Science of the Total Environment 696 (2019) 133982

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

$PM_{2.5}$ bound phthalates in four metropolitan cites of China: Concentration, seasonal pattern and health risk via inhalation

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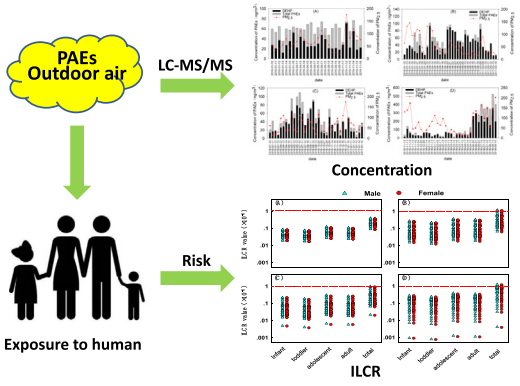
HIGHLIGHTS

- Concentrations of PAEs in low latitudes city were lower than those in high latitudes city.
- Concentrations of PAEs in warm seasons were higher than those in cold seasons.
- DEHP and DBP were the predominant and ubiquitous PAEs in atmospheric $PM_{2.5}$.
- The values of HI and HQs of PAEs were much lower than the value of 1.
- The highest values of 70 years ILCR of DEHP for adults were slightly beyond the U.S. EPA's acceptable limit.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 14 June 2019
Received in revised form 16 August 2019
Accepted 18 August 2019
Available online xxxx

Editor: Jianmin Chen

Keywords:
Plasticizers
Air pollution
Estimated daily intakes
Hazard quotients
Lifetime cancer risk

ABSTRACT

Phthalates (PAEs) are in a group of artificial chemicals with potential adverse effects to human health and they can be frequently detected in environmental matrices due to its extensive usage. However, seasonal patterns of concentrations in atmosphere and risks posed by PAEs in airborne $PM_{2.5}$ to Chinese population have not been well characterized. During the period of November 2015 to March 2017, samples of fine particulate matter ($PM_{2.5}$) were collected in four cities of Guangzhou, Shanghai, Beijing and Harbin, which are major metropolitan areas of various latitudes of China. Concentrations of fourteen PAEs in airborne $PM_{2.5}$ were quantified using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS). Estimated daily intakes (EDIs), hazard quotients (HQs) and hazard index (HI) were calculated. Lifetime average daily doses (LADD) and incremental lifetime cancer risks (ILCR) of di(2-ethylhexyl) phthalate (DEHP) for four age groups, which divide with infant, toddler, adolescent and adult, by inhalation route were evaluated. Dimethyl phthalate (DMP), Diethyl phthalate (DEP), Di-n-butyl phthalate (DBP), and DEHP were the four major PAEs contaminants in these $PM_{2.5}$ samples. The sum concentrations of DMP, DEP, DBP and DEHP in Guangzhou, Shanghai, Beijing and Harbin ranged from 32.5–76.1, 10.1–101, 8.02–107 and 13.5–622 ng/m^3, with mean concentrations of 59.1, 50.8, 43.8 and 136 ng/m^3, respectively. The concentration of total PAEs in $PM_{2.5}$ from higher latitudes city (Harbin) was higher than those from

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https://doi.org/10.1016/j.scitotenv.2019.133982

lower latitudes cities (Guangzhou and Shanghai). Total concentrations of PAEs were significantly higher during warmer seasons than those during colder seasons among the four cities. Although the EDIs, HQs, and HI for all age groups were less than the threshold set by the U.S. Environmental Protection Agency (US EPA) and European Food Safety Authority (EFSA), the highest values of 70-years ILCR from Shanghai and Harbin were 1.2×10^{-6} and 1.3×10^{-6}, which were slightly beyond the acceptable level of 10^{-6}. These findings reveal that the cancer risks of DEHP bound to $PM_{2.5}$ in these two cites should be of particular concern.

