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Review

A critical review on human internal exposure of phthalate metabolites and the associated health risks☆

Senyuan Huang [a, b], Zenghua Qi [a, b], Shengtao Ma [a, b, c], Guiying Li [a, b], Chaoyang Long [d], Yingxin Yu [a, b, *]

[a] Guangdong Key Laboratory of Environmental Catalysis and Health Risk Control, School of Environmental Science and Engineering, Institute of Environmental Health and Pollution Control, Guangdong University of Technology, Guangzhou, 510006, PR China
[b] Guangdong-Hong Kong-Macao Joint Laboratory for Contaminants Exposure and Health, Guangzhou, 510006, PR China
[c] Synergy Innovation Institute of GDUT, Shantou, 515041, China
[d] Center for Disease Prevention and Control of Guangdong Province, Guangzhou, 510430, PR China

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ABSTRACT

Phthalates (PAEs) are popular synthetic chemicals used as plasticizers and solvents for various products, such as polyvinyl chloride or personal care products. Human exposure to PAEs is associated with various diseases, resulting in PAE biomonitoring in humans. Inhalation, dietary ingestion, and dermal absorption are the major human exposure routes. However, estimating the actual exposure dose of PAEs via an external route is difficult. As a result, estimation by internal exposure has become the popular analytical methods to determine the concentrations of phthalate metabolites (mPAEs) in human matrices (such as urine, serum, breast milk, hair, and nails). The various exposure sources and patterns result in different composition profiles of PAEs in biomatrices, which vary from country to country. Nevertheless, the mPAEs of diethyl phthalate (DEP), di-n-butyl phthalate (DnBP), di-iso-butyl phthalate (DiBP), and di-(2-ethylhexyl) phthalate (DEHP) are predominant in the urine. These mPAEs have greater potential health risks for humans. Children have been observed to exhibit higher exposure risks to several mPAEs than adults. Besides age, other influencing factors for phthalate exposure are gender, jobs, and residential areas. Although many studies have reported biological monitoring of PAEs, only a few reviews that adequately summarized the reports are available. The current review appraised available studies on mPAE quantitation in human biomatrices and estimated the dose and health risks of phthalate exposure. While some countries lack biomonitoring data, some countries' data do not reflect the current PAE exposure. Thence, future studies should involve frequent PAE biomonitoring to accurately estimate human exposure to PAEs, which will contribute to health risk assessments of human exposure to PAEs. Such would aid the formulation of corresponding regulations and restrictions by the government.

1. Introduction

Phthalates (PAEs), diesters of 1,2-benzenedicarboxylic acids, are a family of ubiquitous synthetic chemicals. Owing to the difference in the phthalic acid side chains (**Table 1**), PAEs are divided into two types, i.e., high-molecular-weight PAEs (used as plasticizers to increase the flexibility and durability of products) and low-molecular-weight PAEs (used to maintain the color and fragrance of products or provide a film or gloss (Frederiksen et al., 2007; Latini, 2005). Nowadays, PAEs are used in multiple trade products (such as building supplies, adhesives, medical devices, food packaging, toys, personal care products, etc.) (Alves et al., 2016c; Heudorf et al., 2007; Schettler et al., 2006; Wormuth et al., 2006). Such diverse use has made PAEs present in the environment at various concentrations.

Environmental PAEs, identified as endocrine-disrupting compounds, have been shown to exhibit anti-estrogenic, anti-androgenic, anti-progestogenic, and anti-thyrogenic properties, associated with adverse health effects (Hannon et al., 2015; Johns

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* Corresponding author. Guangdong Key Laboratory of Environmental Catalysis and Health Risk Control, School of Environmental Science and Engineering, Institute of Environmental Health and Pollution Control, Guangdong University of Technology, Guangzhou, 510006, PR China.
E-mail address: yuyingxin@gdut.edu.cn (Y. Yu).

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Table 1
Major parent PAEs and their metabolites.

Full name of parent PAE	Abbreviation	Full name of metabolite	Abbreviation
Di-methyl phthalate	DMP	Mono-methyl phthalate	mMP
Di-ethyl phthalate	DEP	Mono-ethyl phthalate	mEP
Di-n-butyl phthalate	DnBP	Mono-n-butyl phthalate	mnBP
		OH-mono-n-butyl phthalate	OH-mBP
		Mono-(3-carboxypropyl) phthalate	mCPP
Di-iso-butyl phthalate	DiBP	Mono-isobutyl phthalate	miBP
		OH-Mono-iso-butyl phthalate	OH-miBP
Di-cyclo-hexyl phthalate	DCHP	Mono-cyclo-hexyl phthalate	mCHP
Di-n-pentyl phthalate	DnPeP	Mono-n-pentyl phthalate	mnPeP
Butylbenzyl phthalate	BBzP	Mono-benzyl phthalate	mBzP
Di-(2-ethylhexyl) phthalate	DEHP	Mono-(2-ethylhexyl) phthalate	mEHP
		Mono-(2-ethyl-5-hydroxy-hexyl) phthalate	mEHHP (5OH-mEHP)
		Mono-(2-ethyl-5-oxo-hexyl) phthalate	mEOHP (5oxo-mEHP)
		Mono-(2-ethyl-5-carboxy-pentyl) phthalate	mECPP (5cx-mEPP)
		Mono-(2-carboxymethyl-hexyl) phthalate	mCMHP (2cx-mMHP)
Di-iso-nonyl phthalate	DiNP	Mono-isononyl phthalate	miNP
		Mono-(hydroxy-iso-nonyl) phthalate	mHiNP (OH-miNP)
		Mono-(oxo-iso-nonyl) phthalate	mOiNP (oxo-miNP)
		Mono(carboxy-iso-octyl) phthalate	mCiNP (cx-miNP)
Di-iso-decyl phthalate	DiDP	Mono-carboxynonyl phthalate	mCNP
		Mono-(carboxyisononyl) phthalate	mCiNP
Di-n-octyl phthalate	DnOP	Mono-n-octyl phthalate	mnOP
		Mono-(3-carboxypropyl) phthalate	mCPP

et al., 2015; Kay et al., 2014; Yao et al., 2020). Several epidemiological studies have shown the association between the exposure to PAEs and adverse health effects including oxidative stress, diabetes, asthma, allergic rhinoconjunctivitis, and atopic dermatitis (Callesen et al., 2014; Campbell et al., 2018; Choi et al., 2019; Piecha et al., 2016; Smerieri et al., 2015). Recently, some emerging evidence of adverse health effects of PAE exposure on the thyroid system has been found (Kuo et al., 2015; Park et al., 2017; Romano et al., 2018; Wang et al., 2018a,b,c). Moreover, PAEs portend reproductive and developmental toxicity toward humans. For example, PAE exposure was implicated in the change of semen quality parameters (e.g., semen volume, motion parameters), decreased levels of testosterone and sex hormone, and disrupted folliculogenesis (Du et al., 2018; Johns et al., 2015; Meeker and Ferguson, 2014; Wang et al., 2016). Furthermore, some researches have also shown that PAE exposure could cause recurrent episodes of abortion and increased risk of clinical pregnancy loss (Mu et al., 2015; Peng et al., 2016).

Due to the potential harm of PAEs to humans, the use of PAEs (such as di-(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DnBP), butyl benzyl phthalate (BBzP), di-iso-nonyl phthalate (DiNP), di-iso-decyl phthalate (DiDP), and di-n-octyl phthalate (DnOP)) has been banned in certain products in Europe (Schwedler et al., 2020; Sicińska, 2019). In the United States, Canada, and China, PAE use is restricted or regulated (An et al., 2020; Schwedler et al., 2020; Wang et al., 2018a,b,c). Despite the regulations, the global annual consumption of PAEs is larger than 6 million tons (Net et al., 2015). Their ease of environmental release via evaporation, leaching, and abrasion is attributed to their non-chemical affinity with various products (Katsikantami et al., 2016; Wormuth et al., 2006).

