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Review article

A review of the transplacental transfer of persistent halogenated organic pollutants: Transfer characteristics, influential factors, and mechanisms

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ABSTRACT

Persistent halogenated organic pollutants (HOPs) are a class of toxic chemicals, which may have adverse effects on fetuses via transplacental transfer from their mothers. Here, we review reported internal exposure levels of various HOPs (organochlorinated pesticides, polychlorinated biphenyls, polybrominated diphenyl ethers, short- and medium-chain chlorinated paraffins, and per- and poly-fluoroalkyl substances) in placenta, and both maternal and umbilical cord sera. We also present analyses of the transplacental transfer and placental distribution characteristics of each class of compounds, and discuss effects of several factors on the transfer and accumulation efficiencies of HOPs, as well as the main mechanisms of HOPs' transfer across the placental barrier. Reported compound-specific transplacental transfer efficiencies and distribution efficiencies, expressed as umbilical cord:maternal serum and placental:maternal serum concentration ratios (R_{CM} and R_{PM}, respectively), are summarized. Average published R_{CM} values of the HOPs range from 0.24 to 3.08 (lipid-adjusted) and from 0.04 to 3.1 (based on wet weights), and are highest for perfluoroalkylcarboxylates (PFCAs) and tetrabromobisphenol A. Average published R_{PM} values range from 0.14 to 1.02 (lipid-adjusted) and from 0.30 to 1.4 (based on wet weights). The broad R_{CM} and R_{PM} ranges may reflect effects of various factors, inter alia physicochemical properties of HOPs, metabolic capacities of mothers and fetuses, placental maturity, and differential expression of influx/efflux transporters in the placenta. Generally, HOPs' R_{CM} values decline linearly with molecular size, and are curvilinearly related to solubility. Plasma protein binding affinity and the difference between maternal and fetal metabolic capacities may also affect some HOPs' transfer efficiencies. HOPs' molecular size may be influential. Transplacental transport of HOPs likely occurs mostly through passive diffusion, although influx/efflux transporters expressed on maternal and/or fetal sides of the placenta may also facilitate or hinder their transport. Overall, the review highlights clear gaps in our understanding of mechanisms involved in HOPs' transplacental transport.

1. Introduction

Persistent organic pollutants (POPs) are a group of widely distributed chemicals that are characterized by long-range dispersal, persistence in the environment, and toxicity to the environment and human body. The use of POPs listed as priority-controlled chemicals under the Stockholm Convention is forbidden or severely restricted globally. Within the POPs, there is a class of persistent halogenated organic pollutants (HOPs), which includes organochlorinated pesticides (OCPs), polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), short-chain chlorinated paraffins (SCCPs, C_{10}-C_{13}), per- and poly-fluoroalkyl substances (PFASs), and some flame retardants (Morello-Frosch et al., 2016; Yu et al., 2014). DDTs (dichlorodiphenyltrichloroethane and its metabolites), hexachlorobenzene (HCB), aldrin, dieldrin, heptachlor, and PCBs were first listed as POPs. Then hexachlorocyclohexane isomers (α-HCH, β-HCH, and γ-HCH), commercial Penta- BDEs, Octa-BDEs, Deca-BDE, perfluorooctane sulfonate (PFOS), hexabromocyclododecanes (HBCDs), and SCCPs were also included in the Stockholm Convention. In addition, perfluorooctanoic acid (PFOA) remains a potential POP, and tetrabromobisphenol A (TBBPA) has been

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classified as a group 2A (probably carcinogenic to humans) compound by the International Agency for Research on Cancer (Grosse et al., 2016). However, there are no current global restrictions on TBBPA production.

Exposure to these compounds and their metabolites has been linked with many adverse health consequences, including neurodevelopmental toxicity, thyroid dysfunction, and negative birth outcomes (Govarts et al., 2012; Vuong et al., 2018). Hence, the toxic effects of human exposure to HOPs are of great concern, especially prenatal exposure, because infants and fetuses are more vulnerable to toxicants than adults (Morello-Frosch et al., 2016; Tsang et al., 2011). As reported in various epidemiological studies, pre- and post-natal exposure to HOPs have been linked to many adverse effects observed in infants and children, such as premature delivery, reduced birth weight, growth retardation, and neurodevelopmental delay (Morello-Frosch et al., 2016; Vuong et al., 2018). For example, OCPs are reportedly associated with changes in circulating thyroid hormone levels and reduced birth weight (Pathak et al., 2009), and increases in BDE153 concentrations in umbilical cord blood are associated with increased odds of low total thyroxine levels, as detected in neonatal blood spot tests (Herbstman et al., 2008).

Furthermore, it has been suggested that developmental exposure to HOPs detrimentally affects physical and mental development, reading skills, externalizing behaviors, full-scale intelligence quotient, executive function, and other cognitive variables (Bytingsvik et al., 2012; Eskenazi et al., 2013; Zhang et al., 2017b). The oxidative metabolites of PBDEs, including hydroxylated/methoxylated PBDEs (OH/MeO-PBDEs), have been mostly found to disrupt endocrine and hormone systems (Cao et al., 2018; Hamers et al., 2006). In addition, adverse effects that may become evident later in life have been associated with toxicant exposure during fetal and infant life stages. For example, the latent early-life associated regulation (LEARn) model suggests that both endogenous and exogenous environmental factors may start to influence human health in early stages of development, disturb gene regulation through a long-term pattern, and gradually manifest as long-lasting effects during later stages life stages (Lahiri et al., 2016). Therefore, there are urgent needs to elucidate multiple effects causing by early exposure to certain environmental contaminants, including health influence of infant, development influence of children and even adults.

Some HOPs have been found to enter the fetal system despite the protective role of the placenta (Needham et al., 2011). Many studies have detected some of these compounds and their metabolites in maternal blood, umbilical cord blood and placenta samples (Beesoon et al., 2011; Cariou et al., 2015; Choi et al., 2018; Dewan et al., 2013; Li et al., 2020a, 2020b; Needham et al., 2011; Rovira et al., 2019; Zhang et al., 2013). HOP exposure does not necessarily have adverse effects, but knowledge of exposure levels is clearly needed to assess risks to fetuses, and adverse outcomes in later life stages. Such risk assessments require clear understanding of placental transport and associated mechanisms. Paired umbilical cord blood and placenta samples have been widely used in studies designed to acquire such understanding, but very limited aspects of the investigations and findings have been recently reviewed (Aylward et al., 2014; Tang and Zhai, 2017). Tang and Zhai (2017) described PBDE levels in human biological samples, while Aylward et al. (2014) summarized and discussed concentration ratios of certain POPs, including OCPs, PBDEs, PCBs, and PFASs. Partly due to the restrictions of these reviews there is a lack of systematic knowledge about effects of key factors on various POPs' transfer mechanisms, despite considerable relevant advances in recent years. Thus, comprehensive analysis of published research on HOPs is required to improve understanding of how members of specific classes of compounds can be transferred from mothers to fetuses.

The transplacental transfer of other, non-persistent pollutants (such as benzophenone-type UV filters, bisphenol A and its alternatives, parabens, and triclosan and triclocarban) has been previously studied (Kolatorova et al., 2018; Krause et al., 2018; Song et al., 2020; Wei, et al., 2017). The detection of these pollutants in cord blood, placenta, and/or amniotic fluid shows that they can pass through the placental barrier and enter fetal blood circulation. Several types of concentration ratios have been obtained for these pollutants, including cord blood: maternal serum (R_{CM}), placenta:maternal serum (R_{PM}) and amniotic fluid:cord blood concentration ratios. For example, Song et al. (2020) presented R_{CM} values for 4-hydro benzophenone, benzophenone-1, benzophenone-4, and benzophenone-3, which ranged from 1.03 to 2.35. Fewer studies have been conducted on these chemicals than HOPs, but more systematic knowledge of all these classes of chemicals is required.

Thus, aims of this review are to provide a comprehensive overview of HOPs' transplacental transfer ratios, factors influencing their transplacental transfer and accumulation efficiencies, and associated transport mechanisms. To meet these aims we present results of a survey of literature concerning their levels in paired mother-fetus samples (maternal blood, umbilical cord blood and/or placenta). The findings highlight needs for comprehensive studies including analyses of HOPs' interactions with trophoblast cell lines, human placental perfusion systems, and animals, as well as evidence from large-scale population data analyses.

2. Methodology

The Web of Science and Pubmed databases were searched to identify studies published before 1st March 2020, that reported measured concentrations of HOPs in placenta, umbilical cord, and maternal sera. The search terms included "placental transfer", "transplacental transfer", or "prenatal exposure" and included studies presented data concerning at least one of the studied pollutants. Relevant reviews were also examined to identify studies that were not found through the literature search. In total, 109 studies met the criteria and were included in the present review. Of these 109 studies, 34, 33, 32, 40, and eight described concentrations of OCPs, PCBs, PBDEs, PFASs, and SCCPs along with other brominated flame retardants, respectively, in paired maternal-fetal samples. Some articles discussed concentrations of more than two kinds of HOPs. The number of published reports from various countries and regions are shown in Fig. S1. Most of the articles included in this review were from Asia (60 reports, mainly from China, Korea, and Japan) and Europe (33 reports).

