Organophosphate flame retardants in pregnant women: Sources, occurrence, and potential risks to pregnancy outcomes

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Abstract

Organophosphate flame retardants (OPFRs) are found in various environmental matrices and human samples. Exposure to OPFRs during gestation may interfere the pregnancy, for example, inducing maternal oxidative stress and maternal hypertension during pregnancy, interfering maternal and fetal thyroid hormone secretion and fetal neurodevelopment, and causing fetal metabolic abnormalities. However, the consequences of OPFR exposure on pregnant women, impact on mother-to-child transmission of OPFRs, and harmful effects on fetal and pregnancy outcomes have not been evaluated. This review describes the exposure to OPFRs in pregnant women worldwide, based on metabolites of OPFRs (mOPs) in urine for prenatal exposure and OPFRs in breast milk for postnatal exposure. Predictors of maternal exposure to OPFRs and variability of mOPs in urine have been discussed. Mother-to-child transmission pathways of OPFRs have been scrutinized, considering the levels of OPFRs and their metabolites in amniotic fluid, placenta, deciduae, chorionic villi, and cord blood. The results showed that bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) and diphenyl phosphate (DPHP) were the two predominant mOPs in urine, with detection frequencies of > 90%. The estimated daily intake (EDI_M) indicates low risk when infants are exposed to OPFRs from breast milk. Furthermore, higher exposure levels of OPFRs in pregnant women may increase the risk of adverse pregnancy outcomes and influence the developmental behavior of infants. This review summarizes the knowledge gaps of OPFRs in pregnant women and highlights the crucial steps for assessing health risks in susceptible populations, such as pregnant women and fetuses.

Keywords: Organophosphate flame retardants; Prenatal exposure; Mother-to-child transmission; Urine; Breast milk; Pregnancy outcome

Synopsis: This article reviews the global prenatal and postnatal exposure of pregnant women to OPFRs and reveals the extent and potential risks to pregnancy outcomes.

1. Introduction

Flame retardants (FRs) are added to various manufactured materials as functional additives to reduce the flammability of materials, prevent the occurrence and spread of fires, and protect human life and property. Polybrominated diphenyl ethers (PBDEs) were the most widely used FRs until the 2000s, but they have been gradually banned because of their persistence, bioaccumulation, and ecotoxicity in the environment.[1] Organophosphate flame retardants (OPFRs) are increasingly being used as alternatives. OPFRs have been widely used in various industries and chemicals, such as textiles, electronics, furniture foams, and plasticizers in rubber products.[2-4] The production and usage of OPFRs have dramatically increased in recent years. The global consumption of OPFRs increased to 680,000 metric tons in 2015, an annual increase of 7.9%.[5] The US, Europe, Japan, and Asia are the four largest markets for flame retardants in the world. Among them, the US and Europe have established stable markets as the earliest producers and users of flame retardants. For example, the production and usage of triphenyl phosphate (TPHP) was the highest in the US and Europe among aryl-OPFRs, and tris(1-chloro-2-propyl) phosphate (TCIPP) accounted for approximately 80% of Cl-OPFRs usage in the US and Europe.[6, 7] In recent years, the flame retardant industries in Asia have increasingly expanded, with the Chinese flame retardant market playing a significant role.[8]

OPFRs are often added to materials physically without chemical bonding, which allows them to be continuously released into the environment through volatilization, abrasion, and leaching.[9] The widespread occurrence of OPFRs has been documented in a variety of environmental matrices, such as water, sediment, air, dust, and soil.[1, 6, 10-13] OPFRs can be detected in surface water and drinking water worldwide, with analogues concentrations as high as tens of ng/mL.[14] High levels of OPFRs in sediments can endanger aquatic ecosystems, leading to exposure to aquatic plants and ingestion by aquatic animals, which in turn can enter the human body through the food chain and potentially affect human health. OPFRs have been

widely detected in both indoor and outdoor air. The levels of OPFRs in indoor air can be as high as hundreds of ng/m^3.[15] Because OPFRs can easily be released from building material, interior decorations, furniture, consumer products, and carpets into the indoor environment the concentration of OPFRs in indoor air is typically 1−3 orders of magnitude higher than that of outdoor air.[16] Similar to air samples, the concentration of OPFRs in indoor dust was significantly higher than that in outdoor dust. OPFRs were detected in indoor dust samples from more than 29 countries, including households, offices, dormitories, daycare centers, and in-vehicle areas, with concentrations ranging from a few to tens of μg/g. Langer et al. studied 10 OPFRs in dust samples collected from children's bedrooms (n = 500) and daycare centers (n = 151), and found higher concentrations of OPFRs in daycare center dust samples than in household dust samples. Since children are more likely to be exposed to OPFRs than adults, this result deserves more attention.[17] In addition, OPFRs have been discovered in many human samples globally, including urine, hair, nails, placenta, breast milk, and amniotic fluid.[18] For example, concentrations of ∑OPFRs in breast milk samples from Asia were as high as 600 ng/g lipid wt, indicating that breastfeeding may result in considerable exposure of newborns to OPFRs.[19] Many toxicological experiments have shown that OPFRs and metabolites of OPFRs (mOPs) could cause different toxic effects on organisms (fish, birds, and humans), including endocrine disruption, neurotoxicity, hepatoxicity, reproductive toxicity, and interference with embryonic development.[20, 21] Studies indicated that OPFRs have adverse effects on female reproduction by damaging the regulatory pathway mediated by the hypothalamic-pituitary-gonadal (HPG) axis.[22, 23] For example, the exposure of female zebrafish to tris(1,3-dichloro-2-propyl) phosphate (TDCIPP) inhibited the expression of genes involved in gonadal development, and resulted in decreased egg production and morphological alterations on the surface of eggs. The reduction in egg quality could eventually lead to poor reproductive outcomes.[24] OPFRs could be considered as typical endocrine disruptors that can interfere with

the regulation of endogenous hormones and lead to abnormal fertility on humans and animals, especially for thyroid hormones.[25, 26] Thyroid hormones have a positive effect on the development, growth, and cell differentiation; disturbance of thyroid hormone levels could result in adverse developmental outcomes such as obesity. Alterations in maternal thyroid function could also affect pregnancy outcomes, which pose potential risks for the growth and development of infants.[25]

However, studies of OPFRs exposure in pregnant women are limited. Exposure to environmental pollutants during fetal development and the whole life stage causes chronic adverse effects on health.[27] Prenatal exposure to environmental pollutants deserves more attention because gestation is a critical period for the formation and development of fetal organs. For pregnant women, prenatal exposure to pollutants not only affects embryonic development, thus interfering with the pregnancy, but also affects the internal environment, thereby endangering prenatal and postnatal health.[28] During pregnancy and lactation, maternal OPFRs could be transmitted to the fetus and baby mainly through transplacental and lactational behaviors. Owing to mother-to-child transmission, pregnant women's exposure to OPFRs from various environmental matrices can also cause adverse effects on the fetuses. Epidemiological and toxicological studies have shown that maternal exposure to OPFRs may result in adverse pregnancy outcomes and affect the development of the fetus. Therefore, a review of prenatal exposure to OPFRs and their potential risks to mothers and their offspring is of great significance.

There have been several review papers on OPFRs, including on the application and synthesis routes of OPFRs;[29] the occurrence, analysis techniques, and toxicity of OPFRs in biota;[14, 16, 20, 30] the concentration of OPFRs in food and human dietary exposure;[31] and the metabolism and metabolic pathways of OPFRs in organisms.[5, 20, 32] However, to the best of our knowledge, a review on the exposure of pregnant women to OPFRs, effects on mother-to-child

transmission of OPFRs, and adverse effects on fetus and pregnancy outcomes is lacking. To this end, based on measurements of urine and breast milk samples from pregnant women worldwide, the occurrence of OPFRs in pregnant women before and after delivery was discussed, and exposure pathways of OPFRs in pregnant women were compared in the current review. The predictors associated with OPFR levels in pregnant women were then examined. Several possible routes of mother-to-child transmission of OPFRs in pregnant women, before and after delivery, are summarized. Furthermore, based on the results of toxicological and epidemiological studies, the potential risks of OPFRs in pregnant women to the next generation were examined in terms of the fetuses, infants, and young children.