Humans are usually exposed to PAEs through inhalation, ingestion, and dermal absorption (Gong et al., 2015; Koch et al., 2005b). When in the human body, PAEs are rapidly hydrolyzed by lipases and esterases to their respective monoester metabolites. The long-branched monoesters can be converted to secondary metabolites (via hydroxylation and oxidation), thereby improving their hydrophilicity. Generally, the phthalate metabolites (mPAEs) are excreted or urinated as glucuronide conjugates (Frederiksen et al., 2007; Koch et al., 2003, 2005a; Silva et al., 2003). Being non-persistent chemicals, the half-lives of PAEs vary from tissues to tissues. When in the human body, PAEs are rapidly metabolized and eliminated in <48 h (Lorber et al., 2010; Zota et al., 2016).

To assess human exposure to PAEs, it is necessary to determine the dose absorbed by humans. Usually, exposure via external and internal routes are assessed. However, it is difficult to adopt PAE environmental levels (e.g., food, air, and water) to estimate the comprehensive human dosage because of their wide use. Thus, assessing internal exposure via mPAE concentrations in human body fluids and tissues is a viable method.

Previous studies have reported PAE monoesters and/or secondary metabolites as markers in monitoring human urine (Feng et al., 2015; Guo et al., 2011b; Kato et al., 2005), serum (Frederiksen et al., 2010; Miao et al., 2019), milk (An et al., 2020; Calafat et al., 2004; Kim et al., 2015), semen (Wang et al., 2016), nail (Alves et al., 2016c; Bui et al., 2017), and hair (Chang et al., 2013; Hsu et al., 2015; Katsikantami et al., 2020). Amongst these options, urine is most commonly used.

Because of their rapid metabolization and elimination, the urinary mPAEs are excellent indicators for acute (short-term) PAE exposures. Compared to urine and serum, hair and nail samples can reflect longer-term (chronic) exposure, spanning from months to years. Moreover, they are easier to obtain and pretreat (Alves et al., 2016a, 2016b; Giovanoulis et al., 2016). However, mPAE concentrations in human hair and nails are negligible.

Because PAEs are ubiquitous and it has found that the PAE exposure of human is associated with adverse health effects, public concerns and scientific interest are increasing. Most of the published studies reported the mPAE concentrations in human biomatrices, while some are appraisals of collected and analyzed the data of mPAEs in human biomatrices (Ramesh Kumar and Sivaperumal, 2016; Wang et al., 2019). In the current review, we appraised the available data of mPAEs in human biological samples from various countries to assess human exposure to PAEs and the cumulative health risk associated with it. Furthermore, the distribution and changes of the concentration of mPAEs among countries and the potential sources were reviewed, and challenges encountered and future research directions are discussed. In the present review, one hundred and sixty (160) English publications related studies on mPAEs in human biomatrices from Web of Science, Science Direct, PubMed, and American Chemical Society (up to September 30, 2020) were obtained.

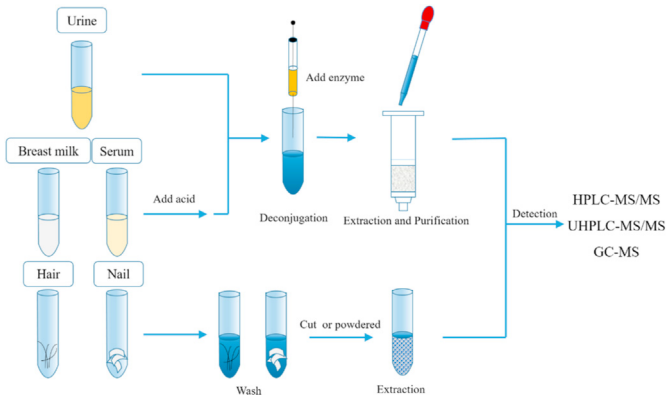

Fig. 1. The general sample pretreatment of human biomatrices.

2. Sample analysis

Several methods have been developed to determine mPAE concentration in biological specimens and environmental media. In general, mPAE determination in human samples can be achieved in three steps (**Fig. 1**): pretreatment of specimens, enrichment and purification, and the separation and detection of analytes.

2.1. Sample treatment protocols

Different matrices have their corresponding preparation protocols to hydrolyze the conjugated biomarkers of target PAEs or for specimen clean up to remove interferences (**Table S1**). In human urine, blood, and milk, mPAEs generally exist as glucuronide conjugates. Therefore, to prepare the samples, β-glucuronidase is usually used to deconjugate the conjugated mPAE biomarker (Dewalque et al., 2014b). Apart from urine, serum and milk samples contain esterases that can hydrolyze parent diester PAEs into their monoester metabolites, thereby interfering with the determination's accuracy. Thus, for serum and milk samples, acid treatment is necessary to neutralize esterases (Hines et al., 2009; Kato et al., 2003). However, hair and nails rarely require deconjugation before extraction. However, the copious washing is essential to eliminate external contamination, after which they are cut into smaller pieces to improve the extraction efficiency (Alves et al., 2016c; Chang et al., 2013; Hsu et al., 2015; Katsikantami et al., 2020).

Then extraction and clean-up procedures enrich and purify mPAEs at trace levels toward obtaining accurate results. Until now, various extraction and purification approaches have been applied, including solid-phase extraction (SPE), liquid-liquid extraction (LLE), QuEChERS (i.e., Quick, Easy, Cheap, Effective, Rugged, and Safe), and solid-liquid extraction (SLE).

Of the options, SPE is commonly used to enrich and purify mPAEs from liquid matrices, such as urine, serum, and milk. The adsorbent, flow rate, pH, and washing and eluting conditions are often optimized to minimize or remove matrix interferences. Several SPE cartridge types (including Oasis HLB, Oasis MAX, Bond Elute NEXUS, ODS-C18, automatic off-line, and online SPE) have been used (Chen et al., 2012; Frederiksen et al., 2010; Heffernan et al., 2016; Villanger et al., 2020). Comparing with traditional SPE, automated off-line and online SPEs have high throughput analysis and less prone to contamination in human biomonitoring. Also, online SPE requires less sample volume and reagents, thereby minimizing human exposure during handling (Frederiksen et al., 2010; Heffernan et al., 2016; Hines et al., 2009; Kato et al., 2005).

To our best knowledge, LLE and QuEChERS are also used to extract mPAEs in human matrices. In human milk (unlike urine that is predominantly made of water and inorganic salt), other substances such as carbohydrates, protein, lipids, vitamins, and immunoglobulins could also exist (Emmett and Rogers, 1997). However, these substances can block the SPE stationary phase. Although combining SPE with other techniques solves this problem, it becomes more expensive and laborious (An et al., 2020). Therefore, choosing the appropriate method is necessary.

By using QuEChERS, the target biomarkers would be separated from other interfering substances while it is extracted into the organic phase (An et al., 2020). Some studies had used QuEChERS to determine mPAEs in human milk (An et al., 2020; Kim et al., 2020). For LLE, it has been replaced by a faster and more sensitive (sample volume < 1 mL) alternative, although some recent studies still used LEE for cleaning and enriching biomarkers (Monfort et al., 2010, 2012; Park et al., 2017; Sun et al., 2013).

For solid matrices, such as hair and nails, SLE is the preferred method. For example, Katsikantami et al. (2020) analyzed seven mPAEs by incubating hair samples with methanol in an ultrasonic bath. They reported recoveries of 93.0%–102.8% and a relative standard deviation (RSD, %) <15%. Before that, Alves et al. (2016c) achieved excellent recoveries (79%–108%) using trifluoroacetic acid-MeOH solution to extract mPAEs from powdered nails in an ultrasonic bath.

2.2. Instrumental analysis

An overview of the instrument measurement of mPAEs is provided in Table S2. High-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS), and gas chromatography-mass spectrometry (GC-MS) are generally used. In addition, gas chromatography-flame ionization detection (GC-FID), high-performance liquid chromatography-photo-diode array (HPLC-PDA), and gas chromatography-high resolution mass spectrometry (GC-HRMS) have also been employed to detect certain mPAE coumpounds (Gries et al., 2012; Sargazi et al., 2017; Wu et al., 2016). Because of their polarity and low volatility, HPLC-MS/MS is commonly employed, having high selectivity and sensitivity (in the low μg/L ranges), with the limits of detection (LOD) between 0.013 and 5.7 μg/L. Moreover, HPLC-MS/MS is faster and easier (especially in sample preparation) than GC-MS, which requires derivatization of mPAEs before analysis (Kondo et al., 2010).