To include comparable transplacental transfer efficiency values, R_{CM} and R_{PM} values for each investigated compound were either taken from the identified publications or calculated from average (mean, median, or geometric mean) concentrations they provided. In efforts to ensure that the evaluated data were reliable, the calculated R_{CM} or R_{PM} values derived from analyses in which compounds were detected in more than 70% of both maternal and fetal samples only, are presented and considered in this review. It should be noted that the R_{CM} value is directly related to the transplacental transfer efficiency, i.e., high R_{CM} values indicate that the pollutant concerned readily moves from maternal to fetal circulation. R_{PM} values are also very important transfer indicators, reflecting pollutants' placental distribution and accumulation characteristics.

We assessed relationships between R_{CM}/R_{PM} values and physicochemical parameters using linear or quadratic curve regression fitting coefficients (R^2) and analysis of variance. Thresholds for statistical significance and 'marginal significance' were set at $p < 0.05$ and $p = 0.05–0.1$, respectively. IBM SPSS version 19 software (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses presented here.

3. Transplacental transfer characteristics

3.1. OCPs

The production and use of most OCPs has been widely prohibited. However, DDT, HCH isomers (HCHs), and HCB are still detectable in the environment and human bodies (Yu et al., 2012; Zhang et al., 2018b;

Zhou et al., 2012). DDT and dichlorodiphenyldichloroethylene (DDE) are ubiquitous OCP pollutants that have been detected in both maternal and fetal samples. β-HCH and HCB are other OCPs that have been frequently detected in maternal and fetal samples (Adetona et al., 2013; Zhang et al., 2018b), albeit at lower concentrations than DDTs. For these OCPs (DDTs, HCB, and HCHs), significant correlations have been generally found between concentrations measured in maternal and umbilical cord blood (or placenta) samples, indicating that these chemicals can cross the placental barrier from maternal to fetal circulation (Choi et al., 2018; Dewan et al., 2013; Li et al., 2014; Needham et al., 2011; Zhang et al., 2018b). However, some reported correlations have been weak observed because the concentrations were close to the limits of detection.

The transplacental transfer of OCPs was first studied by Waliszewski et al. (2001), followed by Covaci et al. (2002). After these initial investigations, more than 10 studies have been conducted, most published since 2010. For example, Needham et al. (2011) measured concentrations of 87 environmental pollutants, including DDTs, HCH, and pentachlorobenzene (PeCB), in blood samples from 15 mothers and their newborns from the Faroe Islands. They found the maternal concentrations to be 1.7 times greater than cord serum concentrations, resulting in a lipid-adjusted R_{CM} value of 0.57. Similarly, median lipid-adjusted R_{CM} values of 0.70, 0.75, and 0.68 were obtained for HCHs, HCB, and *p,p'*-DDE, respectively, by Vizcaino et al. (2014), who monitored 14 OCPs in 308 maternal-umbilical cord blood pairs. In most studies, the lipid-adjusted concentrations of OCPs have been higher in maternal blood than in cord blood (Choi et al., 2018; Müller et al., 2019; Needham et al., 2011; Tsang et al., 2011; Zhang et al., 2018b). However, Lopez-Espinosa et al. (2016) and Morello-Frosch et al. (2016) reported conflicting results, more specifically they detected higher HCB and γ-HCH levels in fetal blood than in maternal blood samples.

The R_{CM} value is an important indicator of a focal compound's transplacental transfer characteristics. Some researchers have suggested that the transfer process is strongly affected by the lipid fraction, as lipophilic compounds can move across the placenta from maternal to fetal circulation. Accordingly, the lipid-adjusted ratio of concentrations in fetal and maternal circulation (R_{CM}) should be close to one (Fukata et al., 2005; Vizcaino et al., 2014). The available R_{CM} values for OCPs are shown in Fig. 1. As OCPs are lipophilic, most of these values are around one, although the median lipid-adjusted R_{CM} values vary widely, e.g., ranges of values for *p,p'*-DDT, *p,p'*-DDE, β-HCH, and HCB are 0.62–1.8, 0.37–1.34, 0.36–1.19, and 0.70–2.31, respectively (Table S1). It should be noted that R_{CM} values calculated from volume-based data are much smaller (e.g., 0.2–0.91, 0.11–0.82, 0.18–0.72, and 0.20–0.60, respectively, for these compounds), because umbilical cord blood contains lower levels of lipids than maternal blood (Table S2). Previous literature usually presents lipid-adjusted R_{CM} values, and all of the data presented hereafter reflect lipid-adjusted R_{CM} values unless otherwise specified.

Data on prenatal exposure to several other OCPs, including aldrin, dieldrin, endosufan isomers, chlordanes, and heptachlors, among others, have also been reported. However, very few R_{CM} values could be obtained for these compounds, because low detection frequencies (usually < 50%) have been reported for them (Table S1). To the best of our knowledge, only one published study has addressed prenatal exposure to methylsulfonyl metabolites of DDE ($MeSO_2$-DDE), based on analysis of 10 paired serum samples from eastern Slovakia (Linderholm et al., 2007). The results included lipid-adjusted R_{CM} values close to one, and findings that 3-$MeSO_2$-DDE was the major methylsulfonyl

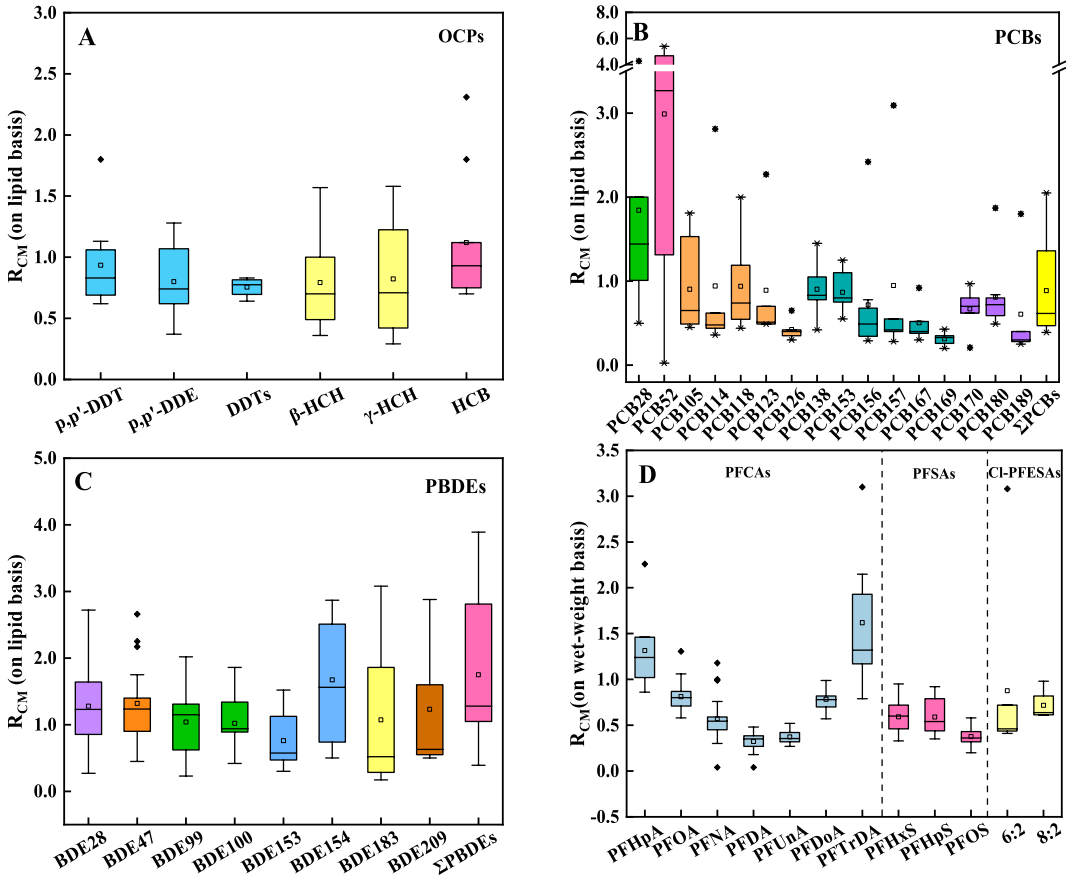

Fig. 1. Distributions of fetal cord serum to maternal serum concentration ratios (R_{CM}) of OCPs, PCBs, PBDEs, and PFASs. The upper and lower limits of each box indicate the 25th and 75th percentiles, while the line and square in the middle represent the mean and median values. The whiskers extend to the last observation within 1.5 times the interquartile range. The crosses outside of the whiskers represent outlier values (data were obtained from references listed in Table S13).

metabolite in most of the samples.

