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National-scale urinary phthalate metabolites in the general urban residents involving 26 provincial capital cities in China and the influencing factors as well as non-carcinogenic risks

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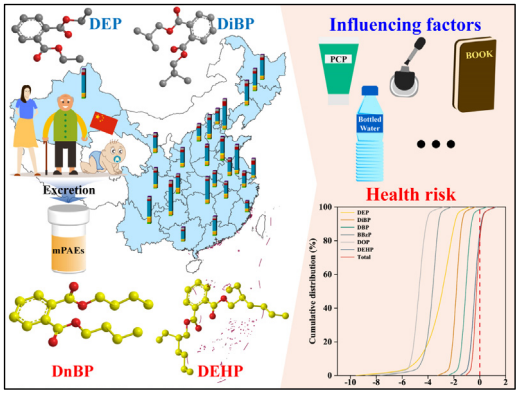
HIGHLIGHTS

- The first large-scale biomonitoring of PAE exposure in Chinese general population
- Chinese urban residents were mainly exposed to DnBP and DEHP.
- Age and educational level were found to be related to human exposure to PAEs.
- Northeastern and western China had higher levels of mPAEs than central China.
- The non-cancer risks should be concerned for one-fifth of Chinese urban residents.

GRAPHICAL ABSTRACT



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ABSTRACT

Phthalates (PAEs) are widely used in daily products but can cause a variety of adverse effects in humans. Few studies have been carried out on human internal exposure levels of PAEs on a large-scale, especially in developing countries. In the present study, 1161 urine samples collected from residents of 26 provincial capitals in China were analyzed for nine phthalate metabolites (mPAEs). The chemicals were widely detected, and the median specific gravity adjusted urinary concentration of Σ_9mPAEs was 278 μg/L. Di-(2-ethylhexyl) phthalate (DEHP) and di-*n*-butyl phthalate (DnBP) were the main parent PAEs that the residents were exposed to. Demographic characteristics, such as age and educational level, were significantly associated with PAE exposure. Children and the elderly had higher mPAE levels. Subjects with lower educational levels were more frequently exposed to DnBP and DEHP. However, mono-ethyl phthalate showed the opposite trend, i.e., higher concentrations in subjects aged 18–59 years and with higher educational levels. Geographic differences were detected at the national scale. Residents in northeastern and western China had higher levels of mPAEs than those in central China, most likely because of different industrial usage of the chemicals and different living habits and living conditions of the residents. Health risk assessment showed that hazard indices of PAEs ranged from 0.07 to 9.34, with 20.0% of the subjects being concern for potential non-carcinogenic risk as assessed by Monte Carlo simulation. DEHP and DnBP were the primary contributors, representing 96.7% of total

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risk. This first large-scale study on PAE human internal exposure in China provides useful information on residents' health in a developing country, which could be used for chemical management and health protection.

1. Introduction

Phthalates (PAEs) are a group of synthetic organic compounds widely used in commercial products as solvents, plasticizers and lubricants (Yang et al., 2020). High molecular weight PAEs, e.g., butyl benzyl phthalate (BBzP), di-*n*-octyl phthalate (DnOP) and di-(2-ethylhexyl) phthalate (DEHP), are mainly added in plastic products, e.g., children's toys, building materials, and food packaging and containers (Li et al., 2019a). Low-molecular-weight PAEs, e.g., di-ethyl phthalate (DEP), di-methyl phthalate (DMP), di-isobutyl phthalate (DiBP) and di-*n*-butyl phthalate (DnBP), are commonly used in personal care products, medications, coatings and solvents (Huang et al., 2021). Due to their widespread usage and non-covalent bonding to products, PAEs may be easily released into the environment (Wormuth et al., 2006). The chemicals have been found in a variety of media, including water, air, dust, soil, sediments, food and even organisms, including humans (Ding et al., 2019; Guo et al., 2011a; Wang et al., 2015; Wormuth et al., 2006; Yang et al., 2020; Zhang et al., 2021; Zhu et al., 2019).

Several studies have demonstrated that PAEs can cause varied toxicities to organisms (Gray et al., 2000; Wang et al., 2016). As endocrine-disrupting compounds, PAE exposure has been associated with allergic rhinoconjunctivitis, diabetes, atopic dermatitis, asthma, hypertension and obesity (Callesen et al., 2014; Campbell et al., 2018; Piecha et al., 2016; Whyatt et al., 2014). PAEs may also have other toxic effects, such as reproductive and developmental toxicity (Mu et al., 2015; Aimuzi et al., 2022), neurotoxicity (Zhang et al., 2019) and even adverse health effects on offspring (Al-Saleh et al., 2021; Engel et al., 2010). Therefore, it is important to understand the human body burden exposure to PAEs.

PAEs can enter the human body through oral ingestion, dermal contact and inhalation (Dong et al., 2017; Fisher et al., 2019; Guo and Kannan, 2011). They are primarily hydrolyzed into monoester metabolites by lipase and esterase and then excreted in urine as glucuronide conjugates (Frederiksen et al., 2007). The monoester metabolites of high molecular weight PAEs can also be transformed further to secondary metabolites through hydroxylation and oxidation, which can improve the hydrophilicity of the metabolites (Koch et al., 2012) and make them easier to be eliminated from the body through urine. Therefore, measurement of phthalate metabolite (mPAE) concentrations in urine is often used to evaluate human exposure to PAEs (Becker et al., 2009; Dong et al., 2017), although other matrices, e.g., milk (An et al., 2020), serum (Miao et al., 2019), nails (Alves et al., 2016), hair (Katsikantami et al., 2020) and semen (Wang et al., 2016), have also been examined.

Because of the toxicity of PAEs, the European Union and United States have restricted the use of several PAEs, such as DEHP, DnBP, BBzP, DnOP, di-isononyl phthalate (DiNP) and di-isodecyl phthalate (DiDP), in children's toys and personal care products (Yang et al., 2020). In addition, several countries, including Germany, the United States and South Korea, have carried out large-scale national biomonitoring to evaluate human exposure to PAEs (CDC, 2019; Huang et al., 2021). As a major producer and consumer of PAEs, China consumes approximately 2.2 million tons of PAEs annually (Wang et al., 2015). Because of the potential toxic effects, China has also restricted the use of PAEs in personal care products, cosmetics, and toys. However, previous studies into human exposure to PAEs in China have so far only focused on specific populations or certain cities (Gao et al., 2016; Li et al., 2021), and no study has examined exposure to PAEs in the Chinese population nationwide.