Regarding detectors, electrospray ionization (ESI) in the negative mode, coupled with HPLC-MS/MS has been generally applied to analyze mPAEs mainly separated by C18, phenyl or phenyl-hexyl conventional chromatographic columns (Dewalque et al., 2014b; Peng et al., 2016; Yao et al., 2018). However, atmospheric pressure chemical ionization (APCI) in negative mode coupled with the MS has also been used (Blount et al., 2000a; Katsikantami et al., 2020b; Silva et al., 2003). Although some analytes, such as mono-ethyl phthalate (mEP), mono-methyl phthalate (mMP), and mono-isobutyl phthalate (miBP), with strong matrix suppression with ESI, evince high sensitivity with APCI, routine maintenance of APCI is more frequent and the solvent consumption is higher than ESI. Therefore, ESI is a better choice for detecting most mPAEs (Heffernan et al., 2016; Myridakis et al., 2015).

Acetonitrile and methanol are the popular organic mobile phases used in HPLC (Chen et al., 2019; Tang et al., 2020). According to previous studies, acetonitrile is generally selected because it has lower back pressure and provides better separation performance and better peak shapes than methanol (Feng et al., 2015). Yet, formic acid and acetic acid are mainly added into mobile phases (Heffernan et al., 2016; Koch et al., 2017) to improve retention of

mPAEs on reversed-phase column using neutral mobile phases because at neutral pH, the carboxylic functions are charged negatively (Dewalque et al., 2014b). Therefore, acid compounds (such as PAE monoesters) require some acid to suppress ionic charge, thereby improving resolution and better peak shape (Chen et al., 2012; Dewalque et al., 2014b; Silva et al., 2007). Moreover, in some studies, ammonium acetate was added to the mobile phase to retain and improve the separation of mPAEs in urine samples (Blount et al., 2000a; Holm et al., 2004).

3. Internal exposure of mPAEs

Urine, serum, and breast milk are common biological matrices chosen to assess human exposure to PAEs. Generally, urine is used because of its ethical noninvasiveness, higher detection, and easier collection. However, few studies on the assessment of mPAEs in human serum and breast milk have been carried out. Similarly, few studies on human hair and nails could be found in the open literature. However, to study the distribution and extraction of PAEs after entering into the human body, different biological matrices should be chosen to understand the internal exposure of PAEs better.

3.1. Urinary mPAEs

Unlike serum and milk, urine does not have active esterases that can hydrolyze environmental, parent PAEs to PAE monoesters. Therefore, the measurement of mPAEs in urine is more accurate and precise. Usually, PAE monoesters are determined to assess the exposure of humans to PAEs, such as mMP, mEP, mono-benzyl phthalate (mBzP), and mono-n-butyl phthalate (mBP) which are the monoester metabolites of di-methyl phthalate (DMP), di-ethyl phthalate (DEP), BBzP, and DnBP, respectively. It has been reported that certain secondary and oxidative metabolites of PAEs are more suitable for assessing human exposure. For example, the oxidative metabolites of DEHP, including mono-(2-ethyl-5-hydroxy-hexyl) phthalate (mEHHP), mono-(2-ethyl-5-oxo-hexyl) phthalate (mEOHP), mono-(2-ethyl-5-carboxy-pentyl) phthalate (mECPP), and mono-(2-carboxymethyl-hexyl) phthalate (mCMHP) are the more appropriate biomarkers than the monoester metabolite, mono-(2-ethylhexyl) phthalate (mEHP) (Koch et al., 2005a, 2005b; Preuss et al., 2005). The global distribution of major mPAEs in the urines of adults and children are presented in Fig. 2. The concentration distribution was from studies where the urinary concentrations of mPAEs, mMP, mEP, mBP, miBP, and DEHP metabolites were reported. However, some studies that did not report mMP concentrations are also included. Many studies have reported the urinary mPAE concentrations from Asian, European, and North American countries, with large variations amongst the countries (**Table. S3**).

In Asian countries, the metabolites of DEHP, DEP, DnBP, and di-iso-butyl phthalate (DiBP) were mostly found in urine. Among these countries, Σ_{14}mPAEs and mEP concentrations in urine collected from 22 females and 24 males from Kuwait were highest. The median concentrations of mEP, mBP, miBP, mECPP, mCMHP, and mEHHP were 391, 94.1, 49.4, 67.7, 71.6, and 28 μg/L, respectively, having a median Σ_{14}mPAEs of 1050 μg/L (Guo et al., 2011a). In addition, the median concentrations of mEP in urine from Australia and India were 130 and 131 μg/L, respectively. Although these values are one to two orders of magnitude higher than the other Asian countries, they are similar to those from the United States (Guo et al., 2011a; Tang et al., 2020). In China, mBP and miBP are the major metabolites, higher than other Asian countries except for Kuwait. For instance, the median concentrations of mBP and miBP in urine collected from Chinese children (<18 years old), younger adults (18–50 years old), and older adults (>50 years old) were 225 and 48.1 μg/L, 152 and 32.1 μg/L, and 146 and 31.5 μg/L, respectively (Zhang et al., 2020).

The data collection and analysis require diligence because the age of subjects, sampling time, and analysis methods were different among these studies. For example, the relatively high urinary concentrations (24.7 μg/L) of mMP from 166 school children aged 8–11 years were found to be an order of magnitude higher than other Asian countries (Yu et al., 2021). Children's exposure seems higher than for adults. It can attribute such findings to children's sucking or chewing of PAE-bearing products.

Comparable concentrations of the hydroxylation and oxidation products of DEHP, mEHHP, and mEOHP have been reported in China, Australia, Vietnam, India, Korea, Japan, and Malaysia. However, their median concentrations of mECPP and mCMHP, the secondary metabolites of DEHP, ranged from 6.9 (Malaysia) to 70.9 (China) μg/L and from 3.98 (Korea) to 71.6 (Kuwait) μg/L, respectively. The difference in concentration range may be geographical. The secondary metabolites were the major metabolites of DEHP in the urine samples. Thus, the DEHP secondary metabolites are likely more appropriate biomarkers for DEHP exposure measurement (Koch et al., 2005a; 2005b). As for mBzP, the median concentration is low in these Asian countries, with the highest concentration of 3.2 μg/L observed in Korea (Guo et al., 2011a).

In North America, mEP, mBP, and DEHP metabolites were the dominant chemicals. Contrary to the findings in Asian countries, mEP is 45% of the total mPAEs, with a median range of 24.0–211.4 μg/L. The mEP concentrations were three to ten-fold higher than mBP. The levels of mnBP were less than those in Asian countries, probably because it was restricted or banned in cosmetics and toys by Consumer Product Safety Commission (CPSC) of the United States (CPSC, 2008). However, the urinary concentrations of DEHP metabolites were similar to those observed in Asia, suggesting similar exposure patterns.

Urinary concentrations of mPAEs also have been reported in European countries. DEHP metabolites and mEP, mBP, and miBP were the principal mPAEs found in Europe. In the urine specimens collected from 2256 children and adolescents aged 3–17 years from Germany during 2015–2017, the median concentrations of mEP, mBP, miBP, and DEHP metabolites were 23.1, 21.0, 26.2, and 32.4 μg/L (Schwedler et al., 2020). The depreciation with time is a positive sign. For instance, these values were lower than those from 599 children (age: 3–14 years) in Germany during 2003–2006 (Becker et al., 2009). This concentration reduction might be due to the restriction of DEHP, DBP, and BBzP in toys in Europe since 2009. This downtrend of mEP, mBP, miBP, and DEHP metabolites in Germany was also mentioned in other studies (Koch et al., 2017; Schwedler et al., 2020). Further, mEP was found to have higher median urinary concentrations of 100.3, 105, and 68.6 μg/L in Greece, Norway, and Spain, respectively, comparing with other European countries (Herrero et al., 2015; Myridakis et al., 2015; Villanger et al., 2020). And in several studies from Denmark and Spain, the mEP median concentrations were >47.1 μg/L (Frederiksen et al., 2010, 2013; Warembourg et al., 2019). However, these values were still lower than those reported in the United States. For mnBP and miBP, the ranges of concentrations were 12.2–93.4 and 15.9–88.1 μg/L, respectively. Nevertheless, the urinary concentrations of children were generally higher than adults. As for urinary mBzP, the concentrations found in Europe were consistent with those from the United States, but dissimilar to those from Asia. Moreover, the concentrations of DEHP metabolites were slightly higher in Europe than those countries from Asia and North America.