2. Strategies for literature search and data collection

This review compiled the literature on OPFRs published from January 2012 to December 2022. The literatures were screened on the online database of Web of Science, PubMed, and ScienceDirect using the following keywords: “organophosphate flame retardants”, “organophosphate esters”, “organophosphates”, “prenatal exposure”, “maternal exposure”, “pregnant women”, and “pregnancy”. We screened these literatures based on the following criteria: (1) the studies examined OPFRs of pregnant women in a biological matrix (including urine, breast milk, placental, and amniotic fluid), (2) these studies described the possible effects of maternal levels of OPFRs on the offspring, (3) studies reported the mother-to-child transmission pathways of OPFRs. There is sufficient evidence on the prenatal exposure to OPFRs and the relevant pregnancy outcomes, but limited evidence for each specific pregnancy outcome, which makes the comprehensive evaluation of adverse effects difficult. Therefore, we performed a systematic scoping analysis for the associations between the prenatal exposure of pregnant women to OPFRs and the pregnancy outcomes. The screening strategies of literature were configured based on the PECO (Population, Exposure, Comparator and Outcome)

guidance.[33] The PECO statement was as following: Among pregnant women, what is the effect of the highest OPFR exposure compared to the lowest OPFR exposure on the pregnancy outcomes? P: among pregnant women, what is the effect of, E: the highest OPFR exposure during pregnancy, C: the lowest OPFR exposure during pregnancy, O: pregnancy outcomes. The study selection and data extraction were performed by two authors of this review (Yongting Li and Yaqian Xu). Literatures were further identified based on the following criteria: (1) studies monitoring the urinary mOPs in pregnant women, (2) studies examining the relationships between the prenatal exposure and potential risks of pregnancy outcomes (including neonatal birth weight, neonatal birth size, neonatal anthropometry, miscarriage, spontaneous abortion, gestational age, and neonatal thyroid hormones), (3) studies reporting different levels of the OPFR exposures or different degrees of adverse effects, (4) observational studies (including case control study, cohort study, and cross sectional survey), and (5) peer-reviewed literatures published in English. Exclusion criteria for the literatures were as follows: (1) conference abstracts, review articles, meta-analyses, (2) data originated from the same population or somewhat overlapping populations, and (3) animal research and/or the study populations without pregnant women. Overall, 11 literatures were collected based on the selection criteria, and the quality of final references were critically evaluated (**Figure 1**). Yongting Li and Yaqian Xu separately assessed the design and quality of the 11 included studies using the Newcastle-Ottawa Scale (NOS) for observational studies.[34] Any discrepancies on the scoring were resolved by discussion. Detailed information about the assessment of included studies can be found in **Table S1**.

Available data were collected for ten OPFRs and ten mOPs. The ten OPFRs were: chlorinated-OPFRs: tris(2-chloroethyl) phosphate (TCEP), TCIPP, tris(2-chloropropyl) phosphate (TCPP), and TDCIPP; aryl-OPFRs: TPHP, tricresyl phosphate (TCrP), and 2-ethylhexyl-diphenyl phosphate (EHDPP); alkyl-OPFRs: tri-*n*-butyl phosphate (TNBP),

tris(2-butoxyethyl) phosphate (TBOEP), and tris(2-ethylhexyl) phosphate (TEHP). The ten mOPs were: di-n-butyl phosphate (DNBP, the metabolite of TNBP), bis(2-chloroethyl) phosphate (BCEP, the metabolite of TCEP), bis(1-chloro-2-propyl) phosphate (BCIPP, the metabolite of TCIPP), diphenyl phosphate (DPHP, the metabolite of TPHP), di-cresyl phosphate (DoCP & DpCP, the metabolite of TCrP), isopropylphenyl phenyl phosphate (ip-PPP, the metabolite of mono-substituted isopropyl triphenyl phosphate (mono-ITP)), bis(2-butoxyethyl) phosphate (BBOEP, the metabolite of TBOEP), tert-butyl-phenyl phenyl phosphate (tb-PPP, the metabolite of mono-substituted tert-butyl triphenyl phosphate (mono-TTP)), 1-hydroxyl-2-propyl bis(1-chloro-2-propyl) phosphate (BCIPHIPP, the metabolite of TCIPP), and bis(1,3-dichloro-2-propyl) phosphate (BDCIPP, the metabolite of TDCIPP). The molecular weights, CAS numbers, and log K_{ow} values of the OPFRs and mOPs are listed in **Table S2**.

3. Results and Discussion

3.1. Exposure pathways of OPFRs to pregnant women

The exposure pathways for the pregnant women are generally the same as for the general population.[35-38] Individuals are typically exposed to and ingest OPFRs through dust ingestion, dietary intake, air inhalation, and skin contact. In this section, the exposure pathways of pregnant women to eight predominant OPFRs (TPHP, TNBP, TCEP, TCIPP, TCrP, TDCIPP, TBOEP, and TEHP) are summarized based on the literatures selected by the systematic review. The contribution of each exposure pathway to the total intake of OPFRs varied depending on the class of compounds and the compounds within the same class.

It has been noted that the characteristics of exposure to OPFRs are age-specific and that dietary intake is the main contributor to exposure to OPFRs, followed by dust ingestion.[35] Dietary intake is the primary pathway for TCEP, TCIPP, and TNBP, accounting for 84%, 77%,

and 93% of total ingestion, respectively.[39] OPFRs can be detected in agricultural products such as grains (rice, corn), vegetables (potatoes, cereals, tomatoes, cabbage, rape, carrots, broccoli, onions, and celery), fruits (apples, bananas, oranges, pears, peaches, citrus, strawberries, and grapes), meat, dairy products, and eggs around the world.[29, 38-40] Pregnant women and mothers have a higher daily consumption of OPFRs than other adults, perhaps due to their specialized prenatal and postnatal diets.[35, 41] Throughout the pregnancy and breastfeeding period, women should have a well-balanced diet and refuel frequently in order to obtain sufficient calories and nutrients.[42,43] They may consume more food rich in protein, vitamins, and healthy fats, which maybe contribute to a relative increase in their body burdens of OPFRs.[44] OPFRs can be frequently detected in cereals and meat.[45-47] For example, China has the highest levels of ∑OPFRs in rice worldwide, as high as 802 ng/g dry weight (dw).[48] The median concentration of OPFRs in meats and fish collected from a local market in America was higher than those in dairy and cereal products.[49] The consumption of cereals and meats constitutes a significant portion of the dietary intake of OPFRs. Considering that Chinese and Americans consume rice and meat as staple foods respectively, the intake of OPFRs through rice and meat consumption may pose a potential risk to pregnant women.

Indoor air inhalation and dust ingestion are significant pathways of non-dietary exposure. Some studies have pointed out that the most prevalent exposure routes were indoor air and dust, followed by skin contact.[50, 51] Air inhalation is an important route of exposure to Cl-OPFRs, and it was estimated that the total intake of Cl-OPFRs through air inhalation exceeded that from dust ingestion.[52] The assessment of human exposure to OPFRs via air inhalation, dust ingestion, and dermal contact showed that air inhalation was the primary route of exposure to volatile OPFRs (TCIPP and TCEP), whereas dust ingestion was the most important route for less volatile OPFRs (TBOEP and TPHP).[50, 51] Dermal contact and dust ingestion account for almost 60% of the total intake of TBOEP among the four exposure pathways.[39] Levels of OPFRs in

indoor air and dust are usually higher than those in outdoor, and indoor settings are therefore an important exposure environment.[16, 20] A French cohort study reported that pregnant women spent an average of more than 16.7 hours per day indoors throughout their pregnancy.[53] Similar results were found in several cohort studies from Spain, Canada, and Poland.[54-56] Previous research recommended that future exposure and epidemiological studies should reflect the increase of exposure from indoor environments.[57] Exposure to OPFRs through air inhalation and dust ingestion for pregnant women requires more attention. Considering that women primarily stay indoors during the third trimester and after giving birth, indoor air and dust may be an important exposure pathway for OPFRs. During pregnancy, it is advisable to improve indoor ventilation. Plastic medical devices can also be an important source of exposure to OPFRs during hospitalization. The concentration of OPFRs in the urine of hospitalized infants was higher than that in outpatient infants.[58] This result may be related to the use of medical equipment, which usually contains plasticizers and flame retardants that are composed of OPFRs.

Skin contact also leads to prenatal non-dietary exposure to OPFRs. A study from Nepal revealed that dermal absorption contributed more to human exposure than air inhalation and dust ingestion. The EDIs for $\sum_8$OPFRs for dermal absorption, air inhalation, and dust ingestion were 16.8 ng/kg bw/day, 0.98 ng/kg bw/day, and 0.98 ng/kg bw/day, respectively.[59] In addition, there are some specific pathways for the dermal absorption of OPFRs in women. Urinary mOP levels in women aged 18−44 years were associated with OPFR levels on mobile phones ($p < 0.05$).[60] In the e-waste dismantling areas, levels of OPFRs in hand wipes were similarly greater in females than those in males ($p < 0.01$).[61] Furthermore, more frequent personal care product usage was associated with higher levels of mOPs in the urine of pregnant women.[62] Using silicone wristbands to assess the exposure to pollutants during pregnancy, it was found that the content of TPHP was positively correlated with nail polish usage ($\beta = 0.27$; 95% confidence

interval (CI): 0.00, 0.55).[63] The content of DPHP was related to the usage of nail polish and perfumes in a study of urine samples from pregnant women ($p < 0.05$).[62] The use of nail polish was associated with a 306% increase in urinary DPHP concentrations (95% CI: 129−610%; $p < 0.0001$) among women.[64] This may be due to TPHP replacing dibutyl phthalate as plasticizer to increase the flexibility and durability of nail polish.[64] The use of personal care products was also related to elevated levels of TCEP, TCIPP, TDCIPP, and their metabolites in the urine samples of pregnant women. The concentrations of BDCIPP, BCIPP, and ip-PPP are associated with the use of sunscreen, pesticides, and cosmetics ($p = 0.01$), respectively.[62, 64] TPHP is an aryl-OPFR and has shown various endocrine and metabolic disrupting and abilities, as well as reproductive toxicity to females in animal and human experiments.[65, 66] TCEP, TCIPP, TDCIPP are typical Cl-OPFRs, which interfere with embryonic development, disturb neurodevelopment, and induce vascular toxicity.[67-69] Pregnant women should be careful with personal care products, especially nail polish, throughout their pregnancy. Given the relationship between dermal exposure of pregnant women to personal care products and mOPs in urine, the disparities in racial/ethnic usage patterns of personal care products can influence OPFRs exposure.[70] For example, Latina women use more cosmetics, black women use more hair products. Future prevention measures of OPFR exposure for pregnant women of different ethnicities need to be more differentiated.[71]

Pregnancy is an extremely vulnerable developmental stage. Endocrine system and metabolism of body water, protein, glucose, and lipid change a lot throughout the pregnancy.[72] Environmental and occupational hazards may impair early developmental processes and increase later-life vulnerability to disease.[73] Exposure to toxins might disturb the normal physiological environment of the mother and cause long-term adverse effects.[74, 75] In addition, the placental barrier is not sufficient to block all exogeneous chemicals, which would lead to

direct exposure of the fetus to toxins with adverse effects on fetal development.[76-78]

3.2. Prenatal exposure to OPFRs

Prenatal exposure to OPFRs can be detected in urine samples from pregnant women worldwide. Among these studies, urine is the main biomonitoring tool.[79, 80] Internal exposure estimation of OPFRs through the urinary monitoring can avoid the evaluation errors caused by external exposure assessment. Moreover, biomonitoring on mOPs reveals human exposure to OPFRs and relationships between internal and external exposure.[32] Prenatal exposure of pregnant women to OPFRs will be determined based on urine mOP concentrations (mostly diester metabolites). The mOPs of high concern in urinary monitoring include Cl-mOPs (BDCIPP, BCIPHIPP, BCIPP, and BCEP), aryl-mOPs (DPHP, and DoCP & DpCP), and alkyl-mOPs (DNBP, BBOEP, ip-PPP, and tb-PPP).