Placenta is a highly complex organ in a pregnant woman's body. Serving as a 'barrier', it mediates maternofetal exchange of xenobiotics. Myllynen et al. (2005) regarded it as a two-way monitor and controller of fluxes of xenobiotics, obtaining mean lipid-adjusted R_{PM} values of 0.11–0.66, 0.20–1.98, and 0.19–1.56 for *p,p'*-DDE, β-HCH, and HCB, respectively, and similar wet weight-based values (0.11–2.61) for those compounds (Tables S3-4).

3.2. PCBs

PCBs were previously widely used in various industrial applications (Jarrell et al., 2005; Park et al., 2010). Their lipophilicity and chemical stability, together with their widespread use, has led to sufficiently high concentrations to cause concern in diverse environmental compartments, and human bodies. Hence, their transplacental transfer has received substantial attention. Mori et al. (2014) reported concentrations of PCBs including tri- to deca-CBs in paired maternal blood, umbilical cord blood, and umbilical cord samples. Transplacental transfer efficiencies of more than 30 PCB congeners derived from the data vary widely, although the lipid-adjusted R_{CM} values are consistently under 2, and the wet weight-based R_{CM} values under 1 (Tables S5–6). The overall ranges of lipid-adjusted R_{CM} values were 0.44–1.94 for PCB118 (5Cl), 0.42–1.45 for PCB138 (6Cl), 0.71–1.25 for PCB153 (6Cl), and 0.49–1.87 for PCB180 (6Cl), while corresponding values based on wet weights were 0.12–0.63, 0.2–0.72, 0.18–0.97, and 0.17–0.28, respectively (Tables S5–6). Reported transplacental transfer ratios of PCBs are generally higher than those of OCPs, suggesting that these toxicants are more readily transferred from mother to fetus than OCPs.

R_{PM} values we derived for these compounds were significantly lower than the corresponding R_{CM} values, suggesting that they accumulate more in the cord blood than in the placenta. Average lipid-adjusted R_{PM} values varied from 0.31 to 0.59, for PCB180 and PCB28, respectively (Fig. 2). Jeong et al. (2018) detected the same trend in distributions of PCBs, and suggested that PCBs with relatively low molecular weights are preferentially transported from maternal serum to the fetal circulation, while higher molecular-weight congeners tend to remain in placental tissues. Congener-specific R_{PM} to R_{CM} ratios we calculated ranged from 0.39 to 0.75.

Several PCB metabolites, including hydroxylated and methylsulfonate forms (OH-and $MeSO_2$-PCBs, respectively), have also been detected in humans and shown to traverse the placenta to the fetus (Guvenius et al., 2003; Linderholm et al., 2007; Meijer et al., 2008; Park et al., 2008; Soechitram et al., 2004). Some of these metabolites have been detected in blood, and found to account for approximately 10%−30% of the total PCBs in it (Otake et al., 2007; Park et al., 2009). In a study by Linderholm et al. (2007), the main $MeSO_2$-PCBs found in human blood were *para*-substituted congeners, with overall half-lives of approximately nine years. In addition, average lipid-adjusted levels of four $MeSO_2$-PCBs in maternal samples were about 1.5 times higher than those in corresponding umbilical cord blood samples, giving an overall R_{CM} value of 0.67 for total $MeSO_2$-PCBs, which is lower than the value reported for PCB153 (Linderholm et al., 2007).

For OH-PCBs, wet weight-based transfer ratios reported, with wet weight-based R_{CM} values ranging from 0.37 to 0.6 for 4-OH-CB107, 0.60 to 0.68 for 3-OH-CB153, 0.62 to 1.01 for 3′-OH-CB138, and 0.6 to 2.77

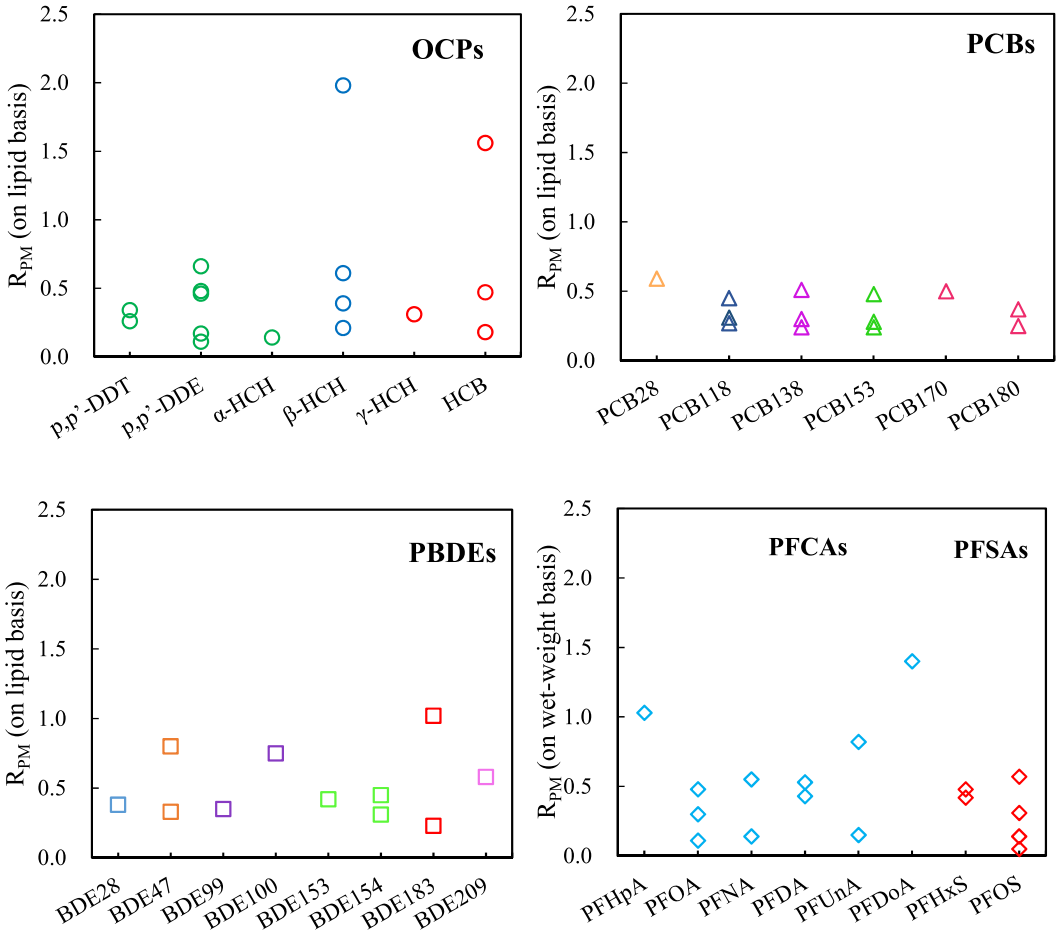

Fig. 2. Distributions of placenta to maternal serum concentration ratios (R_{PM}) of OCPs, PCBs, PBDEs, and PFASs (data were obtained from references listed in Table S13).

for 4-OH-CB187 (Meijer et al., 2008; Park et al., 2008; Soechitram et al., 2004). Higher R_{CM} values have been obtained for hydroxylated metabolites than the parent compounds, suggesting that polar metabolites move across the placental barrier more readily than their non-polar counterparts (Park et al., 2008; Soechitram et al., 2004). Kimura-Kuroda et al. (2007) propose that PCB metabolites may be more toxic than their parent PCBs. Thus, PCBs are dangerous compounds, as not only PCBs but also their metabolites pose health risks for humans (Gómara et al., 2012).

3.3. PBDEs

PBDEs have been widely used in polymers, furniture and electronic devices as flame retardants for safety purposes (Jiang et al., 2019). Although they are being phased out under the Stockholm Convention, human exposure to them will continue for a long time because of their environmental persistence. PBDEs, including BDE28, BDE47, BDE99, BDE100, BDE153, and BDE154, have been detected in high proportions of human blood samples in several studies, with most of the studied pregnant women had been exposed to more than one PBDE congener (Woodruff et al., 2011; Zheng et al., 2017). PBDEs have also been detected in umbilical cord blood and placenta samples.

There are substantial variations in transplacental transfer efficiencies obtained for individual congeners, with average R_{CM} values ranging between 0.76 and 1.67 (Fig. 1). The R_{CM} values for certain congeners vary widely. For example, reported lipid-adjusted R_{CM} values of BDE209 range from 0.5 to 2.88 (Chen et al., 2013; Jakobsson et al., 2012; Li et al., 2013; Vizcaino et al., 2014; Zheng et al., 2017). In addition, a higher range of transfer efficiency values has been reported for BDE209 than for lightly- or moderately-brominated congeners. Several factors may have contributed to this pattern. Among others, due to the short half-life of BDE209 (15 days), differences in sampling intervals between studies might partly explain the variation (Zheng et al., 2017). Furthermore, substantial variation in BDE209 concentrations could be due to inter-individual differences. Similar exposed dose but difference in the time between mothers' exposure to BDE209 and sampling may lead to noticeably different concentrations of the compound (Jakobsson et al., 2012). Moreover, some of the R_{CM} data may be imprecise if the reported concentrations were close to the limit of detection for BDE209 (Jakobsson et al., 2012; Needham et al., 2011).