As a country with a land area of 9.6×10^6 km^2 and a population of over 1.4 billion, it is not easy to study the exposure to PAEs among the entire Chinese population. Therefore, the main objective of the present study was to analyze the PAE exposure of urban residents of provincial capitals in China. Morning urine samples were collected from participants recruited in provincial capitals of the Chinese mainland, except for provincial capitals that were too small to provide sufficient samples for statistical analysis. The influencing factors, geographic differences and health risks of PAE exposure were evaluated. The results from this initial nationwide study help to understand the exposure level and health risks of PAEs in China and provide data that could be used to formulate and implement effective control measures to prevent human exposure to PAEs.

2. Materials and methods

2.1. Reagents and materials

Standards of nine mPAEs, i.e., mono-benzyl phthalate (mBzP), mono-methyl phthalate (mMP), mono-(2-ethylhexyl) phthalate (mEHP), mono-ethyl phthalate (mEP), mono-*n*-octyl phthalate (mOP), mono-(2-ethyl-5-hydroxy-hexyl) phthalate (mEHHP), mono-*n*-butyl phthalate (mBP), mono-(2-ethyl-5-oxo-hexyl) phthalate (mEOHP), mono-isobutyl phthalate (miBP) and their isotope-labeled internal standards (d_4-miBP, $^{13}C_4$-mEHHP, $^{13}C_4$-mEP, $^{13}C_4$-mEHP, $^{13}C_4$-mOP, $^{13}C_4$-mBzP, $^{13}C_4$-mBP, $^{13}C_4$-mMP and $^{13}C_4$-mEOHP) were all purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). Acetonitrile and methanol were purchased from Merck (Darmstadt, Germany). β-glucuronidase/sulfatase was obtained from Sigma Aldrich Corp. (St. Louis, MO, USA).

2.2. Sampling and pretreatment

During September and December 2019, a total of 1281 fasting morning urine samples (10 mL) were randomly sampled from 26 provincial capitals in mainland China based on a population to sample ratio of 200,000:1, as described in our previous study (Huang et al., 2022a). Urine samples were not collected in five other provincial capitals, i.e., Hohhot, Yinchuan, Haikou, Lhasa and Xining, because the small populations would have resulted in too few samples for statistical analysis. All participants signed informed consent forms and filled out questionnaires on sociodemographic information and living habits. In total, 1161 urine samples were used for the detection of mPAEs in the present study after excluding 120 subjects without complete questionnaire information. The study was approved by the Ethics Committee of Guangdong University of Technology.

Similar to our previous study (Li et al., 2021), the β-glucuronidase/sulfatase and isotope-labeled internal standards were added to each 500 μL urine sample and the mixture was incubated at 37 °C overnight. Next, to precipitate protein, 500 μL acetonitrile was added to each urine sample, followed by mixing and centrifugation. Finally, the supernatant was collected for further analysis.

2.3. Instrumental analysis

The analysis of mPAEs was conducted using an on-line solid-phase-extraction high-performance liquid chromatography-tandem mass spectrometry (on-line SPE-HPLC-MS/MS). To enrich and separate urinary mPAEs, an Oasis HLB online column (2.1 mm × 20 mm, 25 μm; Waters) and Poroshell120 EC-C18 column (4.6 mm × 100 mm, 2.7 μm; Agilent) were used, respectively. The gradient elution procedures for enrichment and separation are provided in Table S1 and 100 μL samples were injected. Electron spray ionization and multiple reaction monitoring modes were used. The limit of quantitation (LOQ), limit of detection (LOD) and mass spectrometry parameters of each mPAE were set at 3-fold and 10-fold signal-to-noise ratio (S/N), respectively, and they are shown in Table S2.

2.4. Human health risk assessments

To evaluate the human health risks, the hazard quotient (HQ) and hazard index (HI) representing the individual and cumulative health risks of PAEs, respectively, were used. If an HQ or HI value exceed one, which is considered as there may be concern for potential non-carcinogenic risk from PAE exposure. Otherwise, it indicates that adverse non-carcinogenic effects are not likely to occur, meaning the non-carcinogenic risk is negligible. They were calculated considering the non-carcinogenic endpoint as follows (Yu et al., 2021):

$$HQ = \frac{TEDI}{RfD} \tag{1}$$

$$HI = \Sigma\, HQ \tag{2}$$

$$TEDI = \frac{C_u \times V_u \times MW_1}{f \times BW \times MW_2} \tag{3}$$

where TEDI is the total estimated daily intake of a PAE (μg/kg-bw/day); C_u, V_u and BW are the specific gravity adjusted urinary concentration of the metabolite of the PAE (μg/L), the daily urine excretion volume (L/day) and the body weight (kg), respectively; RfD is the reference dose of the PAE (μg/kg-bw/day); f is the excretion ratio of the PAE in human urine (dimensionless); and MW_1 and MW_2 are the molecular weight of the PAE and its metabolite, respectively (g/mol). In the present study, 2 and 1.28 L/day urine excretion volumes were used for adults and children, respectively (Chen et al., 2019; Yu et al., 2021). f values of 10.9%, 6.2%, 14.9%, 70.3%, 69%, 73%, 69% and 13% were used for mEOHP, mEHP, mEHHP, miBP, mBP, mBzP, mEP and mOP, respectively (Koch et al., 2012; Yu et al., 2021). RfD values of 800, 100, 100, 20, 20 and 800 μg/kg-bw/day were used for DEP, DiBP, DnBP, DEHP, BBzP and DOP, respectively (Yu et al., 2021).

It had been shown that uncertainty can affect the assessment of health risks using the concentrations of mPAEs in spot urine samples (Du et al., 2014). Therefore, a Monte Carlo simulation was conducted to address the uncertainty through repeated sampling of the exposure variables (Qu et al., 2015). The variables included the concentration of mPAEs, body weight and total urine volume per day. The non-carcinogenic health risks of PAE exposure were calculated in the Crystal Ball spreadsheet (Oracle, Redwood City, CA, USA) using 50,000 trials.