3.2.1. Levels of exposure to OPFRs in prenatal pregnant women

Levels of mOPs in the urine of pregnant women worldwide are summarized in **Figure 2**. Analysis of urine samples (before delivery) of pregnant women from the United States, Canada, and China showed that BDCIPP and DPHP were the two predominant mOPs, with detection frequencies (DFs) of > 90% in almost all studies. In 2014, Hoffman et al. studied the levels of BDCIPP and DPHP in the urine samples of eight pregnant women from central North Carolina during different pregnancy stages.[82] BDCIPP and DPHP levels were detected in 38 of 39 urine samples with median concentrations of 1.1 and 1.6 ng/mL, respectively. This is the first study to monitor OPFRs levels in the urine of pregnant women, but the results were limited due to the small sample sizes. The samples were collected between 2011 and 2012. From 2003 to 2006, BDCIPP and DPHP levels in the same location were 1.85 and 1.31 ng/mL, respectively. The concentration of BDCIPP in urine samples collected in North Carolina from 2011 to 2012 decreased by more than 40% from 2002 to 2005, whereas the concentration of DPHP increased by approximately 23%.

Although the sampling time difference between the two studies was several years and the DFs in all samples increased, the levels of BDCIPP and DPHP in the two studies were similar, which is surprising given that the production of OPFRs as alternatives to PBDEs has increased significantly since 2010.[83] Most of the samples collected after 2010 showed higher levels of BDCIPP than those collected from Cincinnati, Ohio from 2003 to 2006, but not all studies met this pattern. Most samples collected after 2010 had lower DPHP levels than those collected from Cincinnati, Ohio.[84, 85] As there were fewer urine monitoring studies conducted to before 2010, this conclusion was insufficiently convincing. The levels of mOPs varied considerably across regions. For example, the concentration of BDCIPP in the urine of pregnant women in North Carolina is twice as high as that in Ohio. The concentration of DPHP in the urine of pregnant women on Rhode Island was lower than that in Ohio and North Carolina, where the concentrations were similar. BCEP, BCIPP, and ip-PPP had high DFs and concentrations in urine samples in the United States, in addition to BDCIPP and DPHP. For Chinese urine samples, the levels of mOPs in samples collected after 2010 were not significantly higher than those collected before 2010. Comparing the two batches of samples collected from Wuhan simultaneously, the DFs of several mOPs were significantly different, which may be related to the method of samples pretreatment. The composition and levels of urinary mOPs in pregnant women from three areas of China were considerably different. It is worth noting that the level of DPHP in pregnant women in Shanghai was approximately 1.75 times higher than that in the e-waste dismantling area of Guangdong Province. This result may be influenced by environmental exposure and living habits of urban women. In China and Canada, the levels of DPHP were an order of magnitude higher than those of BDCIPP. The levels of BDCIPP and DPHP were similar in the U.S. This indicates variances in OPFRs exposure among pregnant women in different countries and reflects the differences in OPFRs production and usage. Detailed information regarding mOPs in the urine of pregnant women is shown in **Table S3 (a)**.

3.2.2. Variation of urinary mOPs in pregnant women

Many researchers have monitored the concentrations of mOPs in urine samples at different stages of pregnancy to assess the temporal variation of mOPs and to test whether a single monitoring during pregnancy can reflect the whole pregnancy.

Using intraclass correlation coefficients (ICCs) to evaluate variability, ICCs values ranged from 0 to 1, indicating no reproducibility or perfect reproducibility. Samples were mainly collected in the first, second, and third trimesters, and after giving birth. Detailed information on the collection times and ICCs is provided in **Table 1**. The results showed that the reproducibility of samples collected from different regions for the same mOPs varies, such as the ICCs of BDCIPP in Northern Puerto Rico (ICCs: 0.23) and Maryland (ICCs: 0.59). Some studies have shown good reproducibility for different mOPs in urine collected from the same location, such as the ICCs of DPHP (ICCs: 0.4) and BDCIPP (ICCs: 0.4) in North Carolina. In general, the concentrations of mOPs are not consistent during the gestation period.[86] For example, data from North Carolina showed that the urine concentrations of BDCIPP and DPHP in this study were well consistent during the pregnancy period.[82] In Baltimore and Maryland, the variation degree of BDCIPP was consistent (ICCs: 0.42, 0.69), but several mOPs (DPHP, ip-PPP, tb-PPP, and BCIPP) exhibited substantial variability during pregnancy. DPHP and BDCIPP levels during pregnancy were consistent with the samples collected from Rhode Island and North Carolina, whereas BCEP showed comparable variability to BDCIPP and DPhP.[82, 87] The researchers examined the variability in urine mOPs of pregnant women from Ohio using a cohort of n = 357. The results demonstrated that the ICCs (0.24, 0.40) of mOPs showed high variability during pregnancy. Poor reproducibility of mOPs during pregnancy was also detected in Puerto Rico.[62] The weak reproducibility indicated that single monitoring during pregnancy in these populations cannot accurately reflect the levels throughout the whole pregnancy. The difference in excretion rate and renal function during pregnancy may account for these findings.

In the subsequent study in Puerto Rico (n = 48), the urine concentrations of mOPs were measured during the three stages of pregnancy. However, the ICCs varied from 0.51 to 0.61, which was much higher than the stability obtained by detecting only the two stages. Similar stability was observed for BDCPP (ICC = 0.60), DPHP (ICC = 0.43), and BCEP (ICC = 0.50) in pregnant women on Rhode Island (n = 59).[87] Urine mOP levels at different periods of pregnancy showed excellent consistency with the mixed samples. The variability of urine mOPs during pregnancy may be associated with physiological changes (e.g., blood volume, renal vascularity, oxygen demand, and energy metabolism) that affect the metabolism and excretion of OPFRs in pregnant women.[72]

3.2.3. Predictors of mOPs in pregnant women before delivery

Researchers investigated the relationships between sociodemographic predictors (such as age, ethnicity, pre-pregnancy body mass index (BMI), education, pregnancy parity, passive smoking frequency, sampling time, and sampling season) and exposure to OPFRs in pregnant women before delivery (**Figure 3**).

A study on the association between the prenatal BMI and mOP levels in urine found that relatively higher prenatal body weight positively correlates with mOP levels.[87, 88] For example, it was found that the concentrations of BDCIPP, DPHP, and ip-PPP in pregnant women with overweight and obesity during pregnancy were higher than those in women with normal BMI. Women with the first pregnancy were found to have lower ip-PPP levels in urine samples (p = 0.02), but the level of DPHP was significantly higher (p = 0.02).[79] Women with lower education had higher ip-PPP concentrations.[79] As for food, lower urine levels of BCEP were associated with more frequent consumption of meat (beef, pork, or lamb), lower urine concentrations of BDCIPP or DPHP were associated with frequent consumption of green leafy vegetables or carrots and citrus fruits, respectively. However, no significant effect of dietary factors on urine BCEP, BDCIPP, and DPHP was observed.[87] Among these studies, there are few studies on the

accumulation of mOPs in food, and no significant association between the dietary habits of pregnant women and mOPs has been found. Further studies on dietary exposures and food packaging analysis should be undertaken in the future to assess the presence of OPFRs. This is helpful for estimating the extent of OPFRs ingested through food. In addition, the sampling season may also affect mOPs levels in pregnant women's urine, and the concentrations of BDCIPP, DPHP, and BCIPHIPP in the samples collected in summer were significantly higher than those collected in winter, and the urine collection season was the most significant predictor of mOP levels.[79, 85] A study of sampling seasons showed similar results: urine concentrations of BDCIPP, DPHP, and ip-PPP are usually the lowest in winter.[89] These results indicate that the collection season could be an important confounder in future epidemiological studies using spot urine samples as a proxy for longer-term OPFRs exposure.[79]

These results further expand our understanding of how pregnant women are exposed to OPFRs and provide evidence for future studies on the potential risks of OPFRs. The relationships between different OPFRs and their structures, exposure pathways, and characteristics need to be further explored. Many epidemiological surveys have discussed only one class of pollutants, but humans are exposed to multiple environmental pollutants. For example, co-exposure of microplastics and TCEP increased oxidative stress and intestinal damage to earthworms comparing to control group, and co-exposure of graphene and TPHP increased TPHP accumulation in tissues of *Mytilus galloprovincialis*.[90, 91] Future epidemiological investigations need to focus on the synergistic effects of mixed exposures to these pollutants and the effects of multiple chemical exposure risks on the same adverse health outcomes and quantify these potential risks.