Few R_{PM} values for PBDE congeners are available (Table S9). Zhao et al. (2013) found that R_{PM} values of specific PBDE congeners vary. We found that reported R_{PM} values are lower than corresponding R_{CM} values, except for BDE183 (Fig. 2). Thus, PBDE accumulation seems to be lower in placental tissue than in umbilical cord blood. However, the findings are based on sparse available data, and more information is needed for deeper analysis.

An important characteristic of PBDEs is that they can be debrominated or oxidized in organisms. Highly brominated congeners can be degraded to more lightly brominated products, which may be more toxic than the parent PBDEs (Cao et al., 2018; Stapleton et al., 2009). Oxidative metabolites of PBDEs, including hydroxylated/methoxylated PBDEs (OH/MeO-PBDEs), are commonly found in humans and other mammals (Haraguchi et al., 2016; Morello-Frosch et al., 2016; Qiu et al., 2007; Zota et al., 2018a). Concentrations of OH-PBDEs in paired maternal and umbilical cord sera were investigated in six of the studies covered in this review. In five of the studies, levels in cord serum samples were found to be higher than to, or equal to, levels in corresponding maternal serum samples (Chen et al., 2013; Morello-Frosch et al., 2016; Qiu et al., 2009; Wan et al., 2010; Zota et al., 2018b). For example, median wet weight-based R_{CM} values of 1.1 and 1.78 for 5-OH-BDE47 have been obtained from analyses of 69 and 20 sets of samples from San Francisco and Cincinnati in the USA, respectively (Chen et al., 2013; Morello-Frosch et al., 2016). Wan et al. (2010), Zota et al. (2018) also found fetal concentrations of 6-OH-BDE47 and 5-OH-BDE47 exceeded the concentrations measured in maternal serum. However, lower 6-OH-BDE47 concentrations were found in cord blood than in maternal blood (0.6 vs. 2.1 pg/g wet weight) in a Japanese study of six mother-neonate pairs (Kawashiro et al., 2008).

Nevertheless, most studies have reported higher wet weight-based concentrations of OH-PBDEs in cord blood than in maternal blood. These results indicate that OH-PBDEs, which are more hydrophilic than the lipophilic parent PBDE compounds, traverse the placental membrane more readily than the parent compounds, in accordance with transfer efficiencies reported for PCBs and their polar metabolites. Thus, like the PCBs, we should be concerned with the occurrence and transplacental transport of metabolites of PBDEs as well as the parental compounds.

3.4. PFASs

PFASs are a group of synthetic chemicals that are widely used in textiles, cosmetics, adhesives, cleaning agents, and food packaging. PFOA, a perfluoroalkylcarboxylate (PFCA) compound, and PFOS are the most commonly encountered PFASs. These compounds show high chemical stability in the environment and have been previously detected in humans. The PFASs most prominently detected in humans include PFOA, PFOS, perfluoroheptanoic acid (PFHpA), perfluorohexane sulfonate (PFHxS), and perfluorodecanoic acid (PFDA). Significant correlations ($p < 0.001$ to 0.05) have usually been found between concentrations of these compounds in paired maternal and umbilical cord sera samples, indicating transplacental transfer, and subsequent prenatal exposure (Beesoon et al., 2011; Cariou et al., 2015; Li et al., 2020a, 2020b; Rovira et al., 2019; Zhang et al., 2013).

Wet weight-based R_{CM} values reported for PFCAs and PFSAs vary between 0.04 and 3.1, and between 0.21 and 1.49, respectively (Table S11). Most of the R_{CM} values for PFCAs with 8–12 carbons and PFSAs with 6–8 carbons are <1, but the ratio reported for perfluorotridecanoic acid (PFTrDA, 13 carbons) is considerably higher than 1 (Fig. 1). The PFASs with the highest mean reported R_{CM} values are PFTrDA (1.63), followed by perfluoroheptanoic acid (PFHpA, 1.14), while the values are lowest for perfluorodecanoic acid (PFDA, 0.33), perfluoroundecanoic acid (PFUnA, 0.37), and PFOS (0.40). Significant differences in these compounds' specific transplacental transfer efficiencies have been consistently observed (Gao et al., 2019; Kim et al., 2011; Li et al., 2020b; Pan et al., 2017; Yang et al., 2016; Zhang et al., 2013).

PFASs are a series of compounds with varying carbon chain length, thus their structures vary greatly from structures of the other HOPs considered in this review (OCPs, PCBs, and PBDEs). All PFASs contain a common hydrophilic functional group at the end of a long hydrophobic carbon chain. In many studies, the R_{CM} values of PFCAs obtained in many studies decreased with increases in the carbon chain length until it reached a certain threshold then increased (Gao et al., 2019; Li et al., 2020b; Pan et al., 2017; Wang et al., 2019; Zhang et al., 2013). In addition, carboxylates have been found to transfer across the placental barrier more efficiently than sulfonates with the same carbon chain length (Pan et al., 2017), suggesting that transplacental transfer efficiency is influenced by functional groups and/or isomer branching patterns. For example, Morello-Frosch et al. (2016) and Zhang et al. (2013) reported R_{CM} values ranging from 0.58 to 1.30 and 0.21 to 0.88 for PFOA and PFOS, respectively. Furthermore, higher transplacental transfer efficiencies have been obtained for branched isomers of PFOS, PFHxS, and PFOA than the linear isomers (Beesoon et al., 2011; Li et al., 2020a; Zhao et al., 2017a). In addition, R_{CM} values of both PFOS and PFOA are generally positively related to the proximity of the branching point to the sulfonate or carboxyl moiety (Chen et al., 2017; Zhao et al., 2017a).

Wet weight-based R_{PM} values reported for some PFCAs and PFSAs vary between 0.11 and 1.40, and between 0.05 and 0.57, respectively (Table S12). Most of the values are <1 (Fig. 2). Differences in these values indicate that specific PFCAs and PFSAs have differing tendencies

to accumulate in placental tissue, and Chen et al. (2017) found that R_{PM} values of branched isomers of PFOS and PFHxS differed from those of corresponding linear isomers.

3.5. Some other HOPs

Other HOPs have received much less attention than those already discussed. However, several flame retardants have received more attention in terms of transplacental transfer than most of the others, and they are the focal compounds in this section. One of these, TBBPA, is commonly used as a reactive or additive brominated flame retardant and its transplacental transport has been investigated in four studies, including a Korean study in which serum samples from newborn infants were used instead of umbilical cord blood (Kim and Oh, 2014). Detection frequencies of TBBPA in umbilical cord blood were usually lower than those of other HOPs discussed in this review. For example, Kawashiro et al. (2008) detected it in 67% of maternal blood and 100% of umbilical cord samples collected in Japan, but not all umbilical cord blood samples. Partly perhaps because of the limited data, there are discrepancies in the correlations between maternal and fetal concentrations. Kim and Oh (2014) reported significant maternal-fetal correlations in TBBPA levels. In contrast, Cariou et al. (2008) obtained a low Spearman coefficient for their entire TBBPA dataset, although it could be strengthened by discarding several extreme values. These R_{CM} values are significantly higher than 1, indicating that TBBPA has relatively high transplacental transfer efficiency.

HBCD is a flame retardant that is applied to polystyrene foams and textiles. Commercial HBCD, which is widely used on a globally, consists largely of three diastereoisomers: α-, β-, and γ-HBCD. To the best of our knowledge, only three studies have investigated HBCD levels in paired maternal and cord sera samples, although HBCDs have commonly been reported in humans (Drage et al., 2017; Kim and Oh, 2014; Roosens et al., 2009). Kim and Oh (2014) obtained R_{CM} values between 0.7 and 1.95 for HBCDs, and higher values for α-HBCD than either β- or γ-HBCD. In addition, HBCDs were not detected in all of the maternal and fetal blood samples analyzed in a French study (Antignac et al., 2008). In summary, available evidence suggests that HBCDs do not traverse the placental barrier as readily as TBBPA (Table 1).