2.5. Quality assurance, quality control and statistical analysis

For each batch of samples, two matrix spikes were used to evaluate the recovery. Two blanks, i.e., a procedural blank and reagent blank, and duplicate samples were also evaluated. Among the nine mPAEs analyzed, the mean recoveries ranged from 92% to 101%, except for mEHHP (124%) and mOP (60%). The linear ranges of the calibration curve ranged from 1.0 to 500 μg/L and the linear correlation coefficients were >0.996.

The software SPSS 13.0 (IBM, USA) was used for data analysis. The concentrations of mPAEs were adjusted by the specific gravity detected using a hand-held refractometer (ATAGO, PAL-10S, Tokyo, Japan), as described in a previous study (Just et al., 2010). Concentrations of mPAEs below LOD were set to zero. Moreover, the urinary mPAE concentrations were replaced by 1/2 LOQ if they were lower than LOQ with a detection frequency greater than 50%, otherwise, 1/4 LOQ was used (GB 17378.2-2007, 2007). To estimate the relationship between variables and PAE exposure, Kruskal-Wallis H and Mann-Whitney U tests were performed. Multivariate linear regression was conducted to assess associations between urinary mPAEs and different variables, such as demographic characteristics and living habits. The Kolmogorov-Smirnov test was used to test the normality of the data and Spearman's correlation analysis was conducted to test relationships among mPAEs due to the non-normal distribution of the data. A p-value <0.05 was set as the statistical significance level.

3. Results and discussion

3.1. Demographic characteristics of participants

Demographic characteristics showed that 53.6% of the participants were male and the mean age was 36 years old among the 1161 subjects (Table 1). More than half the participants had a body mass index (BMI) of 18.5 to 23.9, classed as a normal weight, whereas 28% of the subjects were classified as overweight. 53% of subjects had a bachelor's degree or higher qualification. Almost 49% and 75% ate takeaways and drank plastic bottled water more than once a week, respectively. All subjects were urban residents.

3.2. Concentrations and composition patterns of mPAEs

The detection frequencies and concentrations of mPAEs among the 1161 subjects are summarized in Table 2. The target mPAEs were found in all urine samples with detection frequencies generally >89%, except for mMP (4.34%) and mBzP (2.13%). The median concentration of Σ_9mPAEs (sum of the concentrations of the nine mPAEs) was 278 μg/L and the 75th percentile was 431 μg/L. Metabolites of DnBP and DEHP were the predominant compounds, with median concentrations of 140 and 50.3 μg/L, respectively, followed by miBP (25.9 μg/L) and mEP (23.8 μg/L), the metabolites of DiBP and DEP, respectively. Compared with other regions in China and other countries, the detected concentrations of mPAEs were relatively high, especially for mBP which was one order of magnitude higher than others (Table S3). For miBP and DEHP metabolites, the urinary concentrations of subjects in China were comparable to those in other countries, while the urinary mEP and mBzP in Chinese residents were lower.

The composition profiles of urinary mPAEs in the studied subjects are shown in Fig. S1 based on the medians. As mentioned above, mBP was the predominant mPAE, accounting for 58.3% of mPAEs, followed by DEHP metabolites (21.0%) and miBP (10.8%). Among the nine studied mPAE compounds, mBP, miBP, DEHP metabolites and mEP represented almost all mPAEs found in urine. Similar composition profiles that mBP was the predominant mPAE have been reported in other studies from China (Chen et al., 2019; Li et al., 2021; Yao et al., 2019; Zhang et al., 2020). However, other studies showed that DEHP metabolites were the predominant compounds (Yu et al., 2021). As a principal producer and consumer of PAEs around the world, China produced about one-fifth of the world's PAEs in 2009 and consumed about 1.5 million tons, of which DnBP and DEHP were the major PAEs (Meng et al., 2014). DnBP and DEHP are commonly used as additives in plastic products, such as processed materials in contact with food and food packaging (Huang et al., 2021; Mu et al., 2015). PAEs can be released from food packaging materials into foods, especially those with a high lipid content (Cao, 2010). Dietary intake has been suggested to be the main pathway of human PAE exposure, especially for DEHP (Guo et al., 2012). In addition, low molecular weight PAEs, such DEP and DnBP, are used in building materials, such as paints and adhesives, and personal care products (Huang et al., 2021; Villanger et al., 2020).

To further reveal the sources of PAEs, the results of Spearman's correlation analysis are shown in Table S4 and Fig. S2. Here, mBzP and mMP were not analyzed because of their low detection frequencies (<50%). Except for mOP, the correlation coefficients among the mPAE compounds were 0.167–0.944 ($p < 0.01$), suggesting that significant associations were found among these mPAEs. Unsurprisingly, among DEHP metabolites (mEHP, mEHHP and mEOHP), strong correlations were found, with correlation coefficients of 0.710–0.944. Secondary metabolites of DEHP (mEOHP and mEHHP) were the main metabolites, with median concentrations higher than the monoester metabolite mEHP. Moderate correlations were also found between mBP and secondary metabolites of DEHP (0.225–0.396, $p < 0.01$), which can be interpreted as them originating from common sources. As mentioned above, DnBP and DEHP are generally used in plastic products and polyvinyl chloride polymers, as well as building materials. For low molecular weight PAEs, significant correlations

Table 1
Demographic characteristics of the study population.

Demographic characteristics	Number (%)	Demographic characteristics	Number (%)
Study population	1161 (100)		
Gender		Makeup	
Male	622 (53.6)	Yes	252 (21.7)
Female	539 (46.4)	No	909 (78.3)
Age group (years)		Educational level	
<18	128 (11.0)	Primary school and below	239 (20.6)
18–44	655 (56.4)	Middle school	307 (26.4)
45–59	226 (19.5)	Bachelor's degree	484 (41.7)
>59	152 (13.1)	Master's and above	131 (11.3)
Body mass index (BMI)		Frequency of takeaways	
<18.5	156 (13.4)	Hardly	588 (50.6)
18.5–23.9	681 (58.7)	1–2 times/week	416 (35.8)
>23.9	324 (27.9)	3 times and above/week	157 (13.5)
Smoking status		Frequency of drinking plastic bottled water	
Smoker	409 (35.2)	Never	282 (24.3)
Non-smoker	752 (64.8)	1–2 times/week	479 (41.3)
Passive smoking		3 times and above/week	400 (34.5)
Yes	862 (74.2)	Area of residence	
No	299 (25.8)	Northeast China	123 (10.6)
Drinking		Eastern China	504 (43.4)
Yes	679 (58.5)	Central China	225 (19.4)
No	482 (41.5)	Western China	309 (26.6)

Table 2
Specific gravity adjusted urinary concentrations of mPAEs in urban residents of 26 provincial capitals in China.