3.2.4. Health risks associated with prenatal exposure to OPFRs for women

The frequent detection of mOPs in the urine of pregnant women is a cause for concern, since studies have shown a correlation between the concentration of DPHP in female urine and

serum-free and total thyroid hormone levels.[92] A study on the correlation between mOPs in the urine of premenopausal women and uterine fibroids showed that higher levels of BDCIPP and BBOEP in urine were positively correlated with the occurrence of uterine fibroids ($p < 0.05$).[93] The estimated daily intakes of pregnant women derived from urine levels (EDI_U) are presented in **Table S4**. Values of EDI_U were approximately three orders of magnitude lower than the RfDs, suggesting a low risk of prenatal exposure to OPFRs. However, the molar ratio (F) of OPFRs is an important estimation parameter which has been limited studied.[94, 95] The varied F values of individual OPFRs indicated the necessity for accurate estimation of body burden.

Levels of OPFRs are associated with the occurrence of female-specific tumors, including papillary thyroid carcinoma, breast cancer, and cervical cancer ($p < 0.05$ or $p < 0.01$).[88, 96] Moreover, OPFRs can affect the synthesis of progesterone and human chorionic gonadotropin in human placental choriocarcinoma cells.[97] OPFRs exposure generates oxidative stress and DNA damage, suggesting that OPFR exposure during pregnancy causes DNA damage or oxidative stress in pregnant women, disrupts thyroid secretion, and undermines thyroid homeostasis.[98, 99] Prenatal stress can trigger changes in placental serotonin synthesis during the critical period of embryonic development, affect the development of the fetal brain, and increase the risk of mental illness in later years.[100]

3.3. Mother-to-child transmission

It has been found that exogeneous compounds, such as perfluoroalkyl substances and phthalate metabolites, can cross the placental barrier, enter the embryonic circulatory system, and harm the fetus.[101, 102] Assessing the mother-to-child transmission capacity of exogenous compounds in the womb is essential for understanding the risks to healthy fetal growth. This section summarizes the maternal-infant transmission efficiencies of several OPFRs in amniotic fluid, placenta, cord blood, and other samples and the relevant influencing factors.

3.3.1. Before the placenta matures

During the first eight weeks of gestation, the placenta is immature. Embryos are therefore easily exposed to contaminants. The villi are evenly distributed on the surface of the entire chorionic membrane. As the embryo grows, the villi adjacent to the decidua develop a rich nutrients and blood supply, and the stem branches become luxuriant, called the dense chorion, which constitutes the fetal part of the placenta. As a direct maternal-embryo interface, decidua and chorionic villi are significant components for the exchange and metabolism of nutrients, gas, wastes, and pollutants during pregnancy.[103, 104] Therefore, the maternal transfer of OPFRs was also affected by the different metabolic processes of OPFRs in the deciduae and chorionic villi. In a study of OPFRs levels in human decidua and chorionic villi, EHDPP and DPHP were frequently (DF: 96%) detected in chorionic villi, with median concentrations of 13.6 ng/g dw and 11.1 ng/g dw, respectively, much higher than those of decidua samples. The DFs of most OPFRs were higher in the chorionic villi than in the decidua.[105] To our knowledge, this is the first study to report the levels of OPFRs in human chorionic villi. Before placental formation, the embryo has been exposed to pollutants and has undergone exogenous compound transfer with the mother, according to the results. In addition, the maternal transfer efficiency (CMR) of the target compound was quantitatively assessed by calculating the ratio of the OPFR concentrations in the chorionic villi (containing embryos) to those in the maternal deciduae. It was found that the maternal CMRs were independent of the lipid content of the samples but had a significant positive correlation with the log K_{ow} values of OPFRs ($p = 0.003$).[105] The log K_{ow} values are usually related to the binding ability to proteins. The stronger the binding ability to transthyretin (TTR), the higher the CMRs of EHDPP, TPHP, TNBP, and TCEP, which further indicates that the binding ability contributes to the maternal transfer of OPFRs.[105]

3.3.2. After the placenta matures

The placenta is a vital organ that maintains fetal growth and embryonic development. It connects the fetal and mother's circulatory systems and selectively transports molecules

between them, protecting the fetus from exogenous compounds.[106] Nutrients and oxygen are transported between mother and fetus through the placenta. Even if the placenta has a barrier effect, some exogenous compounds may pass through the placental barrier, causing adverse effects on the fetus.[107] Changes in the maternal can significantly impact placenta implantation, growth, nutrient transfer, and hormones.[101] The analysis of contaminant levels in the placenta is important because contaminant in the placenta are not only biomarkers of internal maternal exposure to these chemicals but are also appropriate biomarkers for prenatal exposure of the fetus throughout pregnancy. A study found that the concentration of TCEP was the highest in the human placenta, accounting for 58% of all OPFRs.[108] Offspring sex-specific accumulation was also found in the placentas of Wistar rats exposed to FM550 during gestation.[109]

As a group of compounds with various physicochemical properties, OPFRs have been shown to have the potential for transplacental transfer in organisms. Experiments with paired samples of cord blood and maternal blood showed that the transplacental transfer of OPFRs and mOPs correlated with their log K_{ow} values. The concentration ratio (C:M) of OPFRs in cord blood versus those in maternal blood showed a parabolic relationship with the increasing log K_{ow} values. Moreover, the transplacental transfer efficiencies of the alkyl-OPFRs were lower than those of the aryl-OPFRs. In addition, the transplacental behavior of OPFRs and mOPs is related to the binding affinity of transporters in the placenta and metabolic enzymes in the fetus. For example, the C:M ratio of TCrP is the highest due to the strong binding affinity between TCrP and TTR for the molecular docking results, suggesting that the transplacental transfer of TCrP is active transport. OPFRs with log K_{ow} of 1.63−4.70 were mainly involved in transplacental transfer by passive diffusion.[110] Di-mOPs were also detected in blood samples at significantly lower concentrations than OPFRs. Moreover, the concentrations of different di-mOPs in cord blood and maternal blood were different, which may be related to their excretion rates and the metabolism of their parent compounds in the fetus.[110] For Wistar rats exposed to

FM550 during pregnancy and postpartum, the transfer of the brominated component by lactation was 200−300 times that of the transplacental transfer, but the organophosphate components were not detected in the fetus. The results indicated that TPHP and ITP had not been transferred by pregnancy or lactation.[111] This may be because liver microsomes quickly metabolize TPHP.[95] The results of whole-body autoradiographic disposition indicated that TCrP can be transported to the fetus via transplacental behavior in ICR mice.[112] More studies are needed on the metabolic profile of different OPFRs to understand their transplacental transfer capacity.

In addition to transplacental transfer, the fetus is exposed to environmental contaminants through amniotic fluid. Amniotic fluid is the only living environment for the fetus before birth, surrounding and protecting the fetus. Among environmental chemicals, the heavy metals mercury, perfluorooctane sulfonates, and organochlorine have been detected in amniotic fluid.[113-115] mOPs were also detected in amniotic fluid samples collected from the e-waste dismantling area, with the highest concentration of DNBP (1.3 ng/mL), followed by DPHP (0.12 ng/mL), and the level of DNBP was an order of magnitude higher than that of DPHP. This result suggests that we need to pay more attention to the use and release of TNBP in electronic products.[116] The distribution and composition of mOPs in urine and amniotic fluid samples from the same mother were similar or consistent. The concentration in amniotic fluid is generally lower than that in urine, which may be due to the role of the placental barrier and the difference in fetal and maternal metabolic capacities.

3.4. Exposure to OPFRs after delivery

3.4.1. Levels of OPFRs in breast milk of among postnatal mothers

The major nutritional source for infants is breast milk, which contains proteins, carbohydrates, vitamins, antibodies, and fats. It also includes many exogenous pollutants resulting from the mother's exposure to food, medicine, and the environment.[117] These