Chlorinated paraffins are widely utilized as plasticizers, flame retardants, and paint additives. They are highly complex halogenated mixtures including three distinct groups of congeners: long-chain chlorinated paraffins (LCCPs, $C_{>17}$), medium-chain chlorinated paraffins (MCCPs, C_{14}–C_{17}), and short-chain chlorinated paraffins (SCCPs, C_{10}–C_{13}) (Li et al., 2019; Zhuo et al., 2019). To date, only a few studies have focused on human exposure to CPs (including SCCPs and MCCPs) (Li et al., 2017; Xia et al., 2017), although numerous studies have evaluated their environmental distributions (Li et al., 2019; Ma et al., 2020; Wang et al., 2019). Three studies have investigated the transplacental transfer of SCCPs in China (Aamir et al., 2019; Liu et al., 2020; Qiao et al., 2018). In these studies, approximately 2–5 times higher wet weight-based concentrations of total MCCPs ($C_{14-17}Cl_{5-10}$) and SCCPs ($C_{10-13}Cl_{5-10}$) were found in maternal blood samples than in umbilical cord blood samples (Table 1). Generally, congener-specific placental transfer efficiencies of SCCPs and MCCPs have been found. Aamir et al. (2019) found that C_{10} to C_{14} CPs have similar R_{CM} values, which are higher than those of CPs with more carbons. However, Qiao et al. (2018) found that their R_{CM} values increase with increases in carbon chain length, and are highest for C_{16}-MCCP. Due to the limited number of

Table 1
Maternal-fetal transfer efficiencies of TBBPA, HBCDs, SCCPs, and MCCPs (lipid-adjusted/wet weight-based).

Location	Sampling time	Number of paired samples	Maternal age (years)	Detection frequency (Maternal/cord)	TBBPA	α-HBCD	β-HBCD	γ-HBCD	t-HBCDs	SCCPs	MCCPs	References
Japan	2005–2006	6	31.1	TBBPA: 67% k/0								Kawashiro et al., 2008
South Korea	2009–2010	38	32.8	TBBPA: 81.6%/84.2% HBCDs: 81.6%–89.5%/78.9%–89.5%	Mean: 3.04 Median: 3.08	1.95[a]	1.64[a]	Mean: 1.42 Median: 0.95				Kim and Oh, 2014
France	2004–2006	90	32.5	TBBPA: 31.9%/30.0%	5.21[a]/1.29[a]							Cariou et al., 2008
France	2005	26	34	TBBPA: not available HBCD: 0/0	/2.81[a]							Antignac et al., 2008
Netherlands	2001–2002	88	32 (median)	HBCD: 98.6%/33.3%					Median: 0.7			Meijer et al., 2008
China	2013	21	28.6	SCCPs: 100%/100% MCCPs: 100%/100%						Mean: 0.55/0.28 Median: 0.46/0.19	Mean: 1.04/0.37 Median: 1.03/0.33	Qiao et al., 2018
China	2015–2016	31	27 (median)	SCCPs: 100%/100% MCCPs: 100%/100%						/0.48[a]	/0.19[a]	Aamir et al., 2019
China	2018	20	27.0	SCCPs: 100%/100% MCCPs: 100%/100%						/0.44[a]	/0.46[a]	Liu et al., 2020

TBBPA, tetrabromobisphenol A; HBCD, hexabromocyclododecane; SCCP, short-chain chlorinated paraffins; MCCP, medium-chain chlorinated paraffins.
[a] Calculated using the mean concentrations.

studies and conflicting results, there is no general consensus about effects of chlorinated paraffins' carbon chain length on their R_{CM} values. Furthermore, Qiao et al. (2018) found that their R_{CM} values seem to increase with increases in chlorination degree, while Aamir et al. (2019) reported that lightly chlorinated (Cl_{5-6}) SCCP congeners have higher R_{CM} values than more heavily chlorinated (Cl_{9-10}) congeners.

Dechlorane plus (DP) and organophosphate esters (OPEs) are both flame retardants. DP is highly chlorinated chemical which was proposed for potential candidate under the Stockholm Convention (Zhang et al., 2020b). OPEs are a type of synthetic phosphoric acid derivatives, which were also used as plasticizers and antifoaming agents in many commercial products (Hou et al., 2020). DP and OPEs were ubiquitously found in environmental matrices and human bodies (Ding et al., 2016; Ge et al., 2020; Hou et al., 2020). For OPEs and DP, the available evidence suggesting the possible transplacental transfer and placental accumulation was very limited, and sometimes the results were contradictory (Ben et al., 2014; Ding et al., 2016). For example, a study reported the transplacental transfer of DP in human (Ben et al., 2014). DP and its dechlorinated analogs were detected in paired maternal blood, cord blood, and placenta samples from an e-waste recycling area, the R_{CM} was 0.45 for *syn*-DP and 0.35 for *anti*-DP (Ben et al., 2014). However, an animal experiment observed undetectable or low DP concentrations in tissues from offspring, which suggested limited tranplacental transport from mother to offspring (Zhang et al., 2020b). Some OPEs and their metabolites were also found in human chorionic villi, deciduae, and placentas (Ding et al., 2016; Zhao et al., 2017b). These phenomena indicated potential maternal-fetal transfer and placental accumulation of OPEs. No transfer ratios for OPEs were reported in previous studies. And more investigations on prenatal exposure of DP and OPEs were needed.

Some previous studies also focused on the tranplacental transfer and placental accumulation characteristics of polychlorinated dibenzo-*p*-dioxins and furans (PCDD/Fs) (Kim et al., 2015; Nakamura et al., 2008). High level of congeners in maternal blood were usually observed, compared to umbilical cord blood (Kim et al., 2015; Mori et al., 2014). The transplacental transfer data were limited in previous studies (Kim et al., 2015; Mori et al., 2014; Needham et al., 2011). For example, Mori et al. (2014) found that the transfer rates of dioxin congeners were differed from those of total dioxins, and the values of the congeners were not always systematically significant correlated with molecular weights.

4. Factors that influence transplacental transfer efficiency

Many factors can affect the transplacental transfer of contaminants. Physicochemical properties (Table S14), such as molecular size, solubility, isomer structure, and metabolism characteristics, are very important factors. These properties are usually interrelated, but not linearly related, due to variations in multiple features of contaminants' structures. Molecular size is linked to steric hindrance, and hence Connolly solvent-excluded volume (SEV), molecular weight (MW), degree of halogenation, and carbon chain length, while solubility in water (Sw), and aqueous systems generally, is affected by lipophilicity (usually expressed as the octanol/water partition coefficient, K_{OW}). Compounds' metabolism characteristics, chemical affinity to plasma protein, and binding affinities to active transporters, which are affected by their structure, also influence how readily they move across the placental barrier. Gestational age, which is linked to placental maturity, is also a significant factor. In this section, effects of various factors are assessed, according to their influence on mean reported R_{CM} or R_{PM} values of particular HOPs.

4.1. Physicochemical properties

4.1.1. Steric hindrance

A significant or marginally significant negative linear relationship has usually been found between SEV and transplacental transfer efficiency (Fig. 3). Despite substantial differences in discussed OCPs' structures, only a marginally negative correlation between the SEV and R_{CM} of OCPs was found (Spearman $R^2 = 0.433$, $p = 0.054$), when extreme values of dieldrin and heptachlor were excluded. R_{CM} values of PCBs significantly decreas as the SEV increased (Spearman $R^2 = 0.694$; $p = 0.001$), according to analysis of available data for the 12 main tri- to hepta-PCB congeners. A similar significantly negative relationship between SEV and R_{CM} value was also obtained for tri- to hepta-BDEs. Interestingly, an analysis of all the studied OCPs, PCBs, and PBDEs also revealed a significant correlation between SEV and R_{CM} value (Spearman $R^2 = 0.268$; $p = 0.006$). For PFCAs, a significantly negative relationship between SEV and R_{CM} was found (Spearman $R^2 = 0.903$; $p = 0.013$) when data concerning PFDoA and PFTrDA (SEV > 280 cubic Ångströms) were excluded. However, analysis of the relationship between SEV and R_{CM} data for $C_7 - C_{13}$ PFCAs resulted in a U-shaped curve (quadratic fitting coefficient $R^2 = 0.923$; $p = 0.005$). Analyses of effects of MW, halogenation degree, and carbon chain length on the R_{CM} value revealed similar relationships for the HOPs considered in this review (Figs. S2-3).

These results show that steric hindrance plays an important role in the transplacental transfer of most HOPs, and solvent-excluded volume is a relatively useful parameter for predicting R_{CM} due to a number of statistically significant relationships. For most of the studied classes of HOPs, R_{CM} apparently decreases in a linear manner as SEV increases. However, this trend reverses for PFSAs when SEV exceeds 280 cubic Ångströms or the MW exceeds 600 Da. Moreover, we found that R_{CM} values of some PBDE congeners, such as BDE154 and BDE209, do not follow the usual relationship with SEV observed for other compounds. Other influential factors, such as metabolism characteristics and plasma protein binding affinity should be considered for higher molecular weight PFAS compounds as well as BDE154 and BDE209.