1. Introduction

Particulate matter (PM), particularly $PM_{2.5}$, is a considerable threat to human health and remains a major public health concern worldwide. The World Health Organization (WHO) has developed guidelines for assessing risks of exposure of humans to $PM_{2.5}$ and the International Agency for Research on Cancer (IARC) has stated that $PM_{2.5}$ is the leading reason of lung cancer caused by air pollution (Martoni, 2018). This is not only due to physical effects of inhalable $PM_{2.5}$ that can reach alveoli and blood circulatory system, but also $PM_{2.5}$ is a carrier of various pollutants, which can be important contributors to adverse health outcomes of $PM_{2.5}$ to human health. To date, some previous studies have focused on several classes of contaminants, including polycyclic aromatic hydrocarbons (PAHs), organophosphate flame retardants (OPFRs) and poly chlorinated biphenyls (PCBs) absorbed on the surface of $PM_{2.5}$ (Chang et al., 2019; Wang et al., 2019). However, the pollution patterns of PAEs in airborne $PM_{2.5}$ were limited, and this situation is important and urgently needed to be addressed in China where air pollution has reached critical levels in some areas.

PAEs are produced worldwide and added as plasticizers in plastics, rubber, paint, toys, furniture, electrical devices and pharmaceutical products in order to increase their flexibility (Chiellini et al., 2013; Hubinger and Havery, 2006; Sun et al., 2012). Because of the extensively usage, PAEs are inevitably leached out of materials and can enter the atmosphere, dust, soil and water (Han and Liu, 2017; Torres et al., 2018; Tran et al., 2017; Wang et al., 2017b). Relatively great concentrations of PAEs and their metabolites have thereby been frequently detected in human urine and serum (Callesen et al., 2014; Guo et al., 2011; Hines et al., 2009; Olsén et al., 2012). PAEs are toxic to animals and humans (Bui et al., 2016; Mankidy et al., 2013; Wei et al., 2011; Xu et al., 2013) and have been identified as endocrine disruptors, leading to endocrine disruption and reproductive toxicity (Lovekampswan and Davis, 2003; Martinoandrade and Chahoud, 2010; Yin et al., 2018). Numerous epidemiological studies have demonstrated significant correlations between exposures to PAEs and reproductive diseases, such as malformation genital development (Suzuki et al., 2012) and precocious puberty in young children (Chou et al., 2009). PAEs exposure can also cause asthma in children (Li et al., 2017), as well as pulmonary function damage, abnormal thyroid metabolism, obesity and diabetes in adults (Buser et al., 2014; Shi et al., 2012a). Consequently, North America, Asia, and Europe had developed regulations to reduce the usage of PAEs (Ramos et al., 2016; Shu et al., 2018). Dimethyl phthalate (DMP), Diethyl phthalate (DEP), Dibutyl phthalate (DBP), Dioctyl phthalate (DOP), Butyl benzyl phthalate (BBP) and Di-2-ethylhexyl phthalate (DEHP) had been listed as priority pollutants in U.S. (Guo et al., 2011).

Recent studies have reported that the frequent presence of PAEs in office and surface water might introduce adverse effect risks on people and animals (Liu et al., 2016; Wei et al., 2017). However, studies regarding PAEs and exposure risk assessment in outdoor airborne in China are relatively rare. A couple of previous studies revealed the concentrations of PAEs in airborne PM in metropolitan cities of Shenzhen, Shanghai, and Tianjin, showing that the contamination of PAEs in airborne PM was more severe in China than those in European countries (Aragón et al., 2012; Lu et al., 2018; Ma et al., 2014; Mandin et al., 2016; Růžičková et al., 2016; Zhu et al., 2016). Besides, the estimated carcinogenic risks by inhalation of PAEs for Chinese general population of Tianjin, Shanghai, Harbin, Shenyang, Mount Tai and Xi'an were ranged from 8.9×10^{-10} to 9.3×10^{-7}. Although, the highest risk value in China (9.3×10^{-7}) was much higher than that in Saudi Arabia (3.3×10^{-8}), all were considered as in the acceptable level (Kadi et al., 2018; H.L. Li et al., 2016; Li et al., 2019; Ma et al., 2014; Wang et al., 2017a; Zhang et al., 2014). However, the risk assessment of these previous studies cannot accurately represent that of Chinese people because the demographic data used for risk assessment were obtained from U.S. EPA. As far as we know, no study has been focused on carcinogenic risk assessment of airborne $PM_{2.5}$ bound PAEs considering age susceptibility by using Chinese exposure parameters.