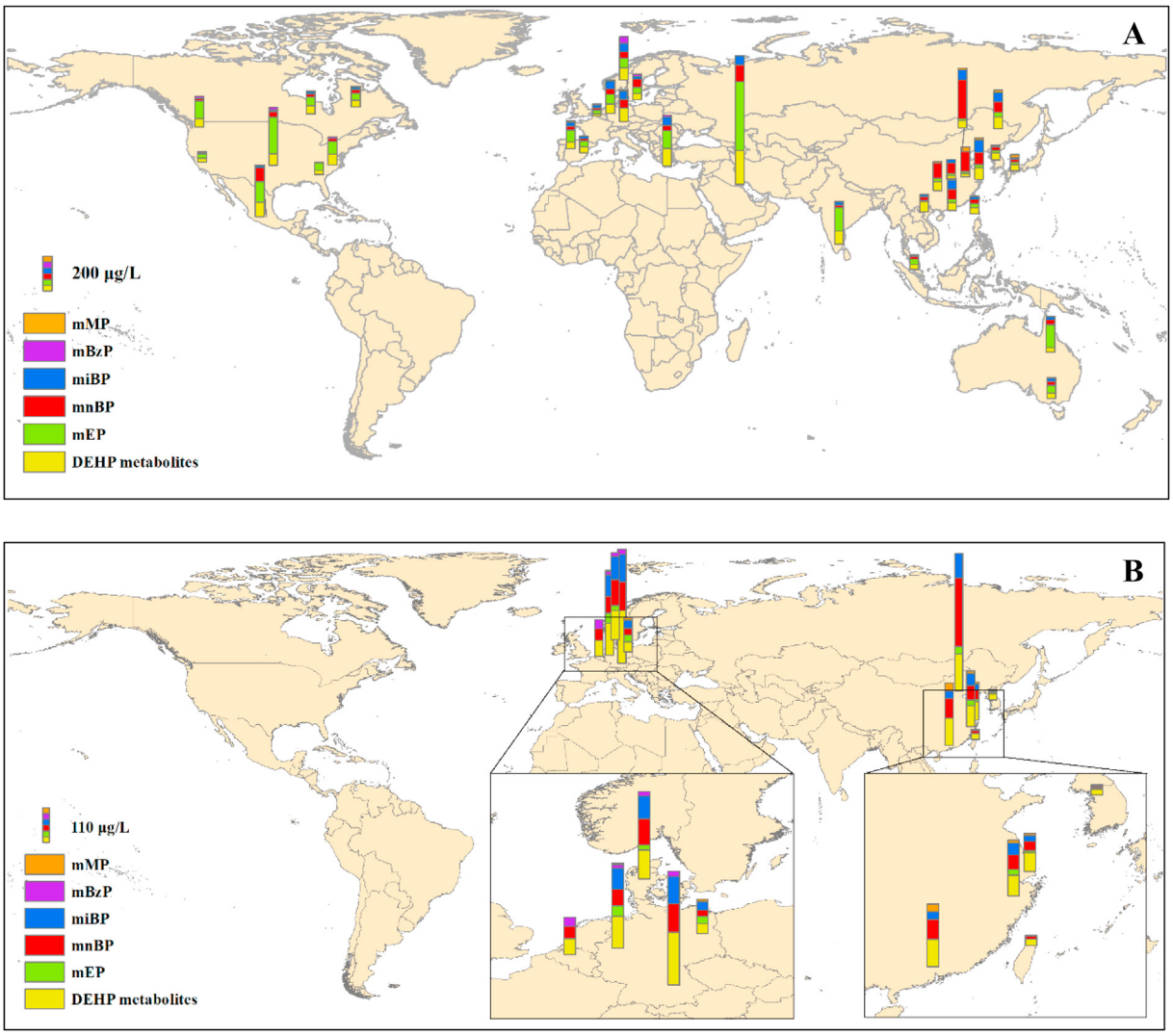

Fig. 2. The urinary concentrations and global distribution of major mPAEs from adults (A) and children (B) in several countries (DEHP: the sum of DEHP metabolites; median concentrations are presented).

3.2. Levels of mPAEs in blood

In the human body, lipases and esterases metabolize PAEs easily to their monoesters. Therefore, monoester metabolites, such as mEP, mBP, miBP, and mEHP, are often detected in the blood. And the mPAEs (Table 2) exist in serum mainly as glucuronide conjugates (Silva et al., 2003). Generally, the mPAE concentrations in the blood ranged from <1 to 12 μg/L. For example, the geometric mean concentrations of mBP, miBP, and mEHP were 5.16, 0.77, and 5.43 μg/L in serum collected from general populations (n = 589) in Korea during 2015–2016 (Choi et al., 2019). In Sweden, miBP and mEP were the most abundant mPAEs, and their median concentrations were 13.5 and 11.6 μg/L, respectively. These values are vastly different from the values obtained from Korea and Denmark, where they were present at lower levels (Lind et al., 2012). However, the above-mentioned serum samples were collected from 70-year-old residents of Sweden. Through the urinary mPAE concentrations, it was reported that the exposure of older adults to DEHP was more profound than with young adults (Zhang et al., 2020). Also, the DEHP metabolites detected in blood samples were predominantly mEHP, ascribed to its low water solubility (Koch et al., 2004). The study from Denmark found that the median concentration of mEHP was 7.88 μg/L in the serum of males (n = 60), whereas other mPAEs were undetected or below the detection limit (Frederiksen et al., 2010). Therefore, there are regional variations of mPAEs, and mEHP is the major DEHP metabolites in human blood.

3.3. mPAEs in human breast milk

Human breast milk is a significant nutritional source for infants. Therefore, the mPAE levels in human milk can reflect the maternal burden of the toxicants and reflects infants' exposure to PAEs. According to the analysis of the breast milk collected from Korea and Sweden, mEHP and mBP were the major mPAEs present.

Generally, the relative mPAE concentrations in breast milk are much lower than those in blood. For example, the geometric mean concentrations of mEHP, mBP, miBP, mEP, and mBzP in breast milk samples collected from lactating women (19 – 42 years old; n = 221) from Korea in 2018 were only 1.44, 0.83, 0.47, 0.17, and 0.06 μg/L, respectively (Kim et al., 2020). In Sweden, the mBzP levels were higher, whereas mBP and mEHP were lower than those found in Korea (Högberg et al., 2008). Nevertheless, the median concentrations of mPAEs from these studies were <2.5 μg/L, generally below the LOD. In addition, PAE-related compounds in

Table 2
Concentrations of major mPAEs in other human matrices except for urine.