As similar correlations were generally found for the studied PCBs, PBDEs, and OCPs, we grouped these chemicals and considered PFCAs as another group in further analyses, in which we assessed effects of SEV (Fig. 3), MW (Fig. S2), halogenation degree, and carbon chain length (Fig. S3) on their transplacental transfer. For PFCAs (C_7–C_{12}), we obtained a similar relationship (described by a U-shaped curve) between SEV and R_{PM} to that obtained for R_{CM} (quadratic fitting coefficient $R^2 =$ 0.889–0.892; $p =$ 0.036–0.037). However, the R_{PM} values for members of the OCPs + PCBs + PBDEs group fluctuated, and no linear correlations were found (Spearman $R^2 =$ 0.001–0.044; $p =$ 0.681–0.988). Further analyses of larger datasets are needed to characterize these relationships rigorously.

4.1.2. Hydrophilicity and hydrophobicity

A curvilinear relationship between lipophilicity and transplacental transfer efficiency was found for all of the studied PCBs, PBDEs, and PFCAs (Fig. 4). With the exception of OCPs, significant curvilinear correlations between logK_{OW} and R_{CM} value were observed for the other HOPs (quadratic fitting coefficients: $R^2 =$ 0.833–0.960; $p =$ <0.001–0.008) when data from BDE154 and BDE209 were excluded. The relationship between logK_{OW} and R_{CM} value for PFCAs (C_7–C_{13}) was distinctly U-shaped. The lowest transfer efficiencies (0.33–0.37) were obtained for the two congeners with the highest logK_{OW} values, PFDA (7.9) and PFUnA (8.6), in accordance with expectations. Aqueous solubility also has a curvilinear effect on transfer efficiencies of PCBs, PBDEs, and PFASs, according to available data (Fig. S4).

Generally, transfer efficiencies of most HOPs are related to their hydrophobicity. Curvilinear relationships between water solubility and transplacental transfer efficiency were found for PCBs, PBDEs, and PFASs. Quadratic curves obtained for PCBs and PBDEs show that their R_{CM} values decrease as logK_{OW} increases, while a U-shaped relationship between these two variables was obtained for PFASs. However, Aamir et al. (2019) reported a negative relationship between log*K*ow and R_{CM} values for SCCPs and MCCPs, and Lancz et al. (2015) suggested that the hydrophobicity (K_{OW}) of compounds (particularly PCBs) plays a key role

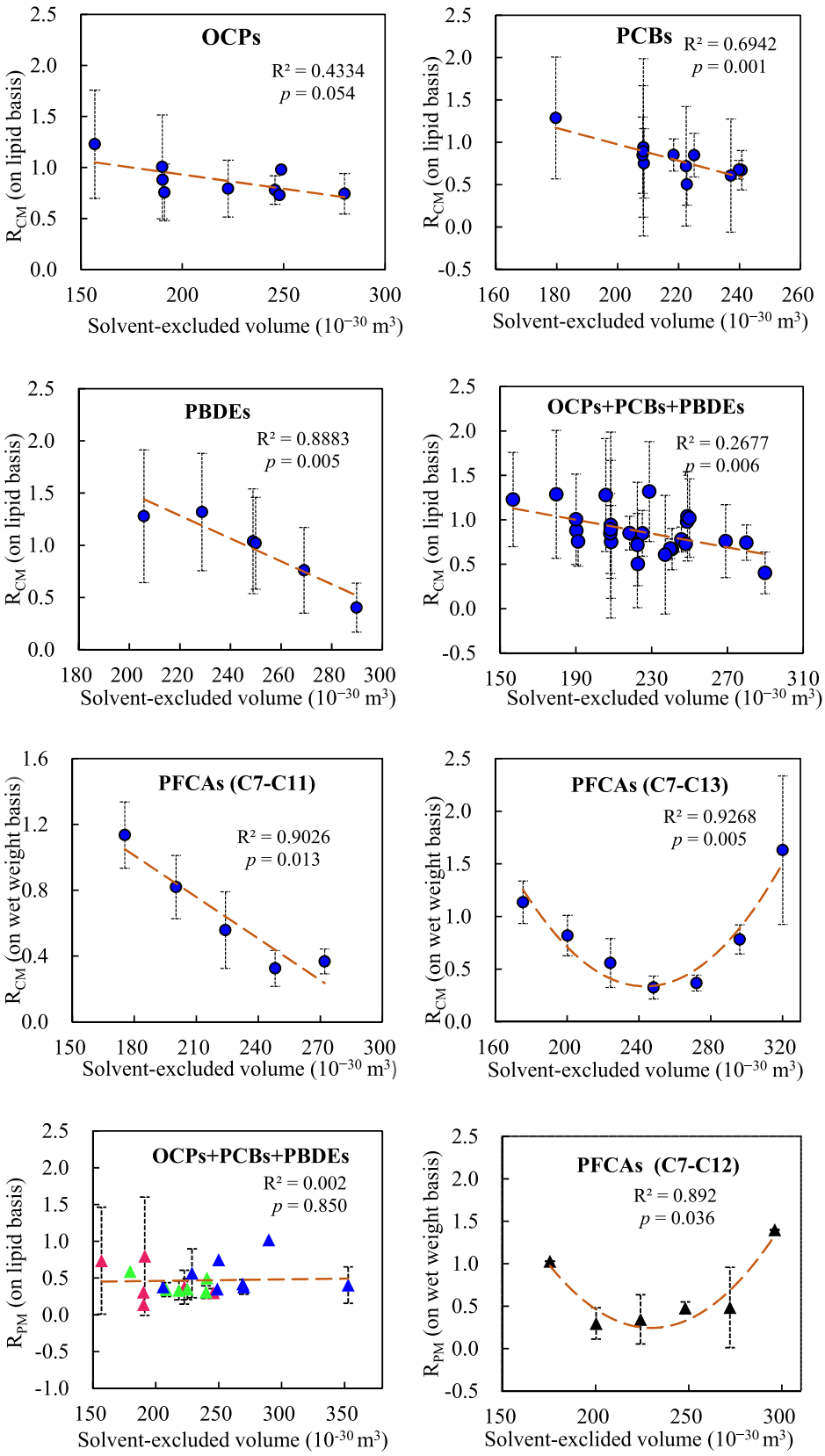

Fig. 3. Relationships between solvent-excluded volume and both transplacental transfer and placental distribution efficiencies for indicated HOPs (red, green, and blue triangles represent data for OCPs, PCBs and PBDEs, respectively. Error bars represent standard deviations. n = 3–30 for R_{CM} values, and n = 2–4 for R_{PM} values. Data were obtained from references listed in Table S13). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in their transplacental transfer efficiency. The transfer efficiencies of most HOPs considered here were clearly influenced by both lipid and aqueous solubility, and highly lipophilic PFASs ($\log K_{OW} > 9$) were found to have exceptionally high R_{CM} values.

For placental distribution (R_{PM}), clearly significant U-shaped associations with $\log K_{OW}$, corresponding to those obtained between $\log K_{OW}$ and R_{CM}, were found for PFCAs (Fig. 4 and Fig. S4), with quadratic fitting coefficients R^2 = 0.887–0.889 and p = 0.037–0.038. However,