In the present study, to address these concerns and develop background information on exposure, airborne $PM_{2.5}$ samples were collected from four metropolitan cities, namely Guangzhou, Shanghai, Beijing and Harbin from November 2015 to March 2017. These cities are at distinct latitudes with a gradient of climate. More specifically, the objectives were to 1) determine the concentrations of 14 PAEs in airborne $PM_{2.5}$ of these four cities by the use of LC-MS/MS; 2) compare concentrations of the PAEs associated with $PM_{2.5}$ among locations and between warm and cold seasons; and 3) obtain more accurate EDIs value of PAEs and assess LADD and 70-years ILCR value of DEHP exposure through inhalation route with Chinese exposure parameters and the age sensitivity factors.

2. Materials and methods

2.1. Chemicals

Totally, 14 targets PAEs compounds were analyzed in this study. The name, abbreviations and CAS number of these PAEs compounds are shown in Table S1. HPLC grade solvents of acetone and methanol were purchased from Merck. (Darmstadt, Germany). Standard stock solutions of mixtures of 14 PAEs were made by the O2si smart solutions (Charleston, USA), which include DMP, DEP, DBP, Diamyl phthalate (DAP), Di-2-ethoxyethyl phthalate (DEEP), Di-2-butoxyethyl phthalate (DBEP), BBP, Dicyclohexyl phthalate (DCHP), DEHP, Di-n-hexyl phthalate (DHXP), Dioctyl phthalate (DOP), Diphenyl phthalate (DPP), Di-2-methoxyethyl phthalate (DMEP) and Di-4-methyl-2-pentyl phthalate (DMPP). Concentrations of all 14 PAEs were 1 mg/mL with the purity of >98%.

2.2. Collection and quantification of airborne $PM_{2.5}$

Four metropolitan cities of Guangzhou, Shanghai, Beijing, and Harbin with a population of >10 million people, were selected for this study to represent south, central, north and northeast regions of China, respectively (Fig. S1 in Supplementary Material). Samples of airborne $PM_{2.5}$ were collected between November 2015 and March 2017. Sampling sites, with typical city characteristics, were <500 m from suburban residential areas and <1000 m from motorways. Prior to collection, to remove residual PAEs, quartz filters (PALL Pallflex Inc., Ann Arbor, MI, USA) with diameters of 90 mm were baked at 550 °C in programmable furnace (NEY 2-525 Series II, USA) for at least 6 h. Airborne $PM_{2.5}$ samples were collected at a constant flow rate of 100 L/min for 24 h, by the use of a moderate-volume $PM_{2.5}$ sample collector (TH-

150C, Wuhan Tianhong Instrument Co., Ltd., China). Totally, 132 samples were collected from Guangzhou (26), Shanghai (37), Beijing (35) and Harbin (34). Before and after collection, quartz filters were weighed on a high-resolution balance (T-214, Denver Instrument, USA). Concentrations of $PM_{2.5}$ in airborne were calculated from the volume of air samples and masses of $PM_{2.5}$. Filters were stored at −20 °C until analysis.

2.3. Quantification of PAEs

Methods for identifying and quantifying PAEs have been described previously (Wang et al., 2015). Briefly, one eighth of quartz filter was transferred into a 10 mL glass tube and then extracted with 5 mL acetone by ultrasound (350 W, below 30 °C) for 20 min. 4 mL extracts were transferred into 5 mL glass tube and concentrated under a gentle stream of nitrogen (5 L/min, below 30 °C) until they were nearly dry. The residual was reconstituted by 1 mL methanol and passed through a 0.22 μm GHP membrane (Waters, Milford, MA, USA). The filter was then diluted 10-fold to instrument analysis.