Compounds	25th percentile	Median	75th percentile	Mean ± SD	Range	DF (%)
mMP	<LOD	<LOD	<LOD	10.0 ± 69.0	<LOD–1166	4.34%
mEP	13.3	23.8	41.2	56.7 ± 216	<LOD–4672	89.3%
mBP	85.9	140	228	186 ± 162	10.6–1535	100%
miBP	16.4	25.9	42.7	34.8 ± 32.8	1.89–604	100%
mEHP	5.65	8.84	15.6	13.6 ± 17.0	0.95–276	100%
mEHHP	17.3	28.4	46.0	41.5 ± 47.8	4.15–539	100%
mEOHP	6.88	12.0	19.8	17.4 ± 20.9	1.01–205	100%
mBzP	<LOD	<LOD	<LOD	0.57 ± 5.37	<LOD–134	2.13%
mOP	0.02	0.04	0.09	0.08 ± 0.14	<LOD–1.98	99.6%
ΣDEHP	31.3	50.3	80.6	72.5 ± 81.6	7.70–821	
Σ_9mPAEs	187	278	431	360 ± 329	32.0–5000	

LOD: limit of detection; DF: detection frequency; mMP: mono-methyl phthalate; mEP: mono-ethyl phthalate; mBP: mono-*n*-butyl phthalate; miBP: mono-isobutyl phthalate; mEHP: mono-(2-ethylhexyl) phthalate; mEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate; mEOHP: mono-(2-ethyl-5-oxohexyl) phthalate; mBzP: mono-benzyl phthalate; mOP: mono-*n*-octyl phthalate; ΣDEHP: sum of urinary concentrations of mEHP, mEHHP and mEOHP; Σ_9mPAEs: sum of urinary concentrations of all nine PAE metabolites.

were found among mEP, mBP and miBP (correlation coefficients 0.285–0.473). DEP, DnBP and DiBP (an alternative to DnBP) are commonly used in cosmetics, such as fragrances, body lotions and shampoos, as well as other personal care products, which might be the main exposure sources for the low molecular weight PAEs.

3.3. Demographic characteristic influence on mPAE levels

Analyzing the factors influencing urinary concentrations of mPAEs can provide a better understanding of the possible sources and routes of PAE exposure. Thus, the influence of demographic characteristics (gender, age, BMI and educational level) and living habits (makeup, smoking, drinking plastic bottled water, takeaway and alcohol consumption) on the concentration of urinary mPAEs was analyzed. The relationships between the factors and the concentrations are shown in Fig. 1, Fig. S3, and Table S5.

From this data, gender differences were observed, although the differences were not significant for some individuals except for miBP, whose median concentration was higher in males ($p < 0.01$) (Fig. S3A). Although mPAEs were not significantly associated with gender, the urinary concentrations of mBP, DEHP metabolites and Σ_9mPAEs in males were slightly higher than females. Similar results were reported by Gao et al. (2016) and Zhang et al. (2020). Conversely, higher median concentrations of mEP were found in females than in males (25.2 vs. 23.1 μg/L). The results indicated that personal care products are not the main source of men's exposure to DnBP and DEHP. In addition, higher urinary concentration of mBP was also found in male without makeup than males with makeup (144 vs. 129 μg/L, median). Therefore, compared with females, males may be exposed to specific PAE sources, which warrants further study.

Significant associations were found between urinary mPAEs and makeup. Subjects with makeup had significant higher concentration of urinary mEP ($p < 0.05$), while other mPAEs were conversely which were significantly higher in the subjects without makeup (Fig. S3D). In the present study, 93% of the subjects with makeup were females who had higher urinary concentration of mEP. A previous study showed that DEP was the most frequently measured PAEs with a detection frequency of 54% in personal care products (Guo et al., 2014). What's more, DEP was the predominant PAEs in perfume, shower gel, and hair care products (Al-Saleh and Elkhatib, 2016; Lim et al., 2019). Another report showed that urinary concentrations of mEP significantly increased when women used cosmetics or body lotion (a personal care product) within the past 24 h and when personal care products was used within 6 h before the collection of urine samples (Fisher et al., 2019). These results demonstrate that differences in lifestyle, such as usage of personal care products and cosmetics, contribute to different PAE exposure.

Significant differences in mPAEs were also found among subjects in different age groups ($p < 0.01$). Children and adolescents (aged <18 years)

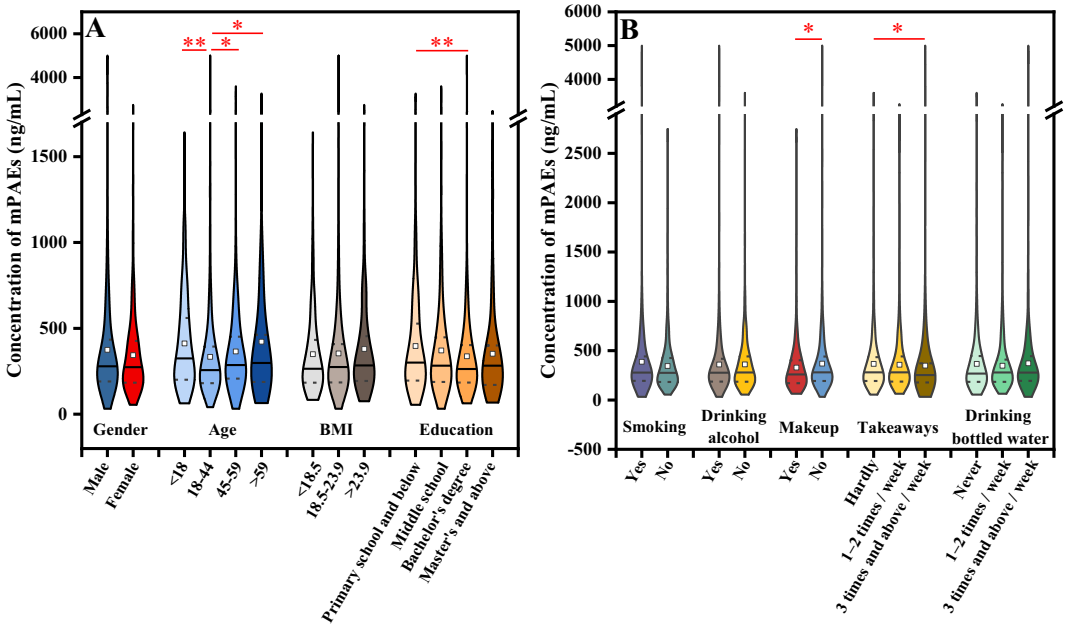

Fig. 1. Specific gravity adjusted urinary concentrations of mPAEs from people with different demographic characteristics (A) and living habits (B). $^{**}p < 0.01$ level (2-tailed); $^{*}p < 0.05$ level (2-tailed).