505 pollutants are the primary causes of newborns' exposure to environmental pollution. Due to the
506 immature immunological and metabolic system of newborns, infants are frequently overloaded
507 with external pollutants compared to their bodies.[118] The study on the level of OPFRs in breast
508 milk helps to understand the OPFRs exposure of infants. Moreover, breast milk has been
509 suggested by the World Health Organization as a perfect matrix for monitoring human
510 environmental pollutants owing to non-invasive sampling and easy accessing.[119, 120]
511 Concentrations of OPFRs in breast milk samples of postnatal mothers worldwide are
512 summarized in **Figure 2**. OPFRs of high concern in breast milk include Cl-OPFRs (TCEP,
513 TCIPP, and TDCIPP), aryl-OPFRs (TPHP, TCrP, and EHDPP), and alkyl-OPFRs (TNBP,
514 TBOEP, and TEHP). Among them, the DFs of TPHP, TNBP, TCIPP, and TEHP were relatively
515 higher (61−99%). The composition and proportion of OPFRs varied greatly in breast milk
516 samples from different countries. Research on OPFRs in breast milk began in 2009, and these
517 samples were collected from regions of the Swedish National Food Administration.[9] The
518 concentration of TCIPP (45 ng/g lipid) was the highest in all samples, followed by TNBP (12
519 ng/g lipid) and TPHP (8.5 ng/g lipid). Moreover, comparing breast milk samples collected in
520 1997, 1998, and 2006 in Uppsala (a city in southeast Sweden), it was found that the
521 concentration of TBOEP ten years ago was much higher than that at present. The DFs of TCIPP,
522 TEHP, and TCEP increased significantly (e.g., the DF of TCIPP increased by 20 to 82% ten
523 years later), whereas the DFs of the remaining OPFRs (TPHP, EHDPP, TNBP, and TBOEP) did
524 not increase significantly. The level of TCIPP in Seattle is an order of magnitude higher than
525 that of the national Children's Study sample repository, and TCIPP has the highest proportion
526 of OPFRs in breast milk samples from the U.S. and Australia.[121] TCIPP accounts for 50% of
527 total OPFRs, which may be attributed to its slow biotransformation in vivo.[122] Nearly 10 years
528 have passed since the samples were collected, which may be related to the increased production
529 and use of TCIPP in the U.S. market in recent years. Nevertheless, the level of TBOEP

decreased by approximately 1 ng/mL.[119, 123] The average and highest EDIs of OPFRs for adults were approximately two orders of magnitude lower than the corresponding reported references doses (RfDs), suggesting a low non-carcinogenic risk of OPFRs in pregnant women.[35, 124] The composition and proportion of OPFRs in breast milk in Asian countries and regions differs from those in Western countries. TCEP, TPHP, and TEHP had the highest percentages of all the OPFRs. The concentration of OPFRs in the Philippines is 1.5−2 times higher than in Japan, Vietnam, and Sweden. This difference may be because the breast milk samples from Filipino were collected from waste facilities. In this study, the DFs of TCEP, TNBP, and TCrP in breast milk samples were similar to those in indoor dust in the Philippines.[125] This finding indicated that the exposure pathways for OPFRs were from sources other than indoor dust, resulting in detectable concentrations of OPFRs in breast milk that are comparable to those of indoor dust. However, the proportion of TCEP in breast milk was higher than that in indoor dust, indicating that TCEP has a higher transfer rate to breast milk or biological accumulation potential than other OPFRs after entering the human body. In human liver microsome incubations, TCEP displayed good persistence with extremely low clearance rates (0.0006 mL/mg protein/min).[94] There have been few studies on mOPs in breast milk samples. Only one study has stated that the DFs of DNBP and DPHP were high. DNBP and DPHP accounted for a large proportion of the total mOPs.[123] The concentrations of DBNP and DPHP were positively correlated with their parent compounds TNBP and TPHP. Although these findings may be associated with the rapid metabolism of TNBP and TPHP in vivo, TNBP and TPHP may be transferred through the maternal blood.

Children could be more easily exposed to OPFRs than adults.[126] EDIs is higher in younger individuals, for infants it is mainly due to the intake of breast milk.[35] Children are also exposed to OPFRs by contact with toys, including dermal contact, hand-to-mouth contact, and mouthing. Although dermal contact is the primary pathway of exposure, the risk of exposure to OPFRs

555 through toys is low.[127] Infants may consume formula or solid foods in addition to breast milk.
556 Although most OPFRs are detected frequently in these foods, the daily consumption of OPFRs
557 by infants did not pose a health risk, with EDIs of OPFRs about 2-3 orders of magnitude lower
558 than those of RfDs.[128] Based on the concentration of OPFRs in breast milk, the EDI_M for infants
559 was estimated to be significantly lower than the corresponding RfDs for OPFRs. Many studies
560 have confirmed that the amount of OPFRs consumed by infants through breast milk were much
561 higher than that through skin contact or dust inhalation. For example, in Australia, the EDI_M of
562 TCEP, TNBP, and TEHP by lactation was higher than that by air and dust ingestion, indicating
563 higher exposure through breastfeeding.[121] Notably, the sample size of this study was small, the
564 results were not representative, and there were significant differences in concentrations among
565 the three samples. The EDI_M of TBOEP (1380 ng/kg bw/day) and TDCIPP (980 ng/kg bw/day)
566 in Japan and the EDI_M of TCEP (1610 ng/kg bw/day) in the Philippines were close to the RfDs,
567 and other EDI_M of OPFRs were lower than their RfDs. The level of OPFRs in Beijing was high
568 and was higher than that in North America, Europe, and other Asian countries, indicating that
569 Beijing infants were highly exposed to OPFRs.[129] OPFRs in breast milk have no significant
570 impact on infants' health. However, additional intake of OPFRs, such as food and dust, by
571 infants may synergistically cause health risks. Detailed information on the OPFRs in breast
572 milk is provided in **Table S3 (b)**. Detailed information about the EDI_M of OPFRs through
573 breastfeeding is shown in **Table 2**.

574 **3.4.2. Predictors of OPFRs exposure among postnatal mothers**

575 Exposure to lipophilic pollutants in human breast milk is often associated with maternal
576 age and dietary preferences.[130]

577 For age, it was observed that the concentrations of TNBP, TEHP, DNBP, Σdi-OPE, and
578 Σtri-OPE were negatively correlated with maternal age ($p < 0.05$).[123] However, there was no
579 significant relationship between the concentrations of OPFRs in breast milk and age. This may

be due to the limited sample size, short half-life of OPFRs in humans, and the fact that the concentration of OPFRs in breast milk only represents short-term exposure. Most OPFRs were not significantly associated with racial characteristics. Only TBOEP was found to be twice lower in Spanish mothers (0.765 ng/mL) than in non-Spanish mothers (1.48 ng/mL) (p = 0.041).[119] Breastfeeding and excretion can reduce the content of OPFRs in the maternal body. Several studies have provided evidence to support this conclusion. The concentrations of TCEP, TEHP, and alkyl-OPFRs in the breast milk of multipara are lower.[19, 129] However, in Japan, this conclusion is contrary, which may be related to Japanese women's occupation, diet patterns, and habits of using products containing OPFRs.[119] Only high concentrations of EHDPP were found in breast milk samples provided by highly educated mothers.[129] The features of pre-pregnancy body weight or pre-pregnancy BMI were rarely found to be associated with the exposure of OPFRs in breast milk. Several studies found no statistical significance between BMI and OPFRs levels, and the difference was not obvious.[19, 119, 123] Only TCEP showed a significant difference in all groups, and pre-pregnancy BMI was positively correlated with the concentration of TCEP in breast milk.[129] Eating habits had little effect on OPFRs concentrations in breast milk. Mothers who ate more eggs had higher levels of TPhP in their breast milk.[129] Dietary habits had little effect on OPFRs accumulation in the placenta. For example, different amounts of visceral consumption during pregnancy resulted in different placental of TPhP (p < 0.05) and TCrP (p < 0.05). Higher consumption of vegetables before pregnancy resulted in higher placental TCIPP concentrations (p < 0.05). Higher concentrations of $\sum_9$OPFRs were associated with higher alcohol consumption in women before pregnancy (p < 0.05).[108] The concentrations of ∑OPFRs were higher in the breast milk of mothers living in the suburbs. The concentration of TNBP is higher in the breast milk of mothers living in urban cities.[129] For behavioral habits, higher concentrations of OPFRs were observed in women with lower handwashing frequencies, although the difference was insignificant.[123] This helps us understand

how mothers behave or eat after delivery could reduce the levels of OPFRs in breast milk and reduce the potential impact of breastfeeding on infants since breast milk is a major food source.

3.5. Potential risks of infants about maternal exposure to OPFRs

3.5.1. Toxicity of OPFRs to the fetus in the womb

Many animal experiments have shown that OPFRs have endocrine disruption effects, acute toxicity, developmental toxicity, reproductive toxicity, neurotoxicity, carcinogenicity, and teratogenicity, causing adverse developmental consequences in larvae. Acute exposure of embryos to OPFRs adversely affects embryo development, including inhibition of proliferation and cardiac differentiation of embryonic stem cells,[131, 132] inhibition of gene expression of HPT and GH/IGF axis,[133, 134] inhibition of gene expression related to neural development,[68, 135] cardiac toxicity during embryonic development,[136-138] and developmental neurotoxicity.[67, 139]

In zebrafish, exposure to TDCIPP at 0.75h after fertilization leads to dose-dependent delay or retardation of the ectoblast during the blastula and gastrula stages.[67] The typical developmental trajectory of zebrafish embryos is changed by inducing the formation of defects and abnormal germ layers of the gastrula, eventually leading to embryo malformation, developmental anomalies, and increased death rates. The developmental anomaly of zebrafish embryos caused by TDCIPP contains adverse effects on embryonic tail fin development, including spinal curvature, defects, and tip damage of tail fin.[140, 141] The dose-dependent inhibition of TDCIPP on vascular development was also observed in zebrafish embryos.[69] The growth and metabolic inhibition that adversely affected health in Japanese quail chicks were related to TPHP exposure during embryonic periods.[142] TCEP was observed to specifically affect cardiovascular development in the shell-less incubation system of chicken embryos.[143] Exposure to OPFRs during the embryonic stage also affects brain development by damaging the normal function of the rat placenta.[144] Early mouse embryo development was dose-dependently inhibited by TDCIPP (Oral LD50 = 2250 mg/kg), with 10 μM TDCPP reducing

blastocyst formation and 100 μM TDCIPP being deadly to mice embryos.[145] Acute exposure to TPHP (Oral LD50 = 1320 mg/kg) inhibited mouse embryonic stem cell growth in a dose-dependent manner.[132] It is noteworthy that specific concentrations of OPFRs causing developmental toxicity, neurotoxicity, cardiotoxicity, and hepatotoxicity in zebrafish are within the upper limit of the levels of OPFRs in indoor dust, human breast milk, plasma, and urine.[146] To clarify the damage to humans, it is required to examine the embryonic development toxicity produced by maternal exposure to OPFRs and to fully comprehend the mechanism and toxicokinetic features.