PAEs were determined using a triple quadrupole mass spectrometer (API4000, AB SCIEX, Framingham, USA) equipped with a high performance liquid chromatography (I Class, Waters, USA). ACQUITY CSH TMFluoro-Pheny column (100 mm × 2.1 mm, 1.7 μm, Waters, USA) was chosen to separate PAEs. Column oven temperature was set at room temperature. Methanol and purified water were used as mobile phases with the following gradients: 0–1.5 min, 50% methanol; 2.5–9 min, 70% methanol; 9.5–14 min, 80% methanol; 18.5–20 min, 95% methanol; 21–26 min, 50% methanol. Aliquots of 3 μL of extracts were injected. The flow rate of mobile phase was 200 μL/min. The details about MS parameters are given in Table S2. Quantification was done by comparing areas of peaks at appropriate retention times and of appropriate *m/z* for selected ions and transition ions to external standards. Quantitative ions and qualitative ions of target PAEs were showed in Table S3. Calibration standards were freshly prepared for every batch of sample analysis, with six concentrations ranging from 0.1 to 200 ng/mL.

2.4. Quality assurance and quality control

Because an external standard was used for quantification and PAEs tend to be ubiquitous contaminants in reagents and laboratories, rigid quality control (QC) was necessary. For each batch of 24 samples analyzed, a method blank (with blank filter) and two blank quartz filter spiked with target standards with known amounts of 10 ng and 100 ng, were analyzed the same as extracts of airborne $PM_{2.5}$ on glass fiber filters. As showed in Table S4, the recoveries of target analytes in matrix-spiked sample of 10 ng and 100 ng were 79.8–109% and 98.9–124%, respectively. The relative standard deviations were all below 21.2%. The limits of detection (LOD) were calculated as a signal-to-noise ratio of 3 and ranged from 0.02 to 0.4 ng/m^3. Correlation coefficients (r) values of the standard curves were all above 0.995. The samples with analytes concentrations below the detection limits were assigned zero values for the following data analysis. Concentrations of PAEs in blank samples, including pipette tips, filters and other plastic materials used, were all less than the LOD. All glassware was rinsed three times with tap water, purified water and methanol, and then baked in a muffle furnace at 450 °C for 6 h prior to use. An isolator column was used to separate contamination with DEHP and DBP in the mobile phase from these analytes in samples.

2.5. Estimation of daily intakes and hazards posed by exposure to PAEs

To assess potential adverse effects of PAEs on people breathing air containing $PM_{2.5}$, hazard quotients (HQs) were calculated for individual PAEs as well as for total concentrations of PAEs. HQs were calculated as the ratio of EDIs and reference limits of PAEs. To assess potential effects of the total exposure to phthalates, instead of using relative potency values for individual PAEs, a hazard index (HI) was calculated as the sum of HQs of individual PAEs. In this scheme, if values of HQs or HI exceeded 1, it was concluded that exposures to PAEs surpassed the tolerable level, indicating potential effects on the people in the four reference cities. EDIs were calculated (Eq. (1)) and then compared with reference doses proposed by U.S. EPA and EFSA. In the present study, since the selected reference limits for inhalation exposure of PAEs were not available, the reference doses (RfDs) for oral exposure proposed by U.S. EPA and tolerable daily intakes (TDIs) suggested by EFSA were used to estimate the HQs and HI values of PAEs exposure. Reference doses (RfDs) were 20 μg/kg /day for DEHP, 100 μg/kg /day for DBP, and 800 μg/kg/day for DEP. TDIs for DEHP and DBP were 50 μg/kg/day and 10 μg/kg/day, respectively (Zhang et al., 2014). Moreover, DEHP exposure was considered for LADD and ILCR assessment (Eqs. (2) and (3)) because this compound has carcinogenic potency. LADD and ILCR models quantitatively estimate the risk for four age groups, group 1: infants (0 to<2 years), group 2: toddlers (3 to<6 years), group 3: adolescents (7 to 17 years) and group 4: adults (17 to<70 years).