had the highest Σ_9mPAEs, followed by adults aged >59 years (Table S5). High mPAE levels in children may be caused by specific behaviors, such as playing and crawling on the ground, which might increase the uptake of dust containing PAEs (Kasper-Sonnenberg et al., 2012; Wittassek et al., 2007). Moreover, chewing toys or other household products containing PAEs may also increase children's PAE exposure (Varshavsky et al., 2018). Similar results have been reported in previous studies. Levels of mPAEs in children from China (aged <18 years) (Zhang et al., 2020), Australia (aged 0–15 years) (Tang et al., 2020) and Germany (aged 2–14 years) (Becker et al., 2009; Koch et al., 2007) have been shown to be higher than those of adults and tend to decrease with age. However, in the present study, the median concentration of mEP in children and adolescents was lower than that in other age groups ($p < 0.01$) (Fig. S3B). This may be attributed to the lower usage frequency of cosmetic and personal care products in children and adolescents. In addition, the Σ_9mPAEs of adults aged 18–44 years was significantly lower than that of adults aged >45 years. A similar trend with higher PAE exposure in children and the elderly has been reported previously (Zhang et al., 2020). Therefore, different lifestyles and behaviors result in varied main sources and routes of PAE exposure for different age groups.

Regarding the factor BMI, the highest Σ_9mPAEs (284 μg/L) was detected in subjects with BMI > 23.9, and the lowest was found in BMI < 18.5 (165 μg/L), although no significant difference was found among the different BMI groups (Table S5). This suggests that obese subjects with BMI > 23.9 were more likely to be exposed to PAEs. Previous studies have also found an association between obesity and PAE exposure (Campbell et al., 2018; Lind et al., 2012). Dietary intake has been suggested as an important source of PAE exposure, especially for DnBP, DiBP and DEHP (Guo and Kannan, 2011; Wormuth et al., 2006), because PAEs can be released into food from polyvinyl chloride pipes, food packaging films, coatings on cookware and printing inks on food packaging during food processing, storage, and transportation (Cao, 2010).

Considering food related effects, the influence of drinking plastic bottled water and consuming takeaways was analyzed. Subjects who drank plastic bottled water had higher Σ_9mPAEs than those who never did (Fig. S3F and Table S5), and they had the highest concentrations of mBP and ΣDEHP. As reported by Otero et al. (2015), DnBP and DEHP are the predominant PAEs in plastic bottles. Thus, PAEs in plastic bottles can be released into water, and the process has been shown to be affected by the time and temperature of storage (Xu et al., 2020). In addition, the release of PAEs to food can occur with the use of plastic containers (Fasano et al., 2012). Studies have reported that the type of food container and food affects the amount of PAE transferred, and the frequency of eating takeaways positively correlates with PAE exposure (Wang et al., 2021; Yao et al., 2019). However, opposite results were found in the present study (Table S5). The highest median of Σ_9mPAEs was observed in subjects who rarely ate takeaways, suggesting other more important factors might have affected the results.

Significant associations between urinary mPAEs and educational levels were found ($p < 0.05$) (Fig. 1). Here, miBP, mBP, ΣDEHP and Σ_9mPAEs were negatively correlated with educational levels, whereas mEP was positively correlated (Fig. S3E). However, the relationship between educational level and urinary mPAEs has been shown to vary in other studies (Arbuckle et al., 2014; Li et al., 2019b; Yao et al., 2020; Zhu et al., 2016). For instance, similar results were observed by Zhu et al. (2016) and Yao et al. (2020), who observed that the concentrations of mBP were negatively correlated to educational level, whereas the opposite trend was observed for mEP. Arbuckle et al. (2014) found that mEOHP and mEHHP, secondary metabolites of DEHP, were significantly elevated in women with higher educational level. These conflicting results might be explained by differences in the sampling time and populations among the different studies and the fact that PAE exposure is influenced by multiple factors rather than educational level alone.

Considering the varied influence of the studied factors, multiple linear regression analysis was conducted to eliminate the multiple factor effect. After adjusting for demographic characteristics, living habits and individual mPAEs, a few significant correlations were found (Table 3). Age was significantly correlated with urinary mEP ($p < 0.01$). As mentioned above, higher concentrations of mEP were found in adults aged 45–59 and 18–44 years who frequently used personal care products and cosmetics containing mEP. However, although no significant association was found between urinary mEP and makeup, subjects who used makeup had higher concentrations of mEP. The results suggested that DEP may have other potential sources in addition to cosmetics and personal care products. Conversely, mBP was negatively associated with makeup ($p < 0.01$). Since 93% of the subjects using makeup were women, a possible explanation was that

Table 3
Multiple linear regression between PAE exposure and variables.