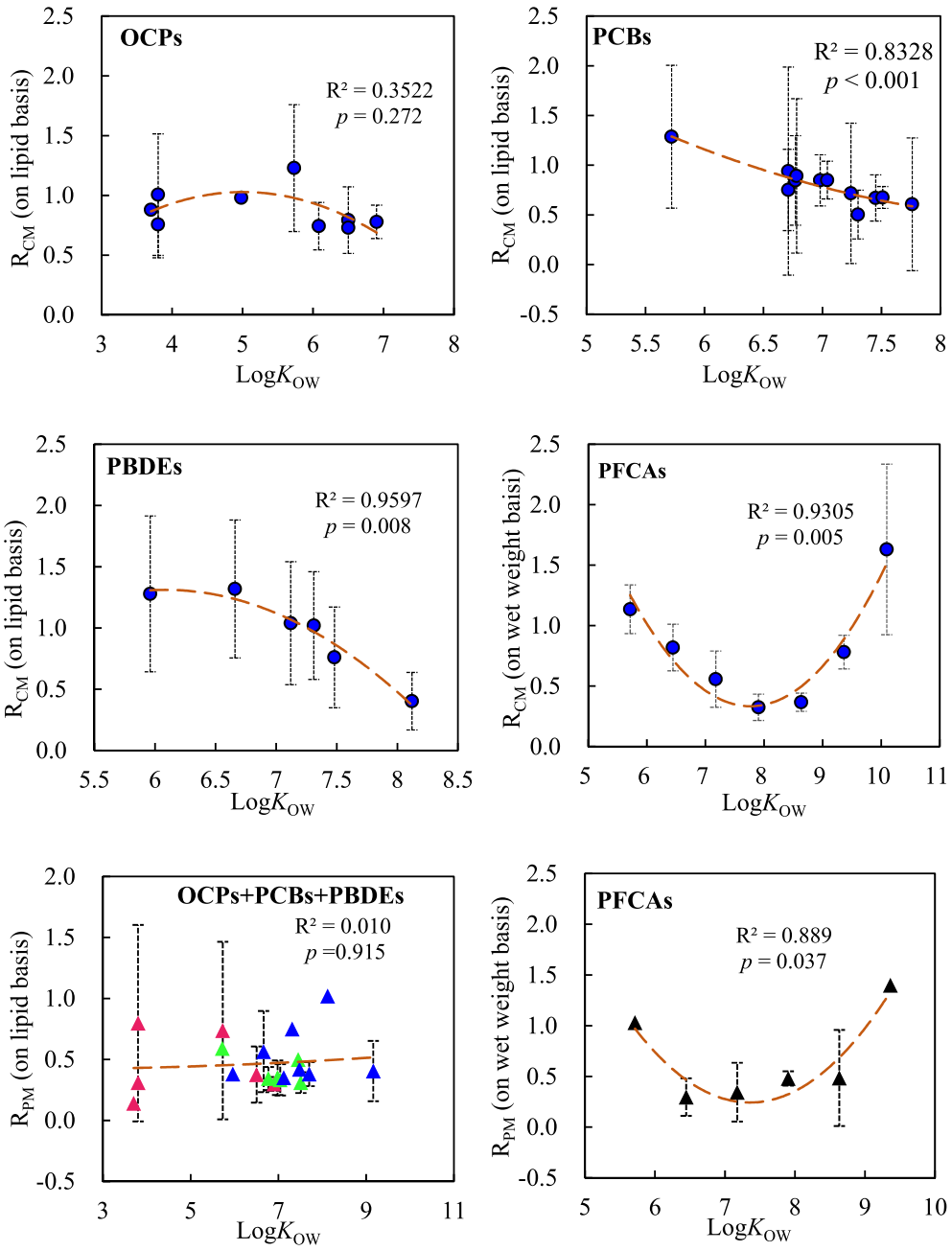

Fig. 4. Relationships between Log*K*ow and both transplacental transfer and placental distribution efficiencies for indicated HOPs (red, green, and blue triangles represent data for OCPs, PCBs and PBDEs, respectively. Error bars represent standard deviations. n = 3–30 for R_{CM} values, and n = 2–4 for R_{PM} values. Data were obtained from references listed in Table S13). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the R_{PM} values for OCPs + PCBs + PBDEs first decrease then increase, indistinctly, as logK_{OW} increases (Fig. 4).

4.1.3. Isomer structure

Isomer structure is important to consider when evaluating the transplacental transfer efficiency of a HOP, and was found to be especially relevant for PFASs. As previously discussed, higher transplacental transfer efficiencies were found for branched isomers of PFOS, PFHxS, and PFOA than for corresponding linear isomers (Li et al., 2020a; Zhao et al., 2017a). Differences in R_{PM} between linear and branched isomers of PFOS and PFHxS have also been observed (Chen et al., 2017). R_{CM} values of branched PFOS and PFOA isomers are generally positively related to the branching point's proximity to the sulfonate or carboxyl moiety (Chen et al., 2017; Zhao et al., 2017a). Kim and Oh (2014) found that α-HBCD has higher transfer efficiency than either β- or γ-HBCD (Table 1). PCBs and PBDEs with the same numbers of halogen atoms also reportedly have congener-specific R_{CM} values (Tables S5 and S8). Furthermore, Yin et al. (2019) and Zhao et al. (2020) detected enantiomer-specific effects on transfer and accumulation efficiencies of chiral OCPs (such as α-HCH and *o,p'*-DDT) and PFAS (perfluoro-1-methylhptanesulfonate), respectively.

4.1.4. Metabolism characteristics

Biotransformation can also influence the transplacental transfer efficiency of HOPs. As already mentioned, R_{CM} values obtained for BDE209 (1.23) and BDE154 (1.67) strongly deviate from linear and quadratic regression equations describing general effects of solubility and molecular size on the studied HOPs' R_{CM} values. The high R_{CM} of BDE209 may be due to differences in metabolic capacities of mothers and their fetuses (Alcorn and McNamara, 2003; Park et al., 2008; Vizcaino et al., 2014). Similar results were obtained for BDE209 and its debrominated metabolites, including three nona-BDEs and five octa-BDEs, in animal model experiments (Cai et al., 2011; Zhang et al., 2011). The high R_{CM} of BDE154 has not been extensively discussed in

previous studies. Vizcaino et al. (2014) proposed that the higher concentraton of BDE154 in mothers than their fetuses may reflect the biotransformation of highly brominated congeners such as BDE183. However, this conflicts with findings that R_{CM} values of BDE154 are higher than those of BDE153 (Table S8). We believe that the high R_{CM} value of BDE154 is more likely due to its metabolism in the human body. Estimated half-lives of BDE153, BDE154, and BDE183 in the human body are approximately 2700, 480, and 1000 days, respectively (Trudel et al., 2011), indicating that BDE154 is more readily metabolized than BDE153 or BDE183. Assuming that BDE154 is metabolized more slowly in the fetus, it should accumulate in the fetus and hence have a higher R_{CM} value.

Differences in the metabolism of HOPs might also explain the high R_{CM} of TBBPA. It has a shorter half-life than BDE209 (3.5–6.6 days vs. 15 days) and HBCD (21–23.6 days vs. 64 days in adipose tissues). Thus, mothers may have lower levels of TBBPA than fetuses, which could explain why transplacental transfer efficiency is higher for TBBPA than for either BDE209 or HBCDs (Geyer et al., 2004; Pan et al., 2017). Additional structure-related factors, such as affinity to plasma proteins and active transporters expressed in the placenta, may also influence the transplacental transfer efficiencies of HOPs. These factors are discussed in the next section.

4.2. Anthropometric parameters

Gestational period can influence the transplacental transfer of contaminants (Hansen et al., 2010; Monroy et al., 2008), an effect mainly attributed to differences in lipid concentrations and placental maturity at different points during pregnancy. Significant (16%−28%) reductions in lipid-adjusted concentrations and 10%−28% increases in wet weight concentrations of OCPs (HCB and *p,p'*-DDE) from the 1st to the 3rd trimester have been detected in a Peruvian study (Adetona et al., 2013). Furthermore, Foster et al. (2011) found that maternal levels of BDE17, BDE66, BDE154, and BDE183 were lower at delivery than during mid-pregnancy. Similarly, a decline in maternal PFAS concentrations during the 3rd trimester was observed in a Chinese study (Pan et al., 2017). Generally, R_{CM} values seem to be highest during the first trimester, then decrease in the 2nd and 3rd trimesters (Fei et al., 2007; Monroy et al., 2008). This trend presumably reflects the protective role of the placenta, which is not yet fully mature – and hence unable to filter out lipophilic contaminants – during the first trimester.

Previous studies have also found that parity, gestational age, maternal age, maternal weight, and gender of the fetus affect HOPs' R_{CM} values (Gao et al., 2019; Lee et al., 2013; Zhang et al., 2018b). For example, Zhang et al. (2018b) found that parity may influence the R_{CM} of *p,p'*-DDE, while Lee et al. (2013) found that maternal PFOA concentrations usually decrease with parity. Pan et al. (2017) detected no significant association between parity and transfer efficiencies of PFASs. However, Li et al. (2020a) observed differences in R_{CM} values for some PFASs associated with preterm and full-term delivery. Pan et al. (2017) also found a positive correlation between maternal age and PFCAs' transfer efficiencies, and higher PFHxS transfer efficiencies were observed for female infants than for male infants in a Chinese cohort study (Liu et al., 2011). It should be noted that the findings discussed above are combined results of multiple factors. Therefore, no general conclusion should be drawn from the available data, as further research is needed to verify, refute or refine the relationships suggested by the research presented in this section.

4.3. Other factors

Several researchers have also proposed that pollutant concentrations and types of blood sample can affect calculated transplacental transfer efficiencies. For example, Müller et al. (2019) detected increases in the transfer ratio of *p,p'*-DDE with increases in *p,p'*-DDE levels in maternal blood, similar to patterns observed for some drugs (Blackburn, 2017). Interestingly, analyses of whole blood samples yielded lower R_{CM} values for PFHxS, PFOS, PFOA, and PFNA than analyses of serum or plasma samples. This could be because packed cell volumes of blood samples from pregnant women are lower than those of corresponding samples from infants, and most PFASs preferentially partition to serum/plasma (Hanssen et al., 2013; Zhao et al., 2017a).

5. Transplacental transfer mechanisms

Various methods have been used to acquire knowledge of the mechanisms whereby HOPs traverse the placenta, considering both the transplacental transfer characteristics and physicochemical properties of the contaminants. In terms of methodologies, *in vivo* animal models, human *ex vivo* placental perfusion systems, and *in vitro* BeWo cell monolayer models have been used in efforts to elucidate the mechanisms involved.