$$\mathrm{EDIs} = (\mathrm{C} \times \mathrm{IR} \times \mathrm{f}_1)/\mathrm{Bw} \tag{1}$$

$$\mathrm{LADD} = [(\mathrm{C} \times \mathrm{IR} \times \mathrm{ET} \times \mathrm{EF} \times \mathrm{ED})/(\mathrm{Bw} \times \mathrm{AT})] \times \mathrm{CF} \tag{2}$$

$$\begin{aligned} 70\text{−years ILCR} = {} & (\mathrm{LADD}_{\mathrm{Infants}} \times \mathrm{CPF} \times \mathrm{ASF}_{\mathrm{Infants}} \times 2/70) \\ & + (\mathrm{LADD}_{\mathrm{Toddlers}} \times \mathrm{CPF} \times \mathrm{ASF}_{\mathrm{Toddlers}} \times 4/70) \\ & + (\mathrm{LADD}_{\mathrm{Adolescents}} \times \mathrm{CPF} \times \mathrm{ASF}_{\mathrm{Adolescents}} \times 10/70) \\ & + (\mathrm{LADD}_{\mathrm{Adults}} \times \mathrm{CPF} \times \mathrm{ASF}_{\mathrm{Adults}} \times 54/70) \end{aligned} \tag{3}$$

where EDIs, LADD and ILCR are the estimations of daily intakes, lifetime average daily doses and incremental lifetime cancer risk, respectively. In Eq. (1), C is sum of the PAEs concentrations (ng/m^3) in both particle and gas phase concentrations. IR is inhalation rate (m^3/d). f_1 is the exposure fraction in outdoor. Bw is body weight (kg). In Eqs. (2) and (3), IR is inhalation rate (m^3/h). EF is exposure frequency (day/year). ED is exposure duration (year). CF is a conversion factor (10^{-6}). AT is the average span time (day). CPF is cancer potency factor, which is 0.014 (mg/kg/d)$^{-1}$ for DEHP from database of IRIS. ASF is age sensitivity factor. All demographic data and exposure factors are referred from The Exposure Factors Hand Book of the Chinese Population (EFHC) and described in Table S5.

2.6. Statistical methods

Statistical analysis was performed using SPSS software version 17.0. The comparison of concentration of total PAEs among different metropolitan cites, and between warm and cold seasons was performed by non-parametric test of Kruskal-Wallis H-Test and Mann-Whitney *U* Test, respectively. Principle Component Analysis (PCA) and significance test of phthalates concentration in warm and cold seasons were conducted by R software version 3.5.2 using basic Prcomp function and Adonis function in "vegan" package. Figures were illustrated by "ggplot2" package. $p<0.05$ was defined as statistically significant.

3. Results and discussion

3.1. Detection rates of PAEs in $PM_{2.5}$

Gas chromatography tandem mass spectrometry (GC–MS/MS) is generally considered as a suitable method for quantitative PAEs in both outdoor and indoor atmospheres (Ma et al., 2014). However, in the present study, LC-MS/MS was introduced, for the first time, to determine PAEs compounds in airborne $PM_{2.5}$. Detection rates of four phthalates of DEP, DMP, DBP and DEHP were 0%, 53.8%, 100% and 100% in Guangzhou, 5.4%, 35.1%, 70.3% and 100% in Shanghai, 14.3%,