3.5.2. Effects on pregnancy outcomes

Epidemiological studies examined the relationships between the concentrations of OPFRs in mothers and the gestational age, birth weight, alternations in neonatal thyroid hormones, and adverse pregnancy outcomes, such as spontaneous abortion and premature delivery. A systematic evaluation of 11 publications examined the effect of the prenatal OPFR exposure on pregnancy outcomes. These included nine cohort studies and two case-control studies, involving 2434 participants in total. Four studies examined the association between the exposure to OPFRs during pregnancy and the neonatal birth weight.[80, 89, 147, 148] Three articles discussed the effects of the prenatal OPFR exposure on neonatal hormones, including thyroid hormone, thyroid stimulating hormone, insulin, and leptin.[89, 149, 150] Four studies investigated the association between the prenatal exposure to OPFRs and the gestational age.[80, 89, 151, 152] Two studies suggested a potential relationship between the exposure to OPFRs during pregnancy and the risk of miscarriage.[153, 154]

Prenatal exposure to OPFRs may disturb fetal growth and influence birth weight. A few studies reported that the levels of urinary mOPs in pregnant women are associated with the birth weight of the newborn.[80, 147] For example, higher concentrations of BDCIPP were associated with a higher BMI in newborns (n = 76).[89] The relationships between urinary mOPs collected

at different stages of pregnancy and birth weight of the newborns were different.[80, 85, 88] For example, the concentrations of ip-PPP, BDCIPP, and BBOEP in the third trimester; 4-HO-DPHP in the second trimester; and DPHP in the first trimester were negatively correlated with birth weight ($p < 0.05$).[80, 148] However, these studies did not find a significant correlation between the prenatal OPFR levels and the neonatal birth weight.[80, 89, 151] Moreover, the effects of mOPs in maternal urine on fetal birth weight were sex-specific. Crawford et al. showed that the levels of BDCIPP during pregnancy (n = 56) were associated with the higher weight gain of the male fetus after the first six weeks of life (β (the mean change in infant anthropometrics at six weeks postpartum) = 0.14 kg, 95% CI: 0.03−0.24, *p*-for-EM (effect modification) = 0.02), but a negative correlation between DPHP and weight gain was found in female fetuses (β = −0.19 kg, 95% CI: −0.36 to −0.02, *p*-for-EM = 0.02).[151] In a Nested Case-Control study in China (n = 339), a significant positive correlation between DPHP in pregnant women's urine and the risk of low birth weight was only observed in female newborns ($p < 0.01$).[147] Similar results were observed in animals. Embryonic chicken exposure to TDCIPP leads to a weight loss of 7% during hatching.[155] Prenatal exposure to TDCIPP leads to the production of lighter-weight rat cubs.[156] Low birth weight is one of the leading causes of newborn mortality and sickness, and it also affects the health of adults.

The concentration of mOPs in maternal urine is positively correlated with thyroid hormone levels in newborn blood.[150] DNBP and DPHP exhibited a positive connection with the neonatal TSH above the 5th quantile ($p < 0.05$) and the 5th−85th quantiles, respectively.[150] A sex-specific association between the prenatal exposure to OPFRs and the neonatal TSH levels was observed in one cohort study (n = 102), but not observed in another cohort study (n = 298).[86, 149] Several animal toxicological studies have demonstrated that embryo exposure to OPFRs disrupted the development of thyroid and altered the release of thyroid hormones.[134, 142, 156-158] TSH plays an essential role in maintenance of normal thyroid function and fetal growth. More studies are

needed to reveal the relationship between prenatal exposure to OPFRs and neonatal TSH levels.

Some studies have also found that urine mOPs in pregnant women are associated with pregnancy duration. An interquartile range-increase in DPHP levels was associated with a decreased risk of gestational age (odds ratio (OR) = 0.40; 95% CI: 0.18−0.87).[152] Urine BDCIPP (95% CI: 1.08−14.78) and ip-PPP (95% CI: 1.23−17.06) were associated with shortened pregnancy and increased risk of premature delivery in female infants, whereas ip-PPP concentrations (OR = 0.21; 95% CI: 0.06−0.68) were associated with a decreased risk of premature delivery in male infants.[80] However, Crawford et al. (n = 56) and Kuiper et al. (n = 76) found no significant associations between the urine mOP concentrations in pregnant women and the gestational age.[89, 151] Toxicological results also confirmed the association between OPFRs exposure and pregnancy time. Exposure to TCEP (> 20 μg/L) in zebrafish embryos could lead to incubation delay due to the disruption of TCEP to thyroid hormone homeostasis.[159]

In a study of urine mOPs of pregnant women with spontaneous abortion (SAB) and healthy controls, the increased risks of fetal chromosome abnormalities and SAB were associated with higher BDCIPP (OR = 2.34; 95% CI: 1.14−4.81) and BCIPP ($p < 0.001$) levels, respectively.[153] Pregnant women exposed to OPFRs before delivery with assisted reproductive technology (ART) may be related to poor pregnancy outcomes ($p < 0.05$).[160] Levels of urine DPHP and ip-PPP are inversely proportional to the proportion of successful fertilization, implantation, clinical pregnancy, and live-born.[154] Early termination of pregnancy may be related to the level of urine DPHP among women conceiving with ART.[161] SAB is the most common adverse pregnancy outcome, defined as fetal demise prior to 20 completed weeks of gestation in North America.[162] Few studies have examined the relationship between prenatal exposure to OPFRs and abortion. Some studies have shown that the concentration of OPFRs in pregnant women is related to oxidative stress. Higher levels of oxidative stress lead to adverse pregnancy outcomes such as premature delivery and preeclampsia. This may be due to the influence of OPFRs and

their mOPs on antioxidant enzyme activity or related gene expression.[163] OPFRs are increasingly being utilized and produced as alternatives to traditional flame retardants, and prenatal exposure to OPFRs will likewise increase. Future studies should focus on the mechanism underlying the relationship between prenatal exposure to OPFRs and a higher SAB risk.

3.5.3. Effects on developmental behaviors of infants

Childhood is a critical period of social behavior development, and bad behavior and habits often persist throughout childhood.[164] Exposure to environmental pollutants may adversely affect their behavioral and emotional development.[165]

Exposure to OPFRs throughout pregnancy and infancy may affect cognitive and behavioral development in infants.[166] Animal experiments showed that exposure of zebrafish embryos to TPHP could interfere with the development of larvae's eyes and muscle tissues.[167] Exposure to TPHP during pregnancy in rats will accelerate the onset of diabetes mellitus type 2 in 3.5 months old rats and lead to adipose accumulation.[168] By affecting lipid metabolism and intestinal function in adult mice, obesity occurs in adult mice with metabolic dysfunction.[169] *Coturnix japonica* (Japanese quail chickens) exposed to TPHP with a low dose (5 ng/g) would be more aggressive, and with a high dose (100 ng/g) would increase their boldness.[170] Exposure of juvenile yellow catfish to TCEP can reduce the survival rate (100 μg/L) and specific growth rate (10 and 100 μg/L).[171] Exposure of mice to OPFRs during pregnancy can also change the movement, and anxiety-like behavior of offspring, and these changes have sex-specific effects.[172] The continuous exposure of male rats to TDCIPP (25−250 mg/kg) within 28 days after birth will inhibit their sexual behavior and reduce testicular growth in a dose-dependent manner.[173] Early-life zebrafish exposure to TDCIPP can inhibit the growth and gene expression of motor neurons, affect the cholinergic system, and lead to anxiety in adult females, resulting in delayed neurotoxicity in adult zebrafish.[135, 174]

Epidemiological findings suggest that prenatal and early life exposure to OPFRs can affect infant cognitive and behavioral development. For example, poor social skills, asthma, and allergic symptoms in children are related to the concentration of OPFRs in indoor dust.[164, 175, 176] The decrease in children's memory and full-scale intelligence quotient was related to maternal prenatal exposure to TPHP.[177] Moreover, the effects of OPFRs on developmental behaviors were sex-specific. The statistical results show that prenatal exposure to chlorinated-OPFRs, especially TDCIPP, may be inversely proportional to neurodevelopment in boys but not in girls.[178] In summary, epidemiological studies on the effects of OPFRs prenatal exposure to OPFRs on children's cognition and behavioral are minimal. Therefore, more robust inferences about the potential developmental risks of OPFRs exposure in children are necessary.

4. Conclusions and perspectives

The exposure of pregnant women to OPFRs varies before and after delivery. The levels and proportions of mOPs in urine and OPFRs in breast milk were distinct. However, it is undeniable that pregnant women are widely exposed to TDCIPP and TPHP before delivery. Although the production of OPFRs has increased rapidly in the past 20 years, analysis of maternal prenatal and postnatal exposure showed no significant increase in concentration over time. The fetus is exposed to OPFRs through the amniotic fluid and breast milk. Many toxicological experiments and epidemiological studies have shown that maternal exposure to OPFRs may affect pregnancy outcomes and growth and development of the next generation. Furthermore, examining the predictors of maternal prenatal and postnatal exposure to OPFRs could help to reduce the potential adverse effects of OPFRs on mothers and fetuses. For better estimation of pregnant woman's exposure to OPFRs, recommendations on epidemiological and toxicological studies are provided as follows:

1) Due to the rapid metabolism of OPFRs in the body and their short biological half-lives,

only monitoring the levels of OPFRs in samples from pregnant women at one or two intervals during pregnancy may lead to bias in exposure doses. It is necessary to repeat monitoring during pregnancy and to estimate ICCs.