Matrix	Country	Studied population	Sampling time	Concentration											Reference
				mMP	mEP	mnBP	miBP	mBzP	mEHP	mEHHP	mEOHP	mECPP	mCMHP	miNP	Unit	
Hair	Greece	Pregnant women (100) (22–44 years old)	–		17.3	19.5	44.4	31.7	20.1	25.9					pg/mg; median	Katsikantami et al. (2020b)
Hair	Taiwan, China	Individuals (10)	–						44.9	5.66	9.17	ND	ND		pg/mg; mean	Chang et al. (2013)
Nail	Belgium	General population (10)	2014		64	74[a]		<LOQ	138	<LOQ	<LOQ				pg/mg; median	Alves et al. (2016c)
Milk	Korea	Lactating women (26)	–			2.3		0.7		ND	ND	ND			μg/L; median	An et al. (2020)
Milk	Korea	Lactating women (62)	2012		0.37	1.7	1.1		2.08						μg/L; median	Kim et al. (2015)
Milk	Korea	Lactating women (221) (19–42 years old)	2018		0.17	0.83	0.47	0.06	1.44					0.10	μg/L; GM	Kim et al. (2020)
Milk	Sweden	Lactating women (42)	2001			0.54		0.50	0.49						μg/L; median	Högberg et al. (2008)
Semen	China	Men (687)	2013		<LOD	0.5	0.85		<LOD	0.79	0.17	0.022			μg/L; median	Wang et al. (2016)
Serum	Sweden	Lactating women (36)	2001			0.5	0.54	0.5		0.49					μg/L; median	Högberg et al. (2008)
Serum	Denmark	Men (60)	2006			<LOD		<LOD		7.88		0.52			μg/L; median	Frederiksen et al. (2010)
Serum	Sweden	Women (70 years old) (502)	2001–2003	1.5		11.6		13.4		4.7					μg/L; median	Lind et al. (2012)
Serum	Sweden	Men (70 years old) (501)	2001–2003	1.5		11.6		13.5		4.3					μg/L; median	Lind et al. (2012)
Serum	Korea	General population (589)	2015–2016				5.16	0.77		5.43					μg/L; GM	Choi et al. (2019)
Serum	Japan	Pregnant women (245)	–			26.7	7.4	<LOD	1.42	<LOD		0.20			μg/L; median	Minatoya et al. (2018)

[a] The sum of mnBP and miBP; mMP: mono-methyl phthalate; mEP: mono-ethyl phthalate; mnBP: mono-n-butyl phthalate; miBP: mono-isobutyl phthalate; mBzP: mono-benzyl phthalate; mEHP: mono-(2-ethylhexyl) phthalate; mEHHP: mono-(2-ethyl-5-hydroxy-hexyl) phthalate; mEOHP: mono-(2-ethyl-5-oxo-hexyl) phthalate; mECPP: mono-(2-ethyl-5-carboxy-pentyl) phthalate; mCMHP: mono-(2-carboxymethyl-hexyl) phthalate; miNP: mono-isononyl phthalate; ND: Not detected; LOD: Limit of detection; LOQ: Limit of quantification; GM: Geometric mean.

breast milk exist as diester and monoester forms, with the former occurring in higher concentrations (Hines et al., 2009; Högberg et al., 2008; Kim et al., 2015, 2020). Hence, the diester forms of PAEs in breast milk should also be diligently monitored.

3.4. Other matrices

Unlike urine and blood, hair and nails can reflect chronic exposure to PAEs. A study from Taiwan measured the concentrations of DEHP metabolites in the hair of 10 individuals. It reported that the mean concentrations of mEHP, mEHHP, and mEOHP were 44.9, 5.66, and 9.17 pg/mg, respectively, whereas mECPP and mCMHP were undetected (Chang et al., 2013). A similar result was also observed from 100 hair samples from pregnant women (22–44 years old) in Greece, where mEHP was also the predominant metabolite, having a 68% detection frequency. The median concentrations of mEP, mBP, miBP, mBzP, mEHP, and mEHHP were 17.3, 19.5, 44.4, 31.7, 20.1, and 25.9 pg/mg, respectively (Katsikantami et al., 2020).

To the best of our knowledge, only one published study researched the mPAEs in human nails (Alves et al., 2016c). In the nails from 10 individuals from Belgium, mEHP, mEP, and (the sum of) mBP and miBP were the main mPAEs, with median concentrations of 138, 64, and 74 pg/mg, respectively. In addition, mBzP was detected in 40% of nails, although the median concentration was lower than its LOQ (4 pg/mg).

Although urine was the general biomatrix to estimate the human exposure to PAEs, human hair and nails can be viable substitute biomatrices owing to the plausible dilution effect (Alves et al., 2016c; Servaes et al., 2013). However, efficient analytical methods for mPAEs in human hair and nails should be developed and optimized to quantify mPAEs with low LOQs and greater precision and accuracy.

3.5. Factors affecting human exposure

Many factors influence human exposure to phthalates, such as age, gender, and geography. As for gender, due to the larger consumption of personal care products and cosmetics compared with males, females are likely more exposure to PAEs. Commonly found PAEs in such products include DEHP, DEP, DiBP, and DBP, and their metabolite concentrations are higher in female urine (Blount et al., 2000b; Herrero et al., 2015). For example, a significant difference in mMP concentrations between male and female urine samples was also observed in India (Guo et al., 2011a); however, some studies reported no differences (Gao et al., 2016; Koch et al., 2017; Zhang et al., 2020). We attribute such inconsistency to the differences in country and lifestyle, such as the different restrictions on the use of PAEs in consumer products in various countries. In addition, the differences in analytical methods, such as background levels, matrix effect and the separation of alkyl chain isomers and homologues, also contributed (Dirtu et al., 2012).

The PAE exposure levels may vary between urban and rural regions, as reported by a few studies. Among the urine collected from 108 Chinese young adults, there were no significant differences between the urinary concentrations of mPAEs from urban and rural areas (Gao et al., 2016). However, the geometric mean concentrations of mPAEs in rural male dwellers' urine were higher than those in the urban area. In contrast, females in the urban regions exhibited higher mPAE concentrations, except for mMP. However, in Australia, the PAE exposure in urban places was higher than in rural ones, with significant differences of mEP, mEOHP, and mEHHP between urban and rural (Hartmann et al., 2015). A similar result was recorded from the urine samples of Korean childbearing-

aged women (Mok et al., 2021). These phenomena may be caused by the diverse sources of PAEs and the usage of PAE-containing products. These contrasting reports indicate that the sources of human exposure to PAEs are complex.

Except for DEP, the exposure levels of most PAEs, such as DEHP, DBP, DiBP, and DMP, decrease as age increases (Becker et al., 2009; Kasper-Sonnenberg et al., 2012; Lin et al., 2016; Schwedler et al., 2020), i.e., children seem more exposed to PAEs than adults. For example, children often make contact with toys or other phthalate-containing products containing phthalates, and via hand-to-mouth behaviors. Therefore, the feasibility of PAE oral intake is high. Besides, children have relatively high dietary intake because they are in the growth and development stage (Tang et al., 2020; Zhang et al., 2020). Because DEP is generally used in adult care products, its metabolite, mEP, is often found in higher concentrations in adults than in children (contrary to other PAE metabolites).

Overall, the difference in individual exposure levels of PAEs is affected by many factors, including gender, age, and residential areas. Moreover, job type and the environment are also relevant, especially waste incineration plants, plastic industries, and industrial regions (Lu et al., 2020; Wang et al., 2015). It is necessary to study further the effects of these factors on the human exposure level of PAEs.

4. Composition profiles and possible sources

4.1. Composition profiles of mPAEs

Compounds of mEP, mBP, miBP, and the DEHP metabolites are the major mPAEs. Compared to urine, the mPAE concentrations in other matrices are limited, apart from hair. Therefore, the following discussion on the composition profiles of mPAEs is focused on urine sources.

The composition profiles of urinary mPAEs show geographical differences (**Fig. 3**), and they also vary among the matrices. Among Asian countries, mEP and DEHP metabolites respectively accounted for 53.8% and 30.6% (from India) and 53.6% and 26.3% (from Kuwait) of the total urinary mPAE concentrations. Whereas, mBP and miBP are the predominant metabolites in China. The percentage of DEHP metabolites in urine from Korea and Vietnam were approximately half of the sum concentrations of mPAEs. However, mMP accounted for 19% of the total mPAEs in Japan. In contrast, other Asian countries exhibited mMP <5% of the total mPAE concentrations, although several studies from China showed that mMP accounted for more than 13% of the totals. However, the highest contribution does not necessarily portend the risk level for human exposure.