40%, 77.1% and 100% in Beijing, and 20.6%, 82.4%, 64.7% and 100% in Harbin, respectively (Fig. S2). In all 132 samples, detection rates of DEP, DMP, DBP and DEHP were 10.6%, 52.3%, 76.5% and 100%, respectively. DMP, DBP and DEHP had the detection rates of >50%, and rates of detection from greater to lesser were: DEHP>DBP>DMP, which indicated that these compounds are widely distributed in $PM_{2.5}$ in the airborne of the four urban areas studied in China. Several previous studies focused on airborne PM in Chinese cities of with >10 million residents such as Beijing, Shanghai and Tianjin showed similar results (Chen et al., 2018; Ma et al., 2014; Zhang et al., 2014). For example, during 2011 and 2012, nine PAEs were studied in airborne of Shanghai. Results of that study demonstrated that BzBP, DIBP, DMP, DEP, DBP and DEHP were observed with rates of detections ranging from 56% to 100% (Ma et al., 2014). BBP, DNOP, DMP, DEP, DBP and DEHP were found in ambient air of Tianjin (Zhu et al., 2016). Similarly, DMP, DEP, DBP, DEHP, DNOP and BBP were detected in both indoor and outdoor airborne $PM_{2.5}$ of Beijing (Chen et al., 2018). However, compared with those studies, only four PAEs, namely DEP, DMP, DBP and DEHP, were detected in our study. This might be due to that the gas volume of each sample in previous studies was larger than those obtained in our study, suggesting that when detecting pollutants in air, a larger sampling volume is needed. Altogether, multiple PAEs were present in a wide geographic range over a long period, which indicated that ambient air in major Chinese cities has persistent contamination by PAEs, among which, DMP, DEP, DEHP and DBP are predominant compounds in $PM_{2.5}$.

3.2. Concentrations of PAEs in $PM_{2.5}$

Four cities showed similar trends of PAEs concentrations (Fig. 1 and Table S6). The maximum concentration of DMP in Guangzhou, Shanghai, Beijing and Harbin were 0.7, 0.4, 2.4 and 6.4 ng/m^3, respectively, and DMP concentration in Harbin was 16 times higher than that in Shanghai. The maximum concentrations of DBP were 47.7, 52, 39.1 and 204 ng/m^3 in Guangzhou, Shanghai, Beijing and Harbin, respectively. Harbin had the highest concentration of DBP, which was 5.2-folds higher than the city of Beijing where concentrations were the least. Harbin also had the maximum concentration of DEP, which was 1.2 ng/m^3, followed by Beijing (0.9 ng/m^3), Shanghai (0.5 ng/m^3) and Guangzhou (not detected). The maximum concentration of DEHP was 456 ng/m^3 in Harbin.

DBP has been used widely in latex adhesives, cosmetics and personal care products, and in 2006, production of DBP used as plasticizers in China is >47.7 kt. DEHP was applied extensively in PVC plastics, building products, clothing, food packaging, children's products and medical devices. In the present study, DBP and DEHP were the prevalent PAEs in airborne $PM_{2.5}$. DEHP was dominant in Shanghai, Beijing and Harbin, contributing >50% of the mass of PAEs in $PM_{2.5}$. Whereas in Guangzhou, concentrations of DBP and DEHP $PM_{2.5}$ were almost the same. Results of this study were consistent with those of previous studies (Chen et al., 2018; Lan et al., 2012; Ma et al., 2014). This is likely due to the fact that DBP and DEHP are the PAEs most widely used in plastics, and are not covalently bound to polymeric matrixes, leading to their extensive emissions to air in more developed cities.

Ranges (means) of total concentrations of PAEs in air (ng/m^3) of the four cities were 32.5–76.1 (59.1) in Guangzhou, 10.1–101 (50.8) in Shanghai, 8.02–107 (43.8) in Beijing, and 13.5–622 (136) in Harbin. According to a previous study (Zhang et al., 2016), productions of PAEs in Guangzhou, Shanghai, Beijing and Harbin were 405, 100, 43 and 0 kt per year, respectively. It was also reported that in densely populated areas, PAEs in outdoor air came mainly from indoor sources. Besides industrial emissions, population was also a vital factor for predicting emissions of PAEs because the number of people is significantly correlated with the consumption of plastic products. Numbers of residents in these four cities in decreasing rank order were: Shanghai (24.2 million) > Beijing (21.7 million) > Guangzhou (14 million) > Harbin (10.7 million). Hence, taken together, this information indicates that concentrations of PAEs in Harbin should be the least among the four cities. However, in contrast, the highest concentrations of PAEs were observed in Harbin, with concentrations ranging from 13.5 to 622 ng/m^3, while concentrations of PAEs associated with $PM_{2.5}$ in air of the three other cities were similar. It is thought that factories in Harbin released more PAEs, however, this unexpected finding in the present study revealed that PAEs in Harbin might not only come from industrial emissions. In industrial areas, pollution of local areas usually could result in larger