2) Human placental sampling in studies of mother-to-child transmission of OPFRs is complex. Animal models are essential for evaluating OPFR transmission in pregnant women and fetuses. Owing to the complexity of multiple physiological changes during pregnancy, more attention should be paid to hormonal alterations, epigenetics, inflammation/oxidative stress, cell injury, and nutrient absorption.

3) Because exposures to pollutants in the environment is complex and varied, much more attention should be paid to the synergistic effect of mixed pollutants in animal models. Future studies should consider the joint effects and nonlinear correlations of chemicals, and quantify the potential risks to mothers and infants.

4) Since the dose of exposure is related to the exposure and metabolism of OPFRs in vivo and the excretion of metabolites, the model test cannot accurately represent the exposure of pregnant women. To better extrapolate the results of animal models to humans, the toxicokinetics and excretion of OPFRs should be examined. A greater number of cohorts can be employed for correlation assessment in epidemiological investigations because the different metabolic abilities of individuals will lead to a significant variation in the mOPs levels of the sample.

5) Recent studies have shown that exposure to OPFRs during pregnancy has adverse effects on pregnant women, fetuses, and developmental risks of infants; however, the underlying mechanisms are unclear. Future research should provide mechanistic understanding of the sex-specific effects and identify the critical window of susceptibility of the fetus after exposure to OPFRs.

6) The OPFRs of mothers are transmitted to infants through breastfeeding, and it is necessary

to study the impact of OPFRs on the development of infants by studying the exposure of mothers after delivery. Analyzing the demographic characteristics of pregnant women such as diet, BMI, and personal care products, can facilitate the prediction and control of OPFRs during pregnancy, and the susceptible population should be managed accordingly.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at XXX.

Newcastle-Ottawa Scale for assessing the quality of included studies (Table S1), details of estimation of daily intakes, molecular structures and CAS numbers of the studied OPFRs and mOPs (Table S2), concentrations of mOPs and OPFRs in pregnant women urine (Table S3), and estimation of daily intake using urinary mOP concentrations (Table S4)

Notes

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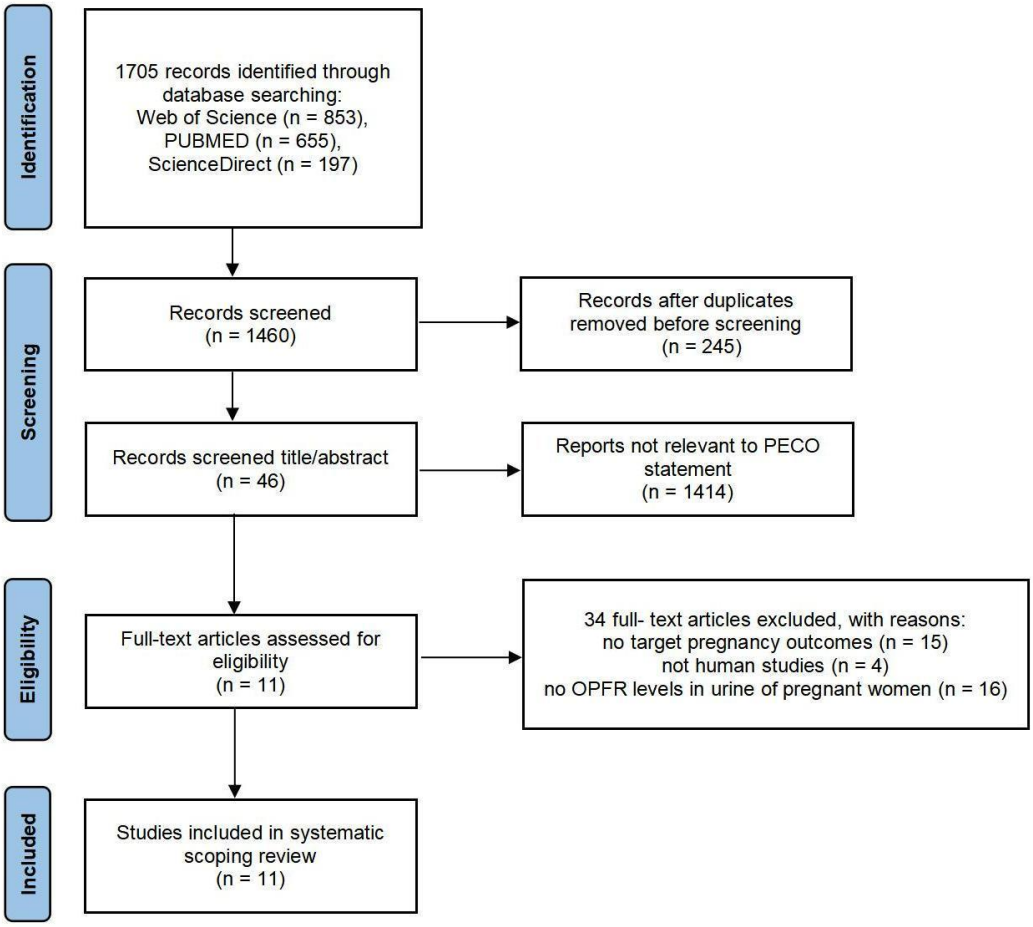

Figure 1. A flow diagram showing the selection of literatures

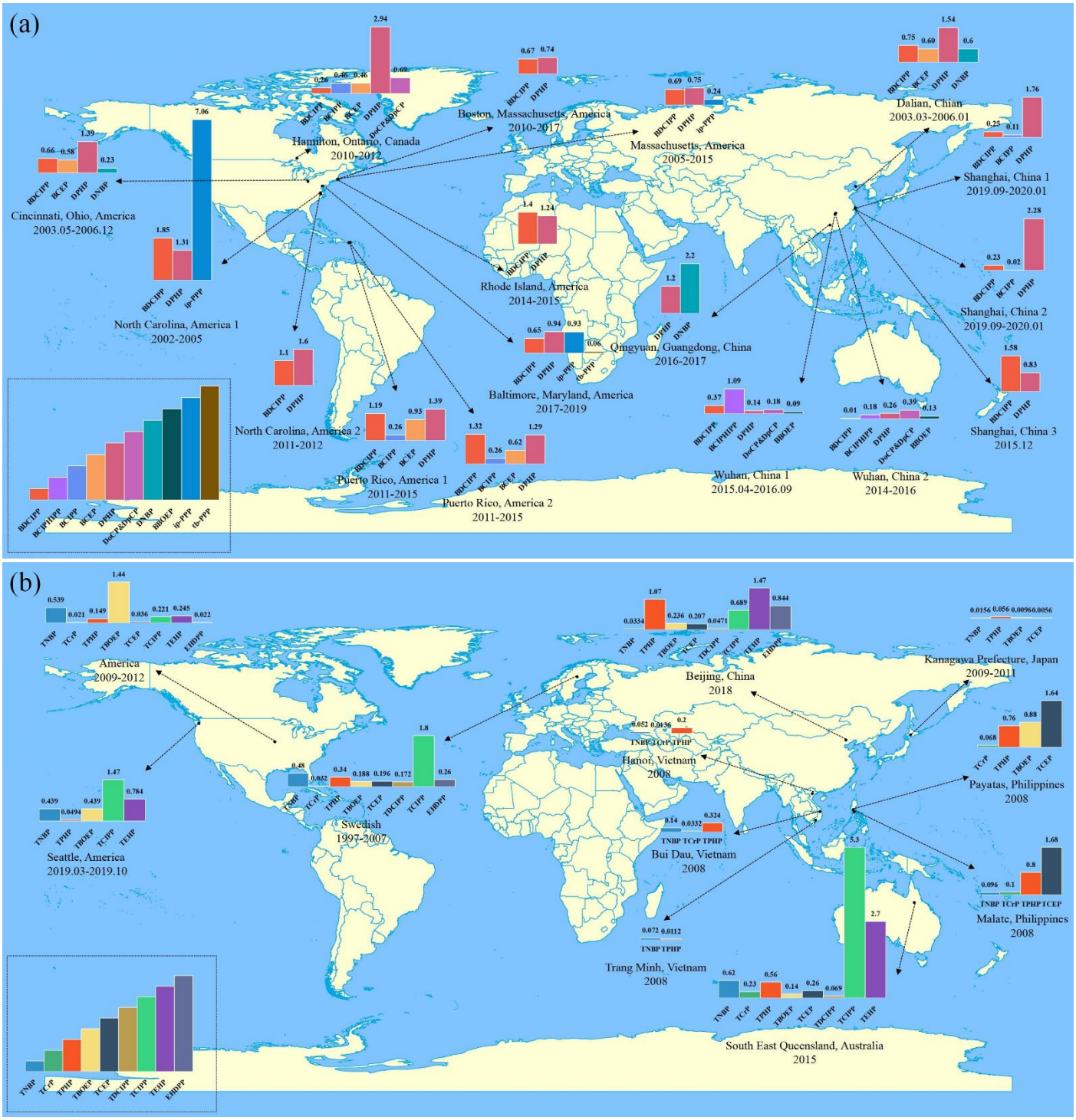

Figure 2. (a) Concentrations of mOPs in urine samples of pregnant women worldwide. **(b)** Concentrations of OPFRs in breast milk samples of pregnant women worldwide. The data above the histogram represents the median concentration of OPFRs or mOPs in ng/mL. The sampling period is below the city. The data for "America 2009-2012" represent the mean concentration of OPFRs. The data of Japan, Philippines, Vietnam, and Swedish were converted from the average lipid content (40 mg lipid/g).[81]