Variable[a]	mEP		miBP		mBP		mOP		ΣDEHP		Σ_9mPAEs	
	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Constant	−63.7 (−168, 40.1)	0.228	19.2 (5.23, 33.2)	<0.01	122 (52.4, 191)	<0.01	−0.02 (−0.09, 0.04)	0.471	69.8 (32.9, 107)	<0.01	342 (187, 498)	<0.01
Sex	−11.8 (−46.0, 22.3)	0.497	−5.14 (−9.75, −0.53)	0.029	21.1 (−1.79, 43.9)	0.071	0.01 (−0.02, 0.03)	0.559	−4.88 (−17.1, 7.34)	0.433	−8.38 (−60.7, 43.9)	0.753
Age	23.7 (6.98, 40.4)	<0.01	−1.39 (−3.65, 0.88)	0.230	−0.76 (−12.0, 10.5)	0.895	0.00 (−0.01, 0.01)	0.966	−5.10 (−11.1, 0.90)	0.096	8.59 (−17.0, 34.2)	0.511
BMI	−5.21 (−26.9, 16.5)	0.637	4.31 (1.39, 7.23)	<0.01	−3.00 (−17.5, 11.5)	0.686	0.00 (−0.01, 0.02)	0.724	0.58 (−7.19, 8.34)	0.884	14.2 (−19.0, 47.4)	0.402
Education	−0.25 (−15.1, 14.6)	0.974	−0.96 (−2.97, 1.05)	0.348	−2.71 (−12.7, 7.24)	0.593	0.00 (−0.01, 0.01)	0.921	−2.72 (−8.03, 2.59)	0.315	−17.6 (−40.4, 5.14)	0.129
Smoking	23.1 (−11.2, 57.5)	0.186	5.21 (0.58, 9.84)	0.028	−7.00 (−30.0, 16.0)	0.551	0.01 (−0.01, 0.03)	0.409	−7.10 (−19.4, 5.19)	0.257	41.9 (−10.7, 94.4)	0.118
Alcohol intake	−13.2 (−44.1, 17.7)	0.404	−2.96 (−7.13, 1.22)	0.165	5.36 (−15.3, 26.1)	0.612	0.01 (−0.01, 0.03)	0.303	−5.16 (−16.2, 5.89)	0.360	−21.8 (−69.2, 25.6)	0.367
Takeaway consumption	4.62 (−14.5, 23.8)	0.636	−0.00 (−2.59, 2.59)	0.999	−5.85 (−18.7, 6.96)	0.370	−0.00 (−0.01, 0.01)	0.865	−1.92 (−8.77, 4.93)	0.582	−13.5 (−42.9, 15.9)	0.367
Drinking bottled water	3.61 (−14.1, 21.3)	0.689	−2.14 (−4.53, 0.25)	0.079	8.36 (−3.48, 20.2)	0.166	0.00 (−0.01, 0.01)	0.551	4.25 (−2.08, 10.6)	0.188	16.3 (−10.8, 43.4)	0.239
Makeup	23.6 (−13.2, 60.3)	0.208	1.99 (−2.98, 6.95)	0.432	−38.3 (−62.8, −13.8)	<0.01	0.02 (−0.01, 0.04)	0.169	4.62 (−8.52, 17.8)	0.491	−9.34 (−65.5, 46.8)	0.744
mEP			0.01 (0.00, 0.02)	0.065	0.05 (0.01, 0.09)	0.018	−0.00 (0.00, 0.00)	0.915	0.01 (−0.01, 0.03)	0.255		
miBP	0.40 (−0.03, 0.83)	0.065			2.08 (1.82, 2.34)	<0.01	0.00 (0.00, 0.00)	0.013	0.17 (0.02, 0.32)	0.030		
mBP	0.10 (0.02, 0.19)	0.018	0.09 (0.07, 0.10)	<0.01			−0.00 (0.00, 0.00)	0.010	0.08 (0.04, 0.11)	<0.01		
mOP	−5.15 (−99.7, 89.4)	0.915	16.1 (3.37, 28.9)	0.013	−83.0 (−146, −19.9)	0.010			166 (133, 198)	<0.01		
ΣDEHP	0.09 (−0.07, 0.26)	0.255	0.02 (0.00, 0.05)	0.030	0.26 (0.16, 0.37)	<0.01	0.00 (0.00, 0.00)	<0.01				

[a] Sex, age, BMI, education, smoking, alcohol intake, takeaway consumption, drinking bottled water and makeup were considered as classification variables. mEP: mono-ethyl phthalate; mBP: mono-*n*-butyl phthalate; miBP: mono-isobutyl phthalate; mOP: mono-*n*-octyl phthalate; ΣDEHP: sum of urinary concentrations of mEHP, mEHHP and mEOHP; Σ_9mPAEs: sum of urinary concentrations of all nine PAE metabolites.

for men, DnBP, the parent compound of mBP, had other exposure sources, e.g., adhesives and dietary supplements. Significantly higher concentrations of miBP were found in smokers, males, and subjects with high BMI ($p < 0.05$). Previous studies have shown that higher urinary mEP concentrations were associated with smoking (Duty et al., 2005; Wang et al., 2018). Thus, the present results indicate that smoking may be a predictor of urinary miBP. Regarding the correlation between miBP and BMI, it has been reported that dietary intake was the main source of DiBP (accounting for more than 60%) in Europe and the United States (Guo and Kannan, 2011; Wormuth et al., 2006). Therefore, excessive food intake causing an increased BMI may be the main source of DiBP in the Chinese population. However, no significant associations were found between ΣDEHP and the variables, which may be because of the wide application of DEHP in daily life with complex exposure sources. The concentrations of DEHP tended to decrease with age, although the *p*-value was close to 0.096. As mentioned above, the specific behaviors of children, such as playing and crawling on the ground and chewing products containing PAEs, may contribute to increased PAE exposure.

3.4. Spatial distribution of urinary mPAEs in China

To reveal the human exposure levels of PAEs at a nationwide level, the concentrations of mPAEs of the participants in different provincial capitals are shown in Table S6 and Fig. 2. A corresponding administrative division map of China is shown in Fig. S4. The median concentrations of Σ_9mPAEs were 316, 281, 278 and 249 μg/L in northeastern, western, eastern, and central China, respectively. Therefore, subjects in northeastern and western China appeared to have higher levels of mPAEs than in central China ($p < 0.05$). This may correlate with the different domestic sources in various regions, such as the proportion of plastics industry and the lifestyle of the residents. A previous study suggested that the production and application of plastic products were the main sources of PAEs in the atmosphere, followed by the usage of personal care products (Huang et al., 2022b). However, the analysis was limited due to the lack of data on the use of personal care products and plastics industry around the subject's residence.