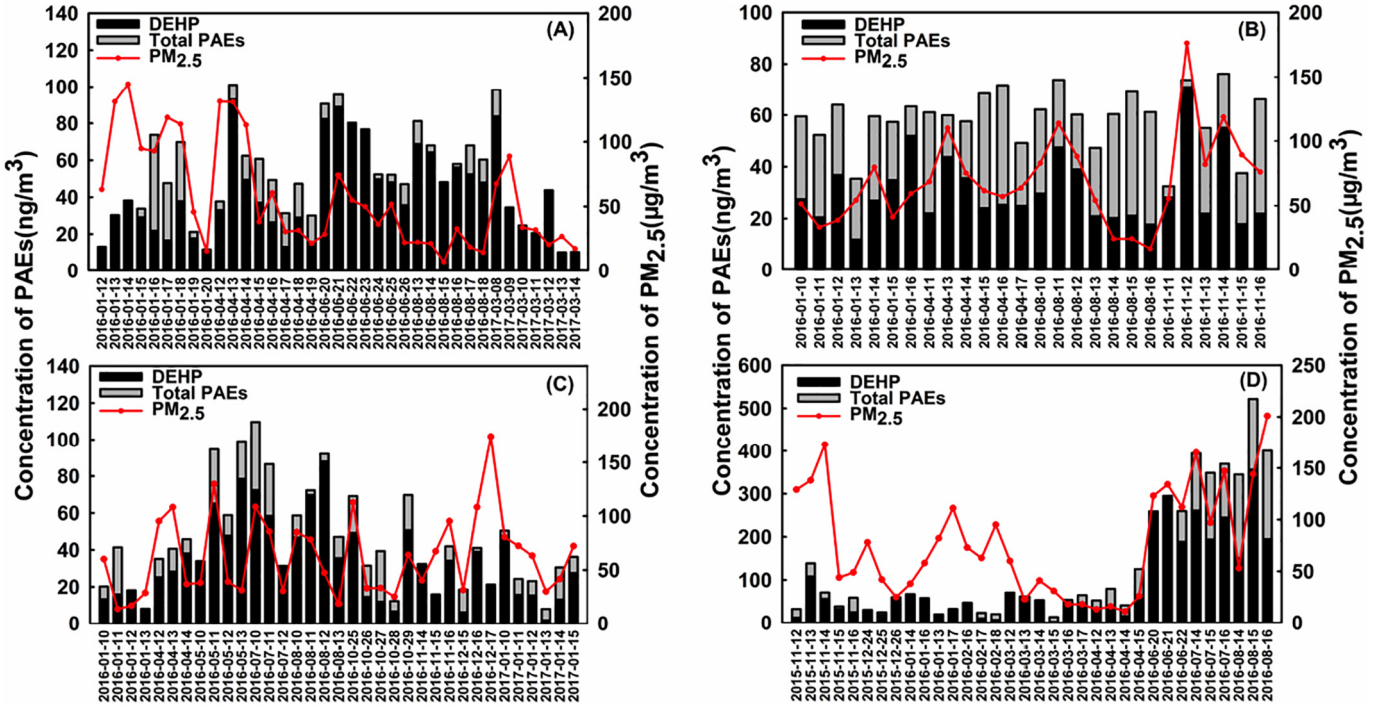

Fig. 1. The concentrations of $PM_{2.5}$ (μg/m^3), total PAEs (ng/m^3) and DEHP (ng/m^3) in outdoor air of four cities of (A) Guangzhou, (B) Shanghai, (C) Beijing, and (D) Harbin between November 2015 to March 2017.

concentrations of PAEs in ambient environments. Nevertheless, concentrations of PAEs in water of an urban lake, river, sewage treatment plant and sediments of Shanghai, Beijing and Guangzhou were higher than those in Harbin. This result could be explained by several factors: 1) atmospheric PAEs were washed out more in southern than in northern regions since the amount and frequency of rainfall were greater in southern China, and/or 2) PAEs in air might be transferred from lower latitudes (e.g. Guangzhou) to higher latitudes (e.g. Harbin). However, data for long-range transport and atmospheric precipitation of PAEs in China are limited.