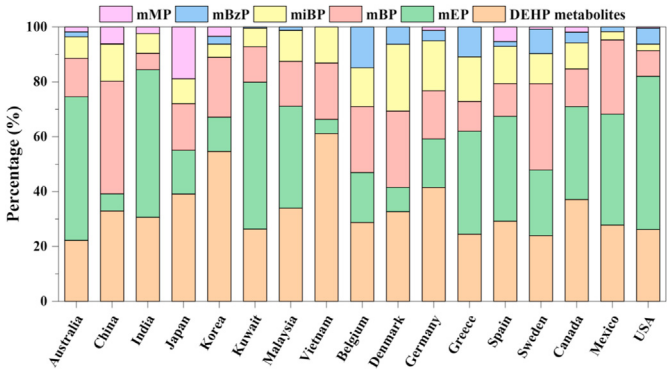

Fig. 3. Composition profiles of major mPAEs (calculate with the means of the median values of each PAE metabolite from the same countries) in urine samples from different countries.

Like some Asian countries, such as India and Kuwait, mEP was the dominant compound in North America. The contributions of mEP to total mPAEs ranged from 45% to 69% in Canada and the United States, respectively. These countries were opined to have similar exposure sources or patterns. For European countries, mEP, mBP, and miBP were the main mPAEs that accounted for >85% of the total urinary concentrations of mPAEs. There, mBP and miBP had similar proportions (10%–41%). Similarly, mEP was the dominant compound in the urine samples from Spain (38%–43%), Sweden (24%), and Greece (35%). In Germany, Denmark, and Belgium, DEHP metabolites accounted for 33%–46% of the total urinary concentrations of mPAEs. The composition profiles of mPAEs in urine differ between countries and between mPAE types. These differences might be related to residents' lifestyle, the usage of consumer products, consumption of PAE-bearing foods, and the environmental conditions.

4.2. Possible sources of mPAEs

Due to the extensive use of PAEs in various products, they are found universally in the environment. Although humans are exposed to PAEs mainly through three pathways already mentioned, we cannot rule out that mPAEs in the human body might be from environmental matrices or foods (Bradley et al., 2013; Jiang et al., 2018).

Based on the side chain length, PAEs can be divided into high molecular weight and low molecular weight PAEs. The high molecular weight PAEs (such as DEHP, BBzP, DiNP, DnOP, and DiDP) are found mainly in polyvinyl chloride (PVC) polymers and plastic products. Diet intake is the major source of high molecular weight PAEs, especially DEHP (Cao, 2010; Li et al., 2019; Tran and Kannan, 2015). The high molecular weight PAEs can migrate from plasticized PVC products (such as plastic containers, tubing, gloves, and conveyor belts) into food during production, shipment, and storage (Dong et al., 2017). Food with high lipid may be more easily contaminated by high molecular weight PAEs (Cao, 2010). Due to the toxic and endocrine-disrupting effects of DEHP, DiNP and di-(2-propylheptyl) phthalate (DPHP) have been used to replace DEHP as a plasticizer in PVC in Europe. Therefore, the exposure of PAE substitutes should be considered in the future because the toxicology data on these substitutes are still limited (Frederiksen et al., 2007; Schütze et al., 2015). In addition, the use of medical devices containing DEHP (such as ventilator tubing, bags for intravenous solutions, and syringes) and pharmaceutical coats that contain DBP are also significant sources of PAEs, especially to patients (Blount et al., 2000a; Heudorf et al., 2007; Schettler et al., 2006).

Low molecular weight PAEs (such as DnBP, DiBP, DEP, and DMP) are generally used in paints, adhesives, and personal care products. Dermal absorption and inhalation are the principal pathways of human exposure to these PAE analogues. Besides, dust ingestion is an as important source, especially for children (Guo and Kannan, 2011). DEP and DMP are usually used in cosmetic and personal care products, the major source of mEP and mMP (Guo et al., 2014; Wormuth et al., 2006). A study reported that the urinary concentration of mEP from women was higher than men probably because of the higher amounts of personal care products and cosmetics used by women (Herrero et al., 2015). Wang et al. (2018a,b,c) found a positive association between the use of facial cleanser/cream and urinary mEP. Furthermore, mEP concentrations in urine collected from children in summer were significantly higher than that during winter, mainly due to increased personal care products in summer (Gong et al., 2015). In addition, high molecular weight PAEs, as well as DBP and DiBP are frequently used in plastic production (such as vinyl flooring or other building products). Because of the ban or restriction of DnBP in Europe and the United States, DiBP has been

used increasingly (Chen et al., 2019; Katsikantami et al., 2020). Further investigation into the correlation between indoor wallpaper usage and urinary concentrations of mBP has been reported (Geens et al., 2014).

5. Human exposure and health risk assessment

To evaluate the human exposure and the associated health risk from pollutants, the estimated daily intake (EDI) (otherwise called estimated daily uptake (EDU) and the total estimated dose (TEDI)) are generally used. The hazard quotient (HQ) for an individual compound and hazard index (HI) for cumulative health risks of multiple toxicants are other factors used for health risk assessment, reflecting the health risk level based on non-carcinogenicity.

5.1. Human exposure assessment

The EDI of a PAE compound can be calculated by Equation (1):

$$EDI(\mu g / kg - bw / day) = \frac{UC_m \times UV \times MW_p}{f \times BW \times MW_m} \quad \text{Eq. 1}$$

where UC_m (μg/L) = concentration of a mPAE in urine, MW_p and MW_m = the molecular weights (g/mol) of parent PAE and the mPAE, respectively, UV (L/day) = human excretion urine volume/day, BW (kg) = body weight, and f (dimensionless) = molar fraction of the urinary mPAE excreted in relation to the oral intake of its parent PAE.

There are 14 reports that reported EDI of PAEs (**Table 3**). The median EDIs of DMP, DEP, and BBzP were well below the TDI or RfD-AA, especially for BBzP. Compared with the three PAEs, humans exposed to DnBP, DiBP, and DEHP are at a greater risk. From the urine samples collected from 166 Chinese school children, the median EDI values of mEHP, mEHHP, and mEOHP were 5.6, 11.1, and 12.4 μg/kg-bw/day (Yu et al., 2021). Further, urine samples were collected from 70 people in China in 2017–2018. Here, the median EDIs of DnBP, DiBP, and DEHP (the sum of mEHP, mEHHP, and mEOHP) were 8.5, 1.9, and 3.3 μg/kg-bw/day, respectively, suggesting that DnBP, DiBP, and DEHP contributed majorly to PAE exposure risk (Zhang et al., 2020). A similar PAE exposure was also reported in other Asian countries (Chen et al., 2019; Guo et al., 2011b; Hyun Kim et al., 2018; Mok et al., 2021; Zare Jeddi et al., 2018). Overall, the median EDIs of DMP, DEP, BBzP, DnBP, DiBP, and DEHP from Asia were 0–0.77, 0.19–1.1, 0–0.06, 0.22–16.8, 1.23–3.52, and 0.03–29.1 μg/kg-bw/day, respectively.

Elsewhere, the median EDIs of DMP, DEP, BBzP, DnBP, and DEHP found in Chinese occupational exposure workers were 4.65, 4.11, 0, 25.3, and 45.7 μg/kg-bw/day, respectively (Lu et al., 2020). Regarding TDI, RfD, or RfD-AA, the median EDI was below the permissible limit. However, among the urine collected in China from 84 primiparas, 70 people from the general population, and 1490 primary school starters, the median EDIs of DnBP were 9.14, 8.5, and 7.19 μg/kg-bw/day, similar to the TDI of DnBP (10 μg/kg-bw/day). Whereas the median EDI of DnBP of municipal solid waste (MSW) incineration plant workers and nearby residents was higher than the TDI.

In Belgium, the respective median EDIs of children and adults exposed to DEP (1.47 and 1.44 μg/kg-bw/day) and BBzP (0.42 and 0.20 μg/kg-bw/day) were higher than those in Asia, but the median EDIs were lower than the reference values. For BBzP, DnBP, DiBP, and DEHP, the adult EDI values were significantly lower than those for children (Dewalque et al., 2014a). Moreover, the EDIs of BBzP, DiBP, and DEHP of children in Denmark and Czech were comparable with those in Belgium (Puklová et al., 2019; Søeborg et al., 2012). However, among the urine samples from 150 pregnant women in the United States, the EDIs of DEP and DEHP were higher than the above reports from Belgium, Denmark, and Czech, while those of DEP, BBzP, MEHP, MEHHP and MEOHP were 4.72, 0.23, 49.87, 10.57, and 14.26 μg/kg-bw/day, respectively (Yan et al., 2009). Overall, by comparing the EDIs of PAEs in different populations globally, we inferred that Asian countries were mainly exposed to DnBP, DiBP, and DEHP. In contrast, European countries had evidences of greater exposure to DEP and BBzP in relatively high concentrations but lower exposure levels of DnBP and DiBP.

