijing (Wang et al., 2018), using maternal whole blood, maternal serum, cord whole blood, cord serum, and placenta (Table 2).

For PFOS, the linear isomer had higher concentration than others in all studies (Table 2). The reported proportions of *n*-PFOS in maternal and cord blood are usually higher than that in historical ECF PFOS technical products (approximately 70%) (Benskin et al., 2007; Chen et al., 2017; Haug et al., 2011; Rylander et al., 2009; Zhang et al., 2017; Zhao et al., 2017), except for those from the three studies mentioned above (Beesoon et al., 2011; Hanssen et al., 2010; Jiang et al., 2014). These proportions should not be used to quantitatively differentiate the source contributions of PFOS, unless the variations in PFOS isomer profiles due to numerous environmental and metabolic alterations are accounted for. For example, the weaker capabilities of transplacental transfer and renal clearance of *n*-PFOS might contribute to a higher *n*-PFOS percentage in maternal blood (Beesoon and Martin, 2015); and the preferential metabolization of branched PreFOS to *br*-PFOS, compared to linear PreFOS that could be metabolized to *n*-PFOS, might lead to a higher *br*-PFOS proportion found in organisms (Benskin et al., 2009). Additionally, PFOSA, a PreFOS, showed shorter half-lives of branched isomers in rats (Ross et al., 2012). In maternal and cord blood, the sum of perfluoro-3-methylheptane sulfonate and perfluoro-5-methylheptane sulfonate ((3 + 5)*m*-PFOS) often had the highest level among branched PFOS isomers, followed by perfluoroisopropyl-PFOS (*iso*-PFOS). The next was 1*m*-PFOS or perfluoro-4-methylheptane sulfonate (4*m*-PFOS). Finally, total perfluorodimethyl-PFOS (Σm_2-PFOS) showed the lowest level. In placentae, the only research to date reported the concentration rank order of PFOS isomers as n greater than $(3 + 5)m > 4m \approx 1m > iso > \Sigma m_2$ (Chen et al., 2017), which was slightly different from that in blood or serum.

Similar to PFOS, the linear PFOA isomer (*n*-PFOA) consistently comprised the largest portion of total PFOA. In Guangzhou, China, the proportion of *n*-PFOA in cord serum was 99%, followed by perfluoroisopropyl-PFOA (*iso*-PFOA) (Zhang et al., 2017). In maternal whole blood and serum, the reported isomer profiles were similar, with *n*-PFOA ranging from 98.2 to 99% on average (Jiang et al., 2014; Zhao et al., 2017). These *n*-PFOA proportions in real samples were all higher than those in the technical PFOA produced via the ECF process (~80% *n*-PFOA). The highest concentration of *n*-PFOA was 4.73 ng/mL in maternal serum from Tianjin, China, and the highest concentration of *iso*-PFOA was 0.23 ng/mL in cord serum from Guangzhou, China (Jiang et al., 2014; Zhang et al., 2017). In whole blood and serum samples, the concentrations of *iso*-PFOA usually ranked only second to those of *n*-PFOA. In addition, perfluoro-3-methylheptanoic acid (3*m*-PFOA), perfluoro-5-methylheptanoic acid (5*m*-PFOA), and perfluoro-4-methylheptanoic acid (4*m*-PFOA) were also detected. By comparing isomer concentrations of PFOA in paired maternal and cord serum, we found that, in general, the *n*-PFOA concentration in maternal serum was higher than that in cord serum; however, the opposite was true for *iso*-PFOA. This suggests that *iso*-PFOA might transfer across the placenta more easily than *n*-PFOA.

For other PFASs, such as PFHxS, Chen et al. and Nyberg et al. reported the concentrations of *n*-PFHxS and total *br*-PFHxS in maternal serum, cord serum, placenta, and breast milk (Chen et al., 2017; Nyberg et al., 2018). The results showed that *n*-PFHxS levels exceeded the *br*-PFHxS levels in all of these sample types. Two isomers of PFNA, perfluoro-n-nonanoic acid (*n*-PFNA) and perfluoro-7-methyl octanoic acid (*i,p*-PFNA), were measured in breast milk samples from Barcelona, Spain. The compound *i,p*-PFNA (mean: 71.3 pg/mL) showed higher detection frequency and concentration than *n*-PFNA (< 11.5 pg/mL) (Llorca et al., 2010). In addition, other isomers of PFASs and PFAS precursors, such as PFDS, PFOSA, N-methyl perfluorooctane sulfonamidoacetic acid (MeFOSAA) and N-ethyl perfluorooctane sulfonamidoacetic acid (EtFOSAA) were also measured by Nyberg et al (Nyberg et al., 2018).