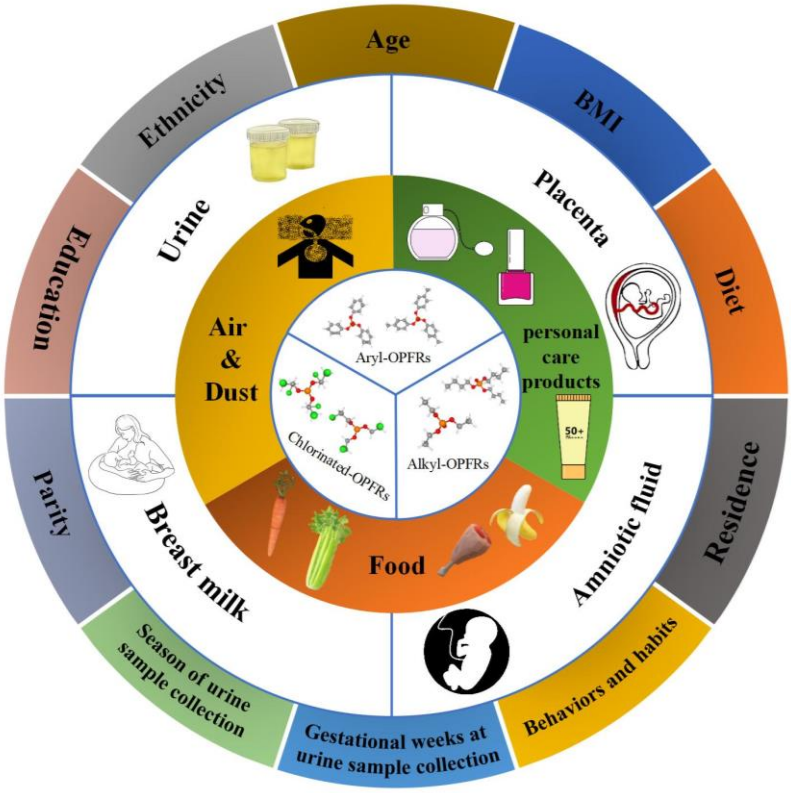

Figure 3. Predictors, sources, and monitoring of OPFRs or mOPs in pregnant women before and after delivery. The figure only contains the predictors, sources, and monitor methods discussed in the review.

Table 1. Sample Collection Times and ICCs

Location	Sampling period	SG-corrected ICCs (95% CI)									
		DNBP	DPHP	BDCIPP	BBOEP	DoCP & DpCP	BCIPHIPP	BCIPP	BCEP	ip-PPP	tb-PPP
Wuhan, China	first (12.9 ± 0.9 weeks), second (24.7 ± 3.6 weeks), and third trimesters (34.0 ± 3.1 weeks)	0.26 (0.14, 0.39)	0.16 (0.04, 0.29)	0.17 (0.05, 0.30)	0.09 (− 0.02, 0.21)	0.19 (0.07, 0.32)	0.16 (0.04, 0.29)	/	/	/	/
Wuhan, China	before 16 weeks and after 28 weeks of gestation	/	0.32 (0.21, 0.46)	0.26 (0.15, 0.41)	0.21 (0.10, 0.37)	0.27 (0.16, 0.42)	0.08 (0.01, 0.38)	/	/	/	/
Cincinnati, Ohio, America	16 weeks, 26 weeks of pregnancy and after delivery	0.20	0.16	0.36	/	/	/	/	0.34	/	/
Northern Puerto Rico, America	18 weeks and 26 weeks of gestation	/	0.25 (0.13, 0.43)	0.23 (0.11, 0.41)	/	/	/	0.34 (0.21, 0.49)	0.03 (0.00, 0.86)	/	/
Baltimore, Maryland, America	15.3 (± 3.1) weeks, 22.3 (± 2.2) weeks at the second visit, and 30.9 (±2.5) weeks	/	0.27 (0.15, 0.43)	0.59 (0.45, 0.73)	/	/	/	/	/	0.09 (0.01, 0.44)	0.19 (0.08, 0.38)
Rhode Island, America	12 weeks, 28 weeks and 35 weeks of gestation	/	0.43	0.6	/	/	/	/	0.5	/	/
North Carolina, America	18 weeks, 28 weeks of pregnancy and 1–10 days after delivery	/	0.4 (0.2, 0.6)	0.4 (0.2, 0.6)	/	/	/	/	/	/	/

ICCs: intraclass correlation coefficients

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Table 2. Estimated Daily Intakes (ng/kg bw/day) of OPFRs of High Concern via Breast Feeding

	Sampling location	OPFRs	TNBP	TCrP	TPHP	TBOEP	TCEP	TDCIPP	TCIPP	TEHP	EHDPP
		RfD	**2400**	**1300**	**7000**	**1500**	**7000**	**20000**	**3600**	**35000**	**600**
Lactational EDIs	South East Queensland, Australian	< 1 month	93	34.5	84	21	39	10.4	795	405	/
		1-3 months	86.8	32.2	78.4	19.6	36.4	9.66	742	378	/
		3-6 months	68.2	25.3	61.6	15.4	28.6	7.59	583	297	/
		6-12 months	51.5	19.1	46.5	11.6	21.6	5.73	439.9	224.1	/
	Beijing, China	< 1 month	5.01	/	160.5	35.4	31.1	7.07	103.35	220.5	126.6
		1-3 months	4.68	/	149.8	33.0	29.0	6.59	96.46	205.8	118.16
		3-6 months	3.67	/	117.7	26.0	22.8	5.18	75.79	161.7	92.8
		6-12 months	2.77	/	88.8	19.6	17.2	3.91	57.19	122.01	70.1
	Tennessee, Wisconsin, South Dakota, Maine, New York, Pennsylvania, North Carolina, and California (America)	< 1 month	80.9	3.15	22.4	216	5.4	/	33.15	36.75	3.3
		1-3 months	75.5	2.94	20.9	201.6	5.04	/	30.94	34.3	3.08
		3-6 months	59.3	2.31	16.4	158.4	3.96	/	24.31	27.0	2.42
		6-12 months	44.7	1.74	12.4	119.52	2.99	/	18.34	20.3	1.83
	Kanagawa Prefecture, Japan	< 1 month	2.34	/	8.4	1.44	0.84	/	/	/	/
		1-3 months	2.18	/	7.84	1.34	0.78	/	/	/	/
		3-6 months	1.72	/	6.16	1.06	0.62	/	/	/	/
		6-12 months	1.29	/	4.65	0.80	0.46	/	/	/	/
	Payatas, Philippines	< 1 month	NA	10.2	114	132	246	/	/	/	/
		1-3 months	0	9.52	106.4	123.2	229.6	/	/	/	/
		3-6 months	0	7.48	83.6	96.8	180.4	/	/	/	/
		6-12 months	0	5.64	63.1	73.0	136.1	/	/	/	/
	Malate, Philippines	< 1 month	14.4	15	120	/	252	/	/	/	/
		1-3 months	13.4	14	112	/	235.2	/	/	/	/

	3-6 months	10.6	11	88	/	184.8	/	/	/	/
	6-12 months	7.97	8.3	66.4	/	139.44	/	/	/	/
Hanoi, Vietnam	< 1 month	7.80	2.04	30	/	/	/	/	/	/
	1-3 months	7.28	1.90	28	/	/	/	/	/	/
	3-6 months	5.72	1.50	22	/	/	/	/	/	/
	6-12 months	4.32	1.13	16.6	/	/	/	/	/	/
Bui Dau, Vietnam	< 1 month	21	4.98	48.6	/	/	/	/	/	/
	1-3 months	19.6	4.65	45.36	/	/	/	/	/	/
	3-6 months	15.4	3.65	35.64	/	/	/	/	/	/
	6-12 months	11.6	2.76	26.89	/	/	/	/	/	/
Trang Minh, Vietnam	< 1 month	10.8	/	1.68	/	/	/	/	/	/
	1-3 months	10.1	/	1.568	/	/	/	/	/	/
	3-6 months	7.92	/	1.232	/	/	/	/	/	/
	6-12 months	5.98	/	0.93	/	/	/	/	/	/
Seattle, America	< 1 month	65.9	/	7.41	65.85	/	/	220.5	117.6	/
	1-3 months	61.5	/	6.92	61.46	/	/	205.8	109.76	/
	3-6 months	48.3	/	5.43	48.29	/	/	161.7	86.2	/
	6-12 months	36.4	/	4.10	36.44	/	/	122.01	65.1	/
Uppsala, Lycksele, Lund, Umea (Swedish)	< 1 month	72	4.8	51	28.2	29.4	25.8	270	/	39
	1-3 months	67.2	4.48	47.6	26.32	27.44	24.1	252	/	36.4
	3-6 months	52.8	3.52	37.4	20.68	21.56	18.9	198	/	28.6
	6-12 months	39.8	2.66	28.22	15.60	16.27	14.3	149.4	/	21.6

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Graphical Abstract