5.2. Health risk assessment

To further assess the potential health risk of PAE exposure, HQ and HI, which consider non-carcinogenic endpoint, are calculated as given in Equations (2) and (3), respectively:

$$HQ = \frac{EDI}{Reference\ limit\ values} \quad \text{Eq. 2}$$

$$HI = \sum HQ_{PAEs} \quad \text{Eq. 3}$$

where HQ (dimensionless) is the ratio of EDI to reference limit value (such as RfD, RfD-AA, and TDI).

TDI is the tolerable daily intake determined through developmental and testicular toxicity in animal models by the European Food Safety Authorities (EFSA). The recommended TDIs for DnBP, BBzP, and DEHP are 10, 500, and 50 μg/kg-bw/day, respectively (EFSA, 2005a; 2005b; 2005c). The RfD-AA, proposed by Kortenkamp and Faust (2010), was an acceptable exposure level specifically based on anti-androgenic endpoints such as the testosterone production and nipples retention of rat fetuses. The recommended RfD-AA values for DnBP, DiBP, BBzP, and DEHP are 100, 200, 330, and 30 μg/kg-bw/day, respectively (Kortenkamp and Faust, 2010). RfD is the reference dose determined by the United States Environmental Protection Agency (USEPA) through the change in organ weight and mortality in animal studies, which has different adverse effects endpoints from the RfD-AA reported by Kortenkamp and Faust (2010). RfD is a daily acceptable exposure dose for human life without significant adverse effects on human health and the RfD values of DEP, DnBP, BBzP, and DEHP were suggested as 800, 100, 200, and 20 μg/kg-bw/day, respectively (USEPA, 1990; 1993a; 1993b; 1993c). When HQ > 1 or 1 < HI < 100, there are potential adverse health effects. At HI > 100, (100 being the limit of unobserved adverse effects), humans exposed to PAEs may exhibit adverse effects (Benson, 2009; Gao et al., 2016).

The potential risk of human exposure to PAEs showed that the EDI of 39% of adult urine samples (n = 183) exceeded the TDI of DnBP. However, all the EDI values were lower than RfD (Guo et al., 2011b). Also, there was a report that 15 of 108 Chinese young adults (13.8%) had values that exceeded the TDI of DnBP (Gao et al., 2016). Several other studies also reported that the potential exposure risk to DnBP was relatively high in China (Chen et al., 2019; Yao et al., 2019; Zhang et al., 2020). For example, 87.6% samples were observed for workers in a municipal solid waste plant (Lu et al., 2020). However, the DnBP exposure risk was lower when the HQ was based on RfD or RfD-AA, because the TDI of DnBP is an order of magnitude lower than those of RfD and RfD-AA. However, unlike DnBP, the RfD of DEHP was lower than those of TDI and RfD-AA.

The HQ or HI was different due to the reference dosages. A study showed that 39 out of 166 school children had the HQ of DEHP >1 based on RfD (Yu et al., 2021). Also, more than 51.7% of municipal solid waste plant workers showed high exposure compared to control subjects (9.3%), with the EDI of DEHP exceeding the RfD (Lu et al., 2020), although the potential risk of DEHP is low when TDI is

Table 3
The estimated daily intake (EDI) of PAEs (μg/kg-bw/day, median) in human urine from countries around the world and the reference values for health risk assessment.

Country	Studied populations	Sampling time	DMP	DEP	BBzP	DnBP	DiBP	DEHP				Reference
								mEHP	mEHHP	mEOHP	ΣDEHP	
China	Adults (183)	2010	0.6	1.1		8.5[a]		2.2	2.2	1.5	3.4[b]	Guo et al. (2011b)
China	School children (782)	2012	0.3	0.7	0.01	1.9	1.5				3.7[c]	Wang et al. (2015)
China	Primiparas (84)	2013–2015	0.26	0.29	0.01	9.14		2.47	1.14	1.39	4.26[d]	Chen et al. (2019)
China	18–22 years old adults (108)	2010	1.68[e]	2.14[e]		4.12[e]	3.52[e]	1.26[e]	2.87[e]	2.98[e]		Gao et al. (2016)
China	General populations (70)	2017–2018	0.4	0.5	0.004	8.5	1.9				3.3[d]	Zhang et al. (2020)
China	Primary school starters (6–8years old) (1490)	2016–2017	0.66	0.42	0.01	7.19	1.23				2.68[b]	Yao et al. (2019)
China	Newborns (1359)	2012	0.00	0.04	0.00	0.22					0.03[d]	Li et al. (2019)
China	School children (8–11 years) (166)	2015			0.03	4.43	1.93	5.6	11.1	12.4		Yu et al. (2021)
China	MSW incineration plant workers (104)	2016–2017	4.65	4.11	0	25.3		20.7	13.3	11.7		Lu et al. (2020)
China	Men (205)	2016–2017	0	0.46	0.04	16.8		9.03	5.04	3.90		Lu et al. (2020)
Korea	Children and adolescents (<age 19, 302)	–				0.87					9.17[f]	Hyun Kim et al., 2018
Korea	Childbearing-aged women (509)	2015–2016	0.04	0.19	0.01	0.11	0.05				1.44[b]	Mok et al. (2021)
Korea	Elderly people (1646)	2008–2014				1.5[e]					8.8[d,e]	Kim et al. (2018)
Iran	Children and adolescents (6–18 years old) (56)	2015	0.77	0.88	0.06	1.1					3.41[d]	Zare Jeddi et al. (2018)
Belgium	Children (52)	2013		1.47	0.42	2.38	2.29				3.37[e]	Dewalque et al. (2014a)
Belgium	Adult (209)	2013		1.44	0.20	1.29	0.88				1.43[e]	Dewalque et al. (2014a)
Denmark	Children and adolescents (129)	–			0.62	4.29[a]					4.04	Søeborg et al. (2012)
Denmark	Young men (33)	2008			0.7	0.9	1.66				2.9[c]	Kranich et al. (2014)
Czech Republic	Children (360)	2016–2017			0.1	2.0	1.3				2.0[d]	Puklová et al. (2019)
USA	Pregnant women (150)	–	0.02	4.72	0.23	0.49[a]		49.87	10.57	14.26		Yan et al. (2009)
Brazil	Children (6–14 years old) (300)	2012–2013	0.29	2.14		1.70	1.75				7.16[b]	Rocha et al. (2017)
	TDI		–	–	500	10	10				50	
	RfD-AA		–	–	330	100	200				30	
	RfD		–	800	200	100	100				20	

[a] The EDI of the sum of DnBP and DiBP.
[b] ΣDEHP is the sum of mEHP, mEHHP, mEOHP, mECPP, and mCMHP.
[c] ΣDEHP is the sum of mEHP, mEHHP, mEOHP, and mECPP.
[d] ΣDEHP is the sum of mEHP, mEHHP, and mEOHP.
[e] The geometric mean of the EDI.
[f] ΣDEHP is the sum of mEHP; TDI: tolerable daily intake; RfD: reference dose; RfD-AA: reference doses for anti-androgenicity; DMP: di-methyl phthalate; DEP: di-ethyl phthalate; BBzP: butylbenzyl phthalate; DnBP: di-n-butyl phthalate; DiBP: di-iso-butyl phthalate; mEHP: mono-(2-ethylhexyl) phthalate; mEHHP: mono-(2-ethyl-5-hydroxy-hexyl) phthalate; mEOHP: mono-(2-ethyl-5-oxo-hexyl) phthalate.

the reference limit value.