5. Specificities of enantiomers among biomatrices

Most isomers of PFOS and PFOA have a chiral center, including 1*m*-, 2-perfluoromethyl- (2*m*-), 3*m*-, 4*m*-, 5*m*-, and 4,5-perfluorodimethyl-(4,5m_2-) PFOS, as well as 2*m*-, 3*m*-, 4*m*-, 5*m*-, and 4,5m_2-PFOA, as shown in Figures S3 and S4. Among these isomers, enantiomers of 1*m*-PFOS and 3*m*-PFOA have been well separated chromatographically by the use of chiral columns and subsequently detected by HPLC-MS/MS or GC-NCI-MS in environmental samples (Naile et al., 2016; Wang et al., 2011). Recently, a derivatization method made it possible to separate chiral isomers of PFOA using a non-chiral GC column (Zhu et al., 2020). In addition, two enantiomers of a synthesized derivative of 1*m*-PFOS, called 1*m*-PreFOS, has also been separated by HPLC-MS/MS (Wang et al., 2009).

Manufactured PFOS and PFOA through abiotic processes are always racemic mixtures with enantiomer fractions (EFs) of 0.5. EF was defined as the ratio of the first-eluting enantiomer peak area to the summed peak area of both enantiomers after enantioseparation on chromatographic instruments. Compounds with EF values above or below 0.5 were non-racemic. If these compounds came from the enzymolysis of their precursors, their EFs would probably deviate from 0.5 because enzymes are always chiral so that their relevant biotransformation is usually enantioselective (Hühnerfuss and Shah, 2009; Kallenborn and Hühnerfuss, 2001; Miralles-Marco and Harrad, 2015). Therefore, the EFs of PFAS enantiomers are helpful to elucidate the relative contributions of the direct source via PFOS and the indirect source via Pre-PFOS. This hypothesis that the EF value of PFOS can be a sign of human exposure through PreFOS is supported by two findings. One is that EFs were associated with the concentration of PreFOS in human sera (Asher et al., 2012; Wang et al., 2011). The other is that the 1*m*-PFOS EF was significantly associated with the percentage of *br*-PFOS, another sign of PreFOS exposure, in Swedish pregnant women and American adults from 1996 to 2000 (Liu et al., 2015).

The different interactions between PFAS enantiomers and chiral biomolecules are likely to elicit diverse transfer and accumulation behaviors in the human body. For instance, the 1*m*-PreFOS enantiomers could be enantioselectively transformed by human liver microsomes with quite different rates (Wang et al., 2009). The enantioselectivity varied among different environmental matrices and biota species. 1*m*-

Table 2
Summary of concentrations of isomers of PFOA, PFOS, and PFHxS in pregnant women and their infants.

Ref.	Sample type		PFOA (ng/mL)							PFOS (ng/mL)	
			n	*iso*	5*m*	4*m*	3*m*	*tb*	*total*	*n*	*iso*
(Zhao et al., 2017)	maternal whole blood	mean	0.966	0.014	0.003	0.001			0.984	16.8	1.08
		median	0.897	0.012	0.002	ND			0.907	5.45	0.304
	cord whole blood	mean	0.551	0.01	0.003	0.001			0.565	3.86	0.229
		median	0.522	0.008	0.002	0.001			0.535	1.04	0.045
(Zhang et al., 2017)	cord serum	mean	3.64	0.23					3.87	4.83	0.53
		median	1.04	0.19					1.23	2.07	0.18
(Li et al., 2017)	cord serum	median	1.0							2.1	0.2
(Zeng et al., 2019)	cord serum	mean	1.03						1.22	2.20	0.19
(Wang et al., 2018)	maternal serum	median	1.30							2.81	0.31
(Jiang et al., 2014)	maternal serum	mean	4.73	0.05	0.003					4.75	0.74
		median	3.95	0.04	0.001					4.31	0.61
(Chen et al., 2017)	maternal serum	mean	1.15	0.053	< 0.028	< 0.046	0.06	< 0.070	1.56	6.971	0.49
		median	1.023	0.052	< 0.028	< 0.046	0.053	< 0.070	1.424	5.236	0.391
	cord serum	mean	0.947	0.067	< 0.028	< 0.046	0.08	< 0.070	1.237	2.713	0.203
		median	0.961	0.065	< 0.028	< 0.046	0.05	< 0.070	1.226	2.513	0.199
	placenta (ng/g)	mean	0.359	< 0.039	< 0.015	< 0.037	0.049	< 0.017	0.484	2.484	0.151
		median	0.352	< 0.039	< 0.015	< 0.037	< 0.048	< 0.017	0.464	1.976	0.124

Ref.	PFOS (ng/mL)					PFHxS (ng/mL)			Sample size	Sampling years	Location
	1*m*	(3 + 5)*m*	4*m*	Σm_2	*total*	*n*	*br*	*total*			
(Zhao et al., 2017)	1.25	1.44	0.536	0.099	21.2				≤63	2014	Hubei, China
	0.115	0.384	0.081	0.005	6.59						
	0.716	0.417	0.142	0.043	5.41						
	0.053	0.083	0.011	0.002	1.35						
(Zhang et al., 2017)	0.21	0.88			6.46				≤321	2013	Guangzhou, China
	0.12	0.37			2.99						
(Li et al., 2017)	0.1	0.4							321	2013	Guangzhou, China
(Zeng et al., 2019)	0.13	0.39			3.17				201	2013	Guangzhou, China
(Wang et al., 2018)	0.14								168	2013	Beijing, China
(Jiang et al., 2014)	0.28	1.04	0.49	0.02					141	2012	Tianjin, China
	0.22	0.86	0.36	0.01							
(Chen et al., 2017)	0.136	0.466	0.157	0.037	8.67	0.247	0.038	0.528	32	2015–2016	Wuhan, China
	0.117	0.381	0.132	0.029	7.012	0.222	0.035	0.463			
	0.226	0.506	0.18	0.049	3.668	0.236	< 0.015	0.331			
	0.137	0.342	0.099	0.03	3.64	0.217	< 0.015	0.309			
	0.148	0.388	0.147	< 0.058	2.842	0.166	0.098	0.216			
	0.130	0.376	0.137	< 0.058	2.416	0.146	0.044	0.207			