Among the provincial capitals, Tianjin, Guiyang, Kunming, and Nanjing had the highest PAE exposure levels, with median concentrations of Σ_9mPAEs of 444, 415, 383 and 380 μg/L, respectively. Few other studies have reported values of urinary mPAEs in the general urban residents from these cities. Median Σ_9mPAEs concentrations of the subjects in Tianjin were higher than those reported in studies from the same city whose subjects were pregnant women (Li et al., 2018) and employees in the Ziya Circular Economy Park and its surrounding area (Li et al., 2019c). Moreover, the median Σ_9mPAEs of subjects in Nanjing in this study was about 1.5 times higher than that of males in the same city reported by Pan et al. (2016). Differences in sociodemographic characteristics and living habits may be the main reason for these variable results (Table S7). Moreover, compared with our previous study, subjects in Guangzhou in this study had lower urinary concentrations of mPAEs than residents in Guangzhou suburbs (241 vs. 312 μg/L, median) (Li et al., 2021). This difference can be attributed to metabolites of DEHP, DnBP and DiBP, which may be increased due to differences in the surrounding environment of residence, especially for the presence of plastic manufacturing and processing plants in the suburbs. What's more, the concentrations of urinary mBP and DEHP metabolites of rural older adults in Anhui, China were higher than those in urban older adults, while mMP and mEP were opposite, which may be due to the differences in surrounding environment, dietary structure, and living habits (Cheng et al., 2021). A previous study also suggested an association between residential characteristics and PAE exposure (Dong et al., 2020). Therefore, the differences in PAE exposure in provincial capitals may be due to different living habits and living conditions.

3.5. Human exposure to PAEs and non-carcinogenic risks

The concentration of DEHP for risk assessment can be calculated from its metabolites, i.e., mEHP, mEHHP and mEOHP, with the highest

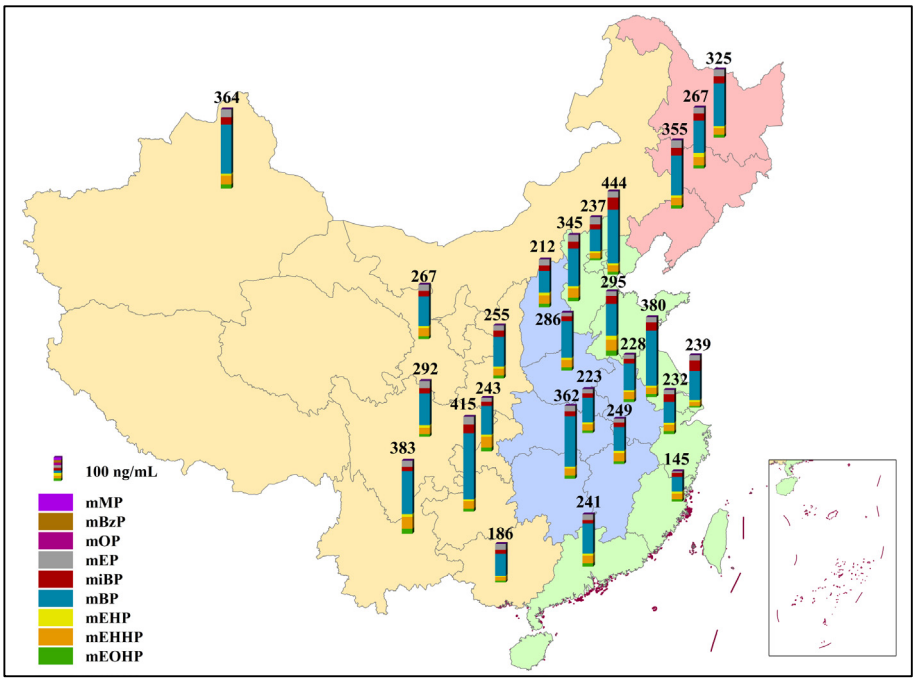

Fig. 2. Specific gravity adjusted urinary concentrations (median, ng/mL) and geographical distribution of mPAEs in the general population from different provincial capitals in China.

concentration used on the basis of the principle of the United States Environmental Protection Agency to protect human health to the greatest extent. As reported in the literature, secondary metabolites of DEHP may be more suitable than DEHP as exposure biomarkers (Koch et al., 2005; Preuss et al., 2005). Thus, the concentration of DEHP derived from urinary mEHHP was used for risk assessment. The TEDI values of total PAEs and individual PAE are shown in Table S8. The TEDIs of PAEs ranged from 3.39 to 346 μg/kg-bw/day, with a median of 22.0 μg/kg-bw/day. DnBP had the highest TEDI (8.36 μg/kg-bw/day, median), followed by DEHP (8.25 μg/kg-bw/day). The TEDI values of DnBP, DiBP and DEP were in accordance with a previous study of adults in China, whereas that of DEHP was higher (Guo et al., 2011b). However, the TEDI values of PAEs were lower than those reported for municipal solid waste incineration plant workers in China (Lu et al., 2020).

To further assess the non-carcinogenic risk to humans exposed to PAEs, HQ and HI values were calculated based on the RfD of each PAE (Table S9 and Fig. S3A). The results showed that the median of HI was 0.55 with a range of 0.07–9.34. 18.3% of participants had a HI value higher than one unit, indicating that the non-carcinogenic risk for general urban residents in China may be concern for potential non-carcinogenic effects because of PAE exposure. For individual PAEs, the HQ values were in the range 0.00–8.83. DEHP was the main contributor, accounting for 80.4% of the HI values (Fig. 3B). In addition, Monte Carlo simulation suggested that there might be concern potential non-carcinogenic risk (lg (HQ) > 0) for 20.0% of the Chinese population exposed to PAEs, and the non-carcinogenic risk for 80.0% of them were negligible (Fig. 3C). DEHP and DnBP were the primary contributors, amounting to 96.7%. As shown in Fig. 3D, the Chinese population exposed to PAEs had a high health risk compared with other regions. However, it should be noted that the subjects in other studies did not all represent a general population.