5.1. Placental transport kinetics of HOPs

Experiments with human *ex vivo* placental perfusion systems have shown that BDE47 traverses the placenta faster than BDE99 (Frederiksen et al., 2010). Similar kinetics were also observed in a trophoblast cell line model. More specifically, Li (2017) found that the concentrations of tetra- and penta-BDEs generally reached a steady-state within 24 h in a BeWo cell monolayer, while BDE28 reached a steady-state in <6 h in the same system. The results revealed PBDE congener-specific transplacental transfer efficiencies, i.e., differences in the time needed to reach a steady-state on the basolateral side (fetal side). In addition, time-dependent transport of MeO-PBDEs was observed in an *in vitro* study with BeWo cells, and pseudo-first-order kinetics were proposed for their movement across the barrier (Zhang et al., 2020a). However, too limited information is currently available, and further studies are urgently needed to clarify the kinetics and associated mechanisms.

5.2. Passive diffusion

Several studies have shown that passive diffusion is an important mechanism of HOPs' transfer across the placental barrier. Two proteins – common plasma protein and a particular plasma transport protein (Transthyretin, TTR) – have been specifically implicated in compounds' diffusion across the placenta, with opposite roles (Fig. 5). Compounds with high affinities for plasma protein do not readily cross placental barrier (Pan et al., 2017; Wang et al., 2019). For example, linear PFOAs and PFOSs reportedly have stronger affinity for maternal albumin than their branched isomers (Beesoon et al., 2011; Beesoon and Martin, 2015), and cross it more slowly than the corresponding branched isomers. Gao et al. (2019) detected significant correlations between R_{CM} values and equilibrium dissociation constants (K_d) for complexes of PFASs with both albumin and serum proteins. Large K_d values indicate weak affinities to proteins in serum, and consequently low levels of PFAS-albumin complexes and more efficient transport of PFAS compounds across the placenta. It should be noted that cord and maternal serum albumin concentrations are positively and negatively related to transplacental transfer efficiencies, respectively. Thus, theoretically there may be competition for contaminants between albumin molecules on the two sides of the placenta. However, fetal albumin levels are generally lower than maternal levels, which may explain the net effect of contaminants' affinity to albumin.

Transthyretin (TTR) is a plasma transport protein that carries thyroxine (T4) across the placenta. Certain OH-PBDEs, such as 6-OH-BDE47, have strong affinity to TTR and thus may displace TTR-bound T4 and traverse the placenta to the fetal side (Wan et al., 2010). Hence, the finding that OH-PCBs and OH-PBDEs have higher R_{CM} values than their parent compounds could be attributed to the strong affinities of hydroxylated PCBs and PBDEs to TTR (Soechitram et al., 2004; Wan et al., 2010).

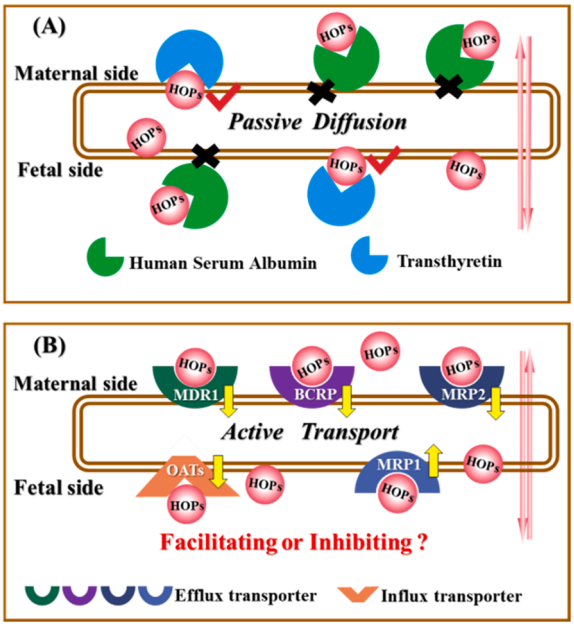

Fig. 5. Schematic diagram of several transplacental transfer mechanisms. A, passive diffusion; B, active transport. HOPs, halogenated organic pollutants; MDR1, P-glycoprotein; BCRP, breast cancer resistance protein; MRP, multidrug resistance-associated protein; OATs, organic anion transporters.

5.3. Active transport

In most, if not all, organisms, two types of active transporters, influx and efflux transporters, can move compounds against their concentration gradients. Influx transporters can drive the bioaccumulation of contaminants in cells, whereas efflux transporters can decrease bioaccumulation (Fig. 5). The BeWo cell monolayer model is often used to study placental transfer mechanisms. Experiments with this model, and other systems, have shown that ATP-binding cassette (ABC) transporters not only limit the transplacental transfer of contaminants, but also act as efflux pumps that remove various xenobiotics from fetal circulation (Prouillac and Lecoeur, 2010). For example, Yin et al. (2020) investigated the transplacental transfer mechanism of OCPs using the model. They found that inhibitors of ATP production significantly inhibited transfer of the studied compounds, clearly indicating that active transport is involved in contaminants' transplacental movement. They also found that efflux transporter of multidrug resistance-associated proteins (MRP1 and MRP2), P-glycoprotein (MDR1), and breast cancer resistance protein (BCRP) are involved in the active transport process (Yin et al., 2020). Zhang et al. (2020a) also suggested that BCRP might transport MeO-PBDEs across the placental barrier based on results from BeWo cell monolayer experiments. Similarly, Li et al. (2020a) found weak and negative correlations between the expression of three efflux transporter proteins (MDR1, MRP2, and BCRP) and R_{CM} values of PFASs detected in preterm infants and their mothers. This indicates that these three efflux transporters may actively transfer PFASs from the fetal to the maternal side, thereby mitigating effects of the compounds' passive diffusion from maternal to fetal circulation.

In contrast, influx transporters can promote bioaccumulation through active transport. For example, Organic Anion Transporters (OATs), influx transporters located on the basal side of the placenta, have been identified as major PFOS transporters (Kummu et al., 2015; Nakagawa et al., 2009). In BeWo cell experiments, Zhang et al. (2020a) found that OATs may be involved in transport of MeO-PBDEs. However, we have limited understanding of how influx transporters participate in contaminants' transplacental transfer. It should be noted that transporters expressed on the maternal and fetal sides of the placenta have opposite effects on transplacental movement. Thus, their combined effects should be clarified to determine net effects of active transport on the transplacental transfer of contaminants (Fig. 5).

6. Future perspective

Numerous studies have detected HOPs in umbilical cord blood and placenta samples, demonstrating that the placenta is not an absolute barrier against HOPs. However, there is currently limited information on the mechanisms involved in their transport across the placental barrier. To address the paucity of relevant information, future studies should combine *in vivo*, *ex vivo*, and *in vitro* approaches when investigating transplacental transport mechanisms of HOPs. Furthermore, broad evaluation of the available data is essential to improve understanding of the transplacental transfer characteristics of xenobiotics. More detailed information on potentially influential factors should also be provided, to facilitate alternative analyses and allow combination of relevant data by other researchers.

The placental transfer characteristics of non-persistent pollutants are also very important. They are commonly found in pregnant women, but analysis of their transfer is hindered by their fast metabolism, quick elimination and consequently short half-lives in human bodies. Thus, analysis of target compounds and their major metabolites in appropriate paired samples of maternal and fetal matrices, together with consideration of key physicochemical properties, will be essential for rigorous elucidation of their transplacental transfer and distribution characteristics. Analysis of transporters and other native substances in the maternal and fetal tissues may also be required to elucidate their transfer mechanisms, which may be similar to or in some cases radically sometimes different from those of HOPs.

7. Conclusions

We have surveyed the occurrence of HOPs in paired maternal and fetal samples, and analyzed the transplacental transfer and placental distribution characteristics of this broad class of contaminants. We have also addressed factors that influence transplacental transfer efficiency and the primary mechanisms that facilitate or hinder movement across the placenta. All the studied compounds except the PFASs and TBBPA can be classified as HOPs with low transplacental transfer efficiencies. The results confirm that numerous factors affect HOPs' transplacental transfer. Generally, their transplacental have negative linear and curvilinear relationships with their molecular volume and lipid solubility, respectively, but a curvilinear relationship between the transfer efficiencies and molecular volumes of PFCAs (C_7–C_{13}) was detected. The relative metabolic capacities of mothers and fetuses may affect HOPs' transfer efficiencies. More specifically, fetal metabolic capacities are negatively related to R_{CM} values. Additionally, R_{CM} values of some HOPs may vary during the course of pregnancy. Passive diffusion and active transport are the two main mechanisms of contaminants' transfer across the placenta. Passive diffusion is influenced by the HOPs' plasma protein binding affinities whereas active transport depends on influx/efflux transporters. Despite intensive research on transplacental transfer of HOPs, many aspects require further attention to elucidate the processes involved and obtain the knowledge required for robust protection of fetuses' health.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supporting information and data associated with the study can be found in Tables S1–S13 and Figs. S1–S4. Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.106224.

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