ND: No peak could be found.

PFOS was racemic in the water and sediment of Lake Ontario (Asher et al., 2012). 3*m*-PFOA was nonracemic in the sediment from the contaminated area in Dalton, GA, USA (Naile et al., 2016). For animals, the EF values of 1*m*-PFOS in lake trout and zooplankton were obviously below 0.5; those in diporeia and mysis were significantly greater than 0.5; and those in sculpin, rainbow smelt, and rats were near 0.5 (Asher et al., 2012; Wang et al., 2011).

Research on chiral PFASs in pregnant women and their infants is very scarce. Three studies reported enantiomers of 1*m*-PFOS in maternal serum. The EF value of 1*m*-PFOS was found to be 0.432 on average in the serum of pregnant women from Edmonton, Canada (Wang et al., 2011). In Sweden, all serum samples of pregnant women also showed nonracemic EF values for 1*m*-PFOS (< 0.480). From 1996 to 2000, 1*m*-PFOS EFs in Swedish pregnant women decreased significantly over time, which implied a growing exposure to its precursor (Liu et al., 2015). Zhao et al. first demonstrated the enantioselective transplacental transfer of 1*m*-PFOS and found that the enantioselective binding affinity of 1*m*-PFOS to human serum albumin may be a key factor (Zhao et al., 2020).

It is noteworthy that the elimination, placental transfer, breastfeeding, and other physiological processes of pregnant women may also be enantioselective, and chiral toxicological investigations of PFASs in pregnant women and their infants have not been performed. Tracking the chiral signature of PFAS enantiomers is meaningful for a better understanding of their related risks on pregnant women and their infants.

6. Conclusion and perspectives

In this literature review, we summarized previously published biomonitoring data for PFASs in maternal blood, cord blood, breast milk, placenta, and other samples, and analyzed these data at the congener, isomer, and enantiomer levels. Based on these data, we critically reviewed the current scientific knowledge of human exposures to PFASs during pregnancy and lactation. The concentrations of PFASs as a group are relatively high in blood but relatively low in breast milk, in comparison with other major persistent and ubiquitous organic pollutants. Among sample matrices, PFAS volume-based concentrations followed the sequence of (maternal, cord, and infant blood) > (placenta and infant organs) > (breast milk and amniotic fluid) in most cases. Maternal and infant exposure to PFASs, especially PFOS and PFOA, is a global problem. PFOA and PFHxS showed significant differences between developed and developing countries while PFOS had no significant geographic differences. The exposure to most PFASs had been increasing before 2000; since then PFOS and PFOA levels have declined in most places, while other PFASs showed regional differences or had unclear temporal trends. We emphasize the importance of research on PFAS isomers and enantiomers as such data are valuable to current and future investigations on contamination sources, cross-matrix transfer mechanisms, toxicities as related to chemical structures, and so on.

By critically summarizing the current knowledge, we have gained better insight into the global situation and the relative significance of various investigations. The number of studies in this research area is far from being sufficiently large, thus efforts must continue. Below are our perspectives for future studies:

a. Given the technical feasibility of separately analyzing PFAS isomers and enantiomers as well as their differences in biological behaviors, we suggest that future biomonitoring and research on health effects be conducted in a manner that differentiates isomers and enantiomers. Such efforts can greatly benefit from the development of more sensitive and less costly analytical instrumentation for PFAS enantiomers.
b. Compared with blood, other biomatrices such as placenta (whole or its components), amniotic fluid, and meconium have been less used. The collection of these samples are noninvasive thus bring minimal risk to the mother and the infant. Data obtained from diverse biomatrices will provide a more comprehensive understanding of maternal-infant transfer and intake of PFASs.
c. In using blood for exposure assessment purposes, we prefer whole blood over plasma and serum. PFAS concentrations in serum and plasma cannot fully represent the internal exposure of mothers and infants. The use of whole blood would help avoid sampling bias because the distribution among different blood matrices appear to differ among individual PFASs and may also be population-dependent.
d. Longitudinal studies with large sample sizes are highly desired in the investigation of the health effects of early-life exposure to PFASs in children and adults.
e. Given that the emerging PFASs may account for a large fraction of the total organic fluorine but have been rarely investigated, further studies on their occurrence and health effects in maternal and infant populations are warranted.

Declaration of Competing Interest

The authors declare no competing interests.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106012.

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