3.6. Uncertainties and study limitations

The present study has several limitations and uncertainties. Firstly, the concentrations of mPAEs only reflected short-term levels of general urban residents exposed to PAEs because the half-lives of PAEs are short in the human body. Secondly, 24-h urine samples may have better reflected actual exposure levels of PAEs than the morning urine samples used here (Koch et al., 2017), although previous studies have demonstrated a significant correlation between concentrations of mPAEs in morning urine and 24-h urine (Frederiksen et al., 2013), as well as the high reproducibility of morning urine (Bastiaensen et al., 2020; Hoppin et al., 2002). Thirdly, RfD was chosen as a reference value for the non-carcinogenic risk assessment. However, other reference values, such as tolerable daily intake (determined using animals by the European Food Safety Authorities via developmental and testicular toxicity) and RfD-AA (acceptable exposure level specifically based on anti-androgenic endpoints) suggested by Kortenkamp and Faust (2010), may affect the estimation of health risk (Huang et al., 2021). Therefore, in the present study, the non-carcinogenic risk of PAE exposure may have been over- or under-estimated because of the reference value used. In addition, the number of subjects in this study was only more than 1000, which may have certain limitations in representing the PAE exposure of the national general population. Finally, owing to potentially detrimental health effects, some PAEs have been restricted or banned in various countries. As substitutes, dioctyl terephthalate (DOTP), di-isononyl phthalate (DiNP), di-isodecyl phthalate (DiDP), di(2-ethylhexyl) terephthalate (DEHTP), di-2-propylheptyl phthalate (DPHP) and di-(isononyl) cyclohexane-1,2-dicarboxylate (DINCH), have been used in commercial products. However, their metabolites were not measured in the present study, which might have led to under-estimation of the health risks. Thus, the alternatives for PAEs should be considered in future investigations.

4. Conclusions

A total of 1161 morning urine samples were measured to estimate the internal exposure of PAEs in the Chinese population from 26 provincial capital cities in China. Furthermore, the potential influencing factors and non-carcinogenic risks of PAE exposure were studied. Among the nine mPAEs analyzed, mBP, ΣDEHP, miBP and mEP were the main detected compounds, with mBP having the highest median concentration. Significantly higher mPAE levels were found in children, elderly aged >59 years and subjects whose educational levels were primary school or below.

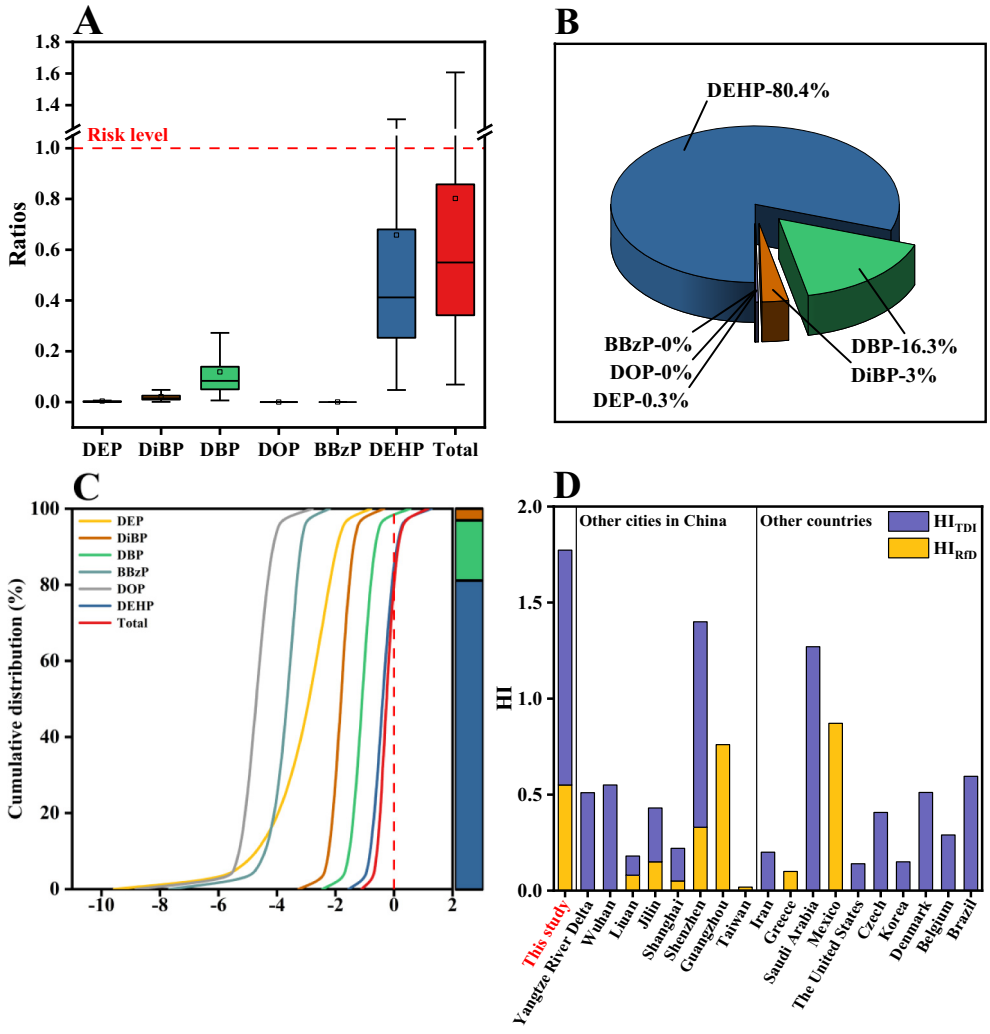

Fig. 3. Health risks of PAE exposure in the Chinese general population estimated in the present study and comparison with other studies. A: individual hazard quotients (HQ) and hazard indices (HI) of PAEs; B: contributions of individual PAEs to the total risk; C: Monte Carlo simulation of the non-carcinogenic risk based on specific gravity adjusted urinary concentrations of mPAEs and the bar represented the contributions of individual PAEs to the total risk; D: HI reported for different studies in China and global regions.

Lifestyle habits such as drinking bottled water and smoking correlated with higher PAE exposure, although no significant differences were found. 20% of the subjects had HI values greater than a unit, indicating that the non-carcinogenic health risk should be concerned for Chinese population exposed to PAEs, with DEHP and DnBP being the primary contributors. Chinese population exposed to PAEs had a higher health risk compared with other countries. This study provides important data on PAE exposure for general residents in most capital cities in China, which could be used by government managers to formulate relevant chemical management strategies regarding PAE exposure and health risk.

Ethics approval

The Ethics Committee of Guangdong University of Technology approved the present study.

Consent to participate

Before the sample collection, an informed consent form was signed by all the participants.

CRediT authorship contribution statement

Senyuan Huang: Methodology, data analysis, and draft preparation.
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Dongwu Wang: Methodology.
Hongli Liu: Methodology.
Guiying Li: Design.
Yingxin Yu: Design, reviewing & editing.

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.scitotenv.2022.156062.

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