Considering HI calculated by the accumulative risks of PAEs, the potential health risks of people exposed to PAEs were assessed. In China, for instance, 19.8% and 48% of Chinese children had the $HI_{TDI} > 1$, respectively (Wang et al., 2015; Yao et al., 2019), while that of the adults ($HI_{TDI} > 1$) were 55% for 84 primiparas and 39.8% for 108 young adults (ages 18–22) (Chen et al., 2019; Gao et al., 2016). With other reference values (such as RfD or RfD-AA), only 9% primiparas had $HI_{RfD} > 1$, and 1.9% of young adults showed $HI_{RfD\text{-}AA} > 1$. However, as reported in previous study, 49 out of 166 children (29.5%) exhibited $HI_{RfD} > 1$ (Yu et al., 2021). Studies on children from Brazil, Belgium, Denmark, and Czech also reported that 32.7%, 25%, 14.7%, and 11% of children had a potential risk of exposure to PAEs with $HI_{TDI} > 1$ (Dewalque et al., 2014a; Puklová et al., 2019; Rocha et al., 2017; Søeborg et al., 2012), whereas only 13%, 0%, 0.8%, 0%, and 0% children showed $HI_{RfD\text{-}AA} > 1$, lower than the percentages based on TDI. As for adults from Belgium and Denmark, only about 6% exhibited $HI_{TDI} > 1$, with lower ratios based on RfD-AA (Dewalque et al., 2014a; Kranich et al., 2014). While estimating the health risk of human exposure to PAEs based on TDI, higher proportions of people may show potential adverse health effects.

To further understand the risks based on the different references, the HI values derived from adding the HQ values of DEHP and DnBP (based on TDI, RfD, and RfD-AA) was done (Fig. 4) because DnBP and DEHP were the main PAEs that humans were exposed to. It was observed that the HI values, based on TDI, were higher than those based on RfD or RfD-AA, probably because the TDI of DnBP was ten times that of RfD or RfD-AA. Above all, Chinese, especially children, had higher exposure of PAEs. Also, it was observed that the selection of reference doses influences the results.

5.3. Limitation and uncertainty of the assessment

However, the present estimations so far are subject to some limitations and uncertainties. According to age, gender, and country, the daily urinary volume and bodyweight vary significantly from person to person. For example, using bodyweight to calculate EDI involves using the center of tendency from the local (provincial) government. This approach might compromise the accuracy of the calculated exposed risk. Therefore, for accurate estimation of phthalate exposure risk, it is more appropriate to use individuals' body weights.

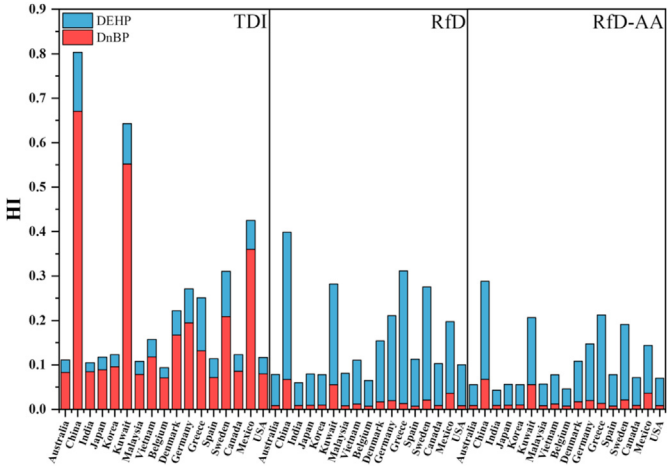

Fig. 4. Hazard indices (HI) for different countries based on different reference values of TDI, RfD, and RfD-AA (calculated from the average urinary concentrations of mPAEs in adults from different countries).

In many studies, single-spot urine or first-void morning urine was collected to measure the mPAE concentrations, reflecting the EDI of recent exposure instead of within 24 h-pool urine. However, the single-spot urine or first-void morning urine may be influenced by the urine dilution ratio and diurnal variation of metabolite. For feasibility check, some researches were taken and they found that mPAE concentrations in single-spot urine and first-void morning urine were significantly positive correlated with the concentrations in the 24 h-pool urine (Frederiksen et al., 2013; Hoppin et al., 2002). Besides, under the same exposure level, the volume of urine excreted will cause differences in urinary mPAE concentrations. Therefore, creatinine correction method was often used to adjust the urinary concentrations of mPAEs. However, creatinine is affected by many factors such as age, dietary habits, muscle mass, and race. Urinary concentrations of mPAEs in pregnant women and children in physical development may not be suitable for adjustment with creatinine because the creatinine concentrations in children varies widely and pregnant women have higher renal blood flow and glomerular filtration rate compared with healthy women without pregnancy (Huang et al., 2007; Langer et al., 2014). What's more, using creatinine-adjustment should be careful due to the rapid metabolism of PAEs in the human body (Christensen et al., 2012; Langer et al., 2014).

Moreover, TDI, RfD, and RfD-AA, as reference limit values, have also been used to calculate HQ. However, since the different reference limit values were often used, it is not conducive to compare the potential exposure risk from studies with different references. Therefore, we recommend using a unified reference value for each PAE for risk assessment, especially DEHP, DnBP, DiBP, and DEP, because of their higher potential risks to humans.

Furthermore, because children are more prone to PAE health risks, the TDI based on adult standards may not apply to children (Kim et al., 2020). So far, the *f* values for children have not been determined. The PAE metabolite concentrations in children's urine, especially the oxidative metabolites, were higher than those found in adults. For instance, the median concentrations of mEHHP and mEOHP (the oxidative metabolites of DEHP) in the urine of Australian children and adults were 31 and 1.6 μg/g creatinine and 3.3 and <LOQ (1.12 μg/L) μg/g creatinine, respectively (Hartmann et al., 2015). Other studies reported a similar trend in the relatively higher PAE exposure levels of children (Dong et al., 2018; Schwedler et al., 2020; Zhang et al., 2020). Therefore, the health risk of children may be underestimated. Also, the cumulative health risks of PAE replacements (such as DPHP and DiNP, and other endocrine-disrupting chemicals, like bisphenol A, triclosan, and paraben with toxic effects) should be further evaluated.

6. Summary and perspective

PAEs have been ubiquitously distributed in the environment due to their wide application in various products. Previous studies have demonstrated the association between exposure to PAEs and some diseases. Therefore, human biomonitoring is essential for assessing human exposure to PAEs. Human urine, serum, breast milk, hair, and nails have been used to estimate exposure levels and health burdens of PAEs. Some analytical methods for quantifying mPAEs in biological matrices also have been developed. Urine is the preferred matrix for exposure assessment because mPAEs are mainly found in urine. The metabolite compounds including mMP, mEP, mBP, miBP, and DEHP metabolites were the predominant mPAEs observed. The composition profiles of urinary mPAEs varied among countries owing to the difference in sources and patterns of PAEs. Different analytical methods, such as background levels, matrix effect and the separation of alkyl chain isomers and homologues, may also lead to differences in mPAE concentrations between or within

countries. Overall, human exposure to DEHP, DnBP, and DiBP portend higher risk levels.

We noted that the total metabolite concentrations and health risks of PAEs might be underestimated because, in some studies, secondary metabolites or other PAE replacements were not measured. Also, in addition, the health risks of other PAE analogues were not considered due to lack of toxicology data or molar fraction data (f), which may compromise the integrity of the estimations done on health risk. Furthermore, contaminations with endocrine-disrupting properties similar to PAEs should be considered in future studies. The EFSA has only set TDI for DEP, DnBP, DiBP, BBzP, and DEHP, with none for children, limiting PAE exposure risk assessment.

In conclusion, although the restrictions and regulations on PAEs have been formulated in various countries, long-term monitoring of human exposure is essential. In the future, the exposure assessment should be improved and prioritized. To achieve this objective, more experimental data is needed to verify the cumulative health risks of phthalates. South America and African countries lacking biological monitoring data on PAE exposure warrant further research.

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 data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2021.116941.

Author statement

Senyuan Huang, Draft preparation & editing. Zenghua Qi, Data collection & draft preparation. Shengtao Ma, Data collection. Guiying Li, Data collection. Chaoyang Long, Data collection. Yingxin Yu, Design, Writing, reviewing & editing.

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