The concentrations of the sum of PAEs in $PM_{2.5}$ were as great as 341 ng/m^3 and 186 ng/m^3 of Shanghai in 2003 (Wang et al., 2006) and 2014 (Ma et al., 2014), and concentrations were as great as 125 ng/m^3 in Beijing at 2015 (Chen et al., 2018). Total concentrations of PAEs reported here were less than those reported in earlier reports, indicating that concentrations of PAEs in $PM_{2.5}$ in the air of both Shanghai and Beijing have decreased during the past several years. Nevertheless, total concentrations of PAEs in major cities of China were still several times higher than those in other more developed countries, such as the U.S. (37 ng/m^3), France (39 and 57 ng/m^3), Greece (21 ng/m^3), Netherlands (12 ng/m^3) and Germany (20 ng/m^3) (Fromme et al., 2010; Gaspar et al., 2014; Peijnenburg and Jaap, 2006; Salapasidou et al., 2011; Teil et al., 2006; Teil et al., 2016). Hence, although great efforts have been made by the Chinese government, air pollution in China is an ongoing challenge.

3.3. Correlation between concentrations of PAEs on $PM_{2.5}$ and $PM_{2.5}$ in air

No significant correlations were observed between total concentrations of PAEs, DEHP, DBP, DMP and DEP, with mass concentrations of $PM_{2.5}$ in air of Shanghai, Beijing or Harbin. However, concentrations of DBP and DEHP on $PM_{2.5}$ were positively correlated with concentration of $PM_{2.5}$ in air of Guangzhou ($p < 0.05$), which is situated in southern China where temperatures change less among seasons than that of the other three cities. Meanwhile, a similar correlation between concentrations of PAEs on $PM_{2.5}$ with masses of $PM_{2.5}$ in air was observed during the warmer season, from April to October, in Beijing and Shanghai. This finding was similar to that of a previous study (Ma et al., 2014) and indicates that adsorption of PAEs on $PM_{2.5}$ are influenced by ambient temperatures.

3.4. Seasonal changes of PAEs

Concentrations of the sum of the four PAEs ($\sum$PAEs) varied between the warmer season (April to October) and the colder season (November to March) in four cities (Fig. 2). During the warmer season concentrations of PAEs were higher with means of 61.5 ± 7.83, 62.4 ± 20.1, 59.8 ± 21.7 and 276 ± 167 ng/m^3 in Guangzhou, Shanghai, Beijing and Harbin, respectively, than they were during the colder season of 56.4 ± 13.9, 36.2 ± 25.5, 28.9 ± 12.6 and 53.5 ± 27.6 ng/m^3, respectively (Fig. 2). A similar pattern was reported for Shanghai and Beijing (Ma et al., 2014; Wang et al., 2006). PAEs are semi-volatile chemicals, which can be released into the air from polymeric matrixes, its release from indoor appliances and outdoor architectural structures would likely increase as a function of temperature. Relatively greater amounts of PAEs were released during warmer seasons than colder seasons. Therefore, PAEs were found to be more abundant in warmer season than colder season in this study, probably due to enhanced vaporization from plastics followed by adsorptive deposition on the pre-existing particles. Although it is reported that atmospheric PAEs can be removed fairly rapidly by photochemical reactions with free radicals and rainfall during warmer seasons, PAEs were still higher during warmer months. This result states clearly that the total emission of PAEs in warmer season were much more than in colder season. Moreover, in comparison of the $\sum$PAEs concentration in different seasons, an interesting result was found that $\sum$PAEs in Guangzhou in warmer season was slightly higher than that in colder season, and it was significantly higher than those in other three cities. It is because of the fact that the less temperature

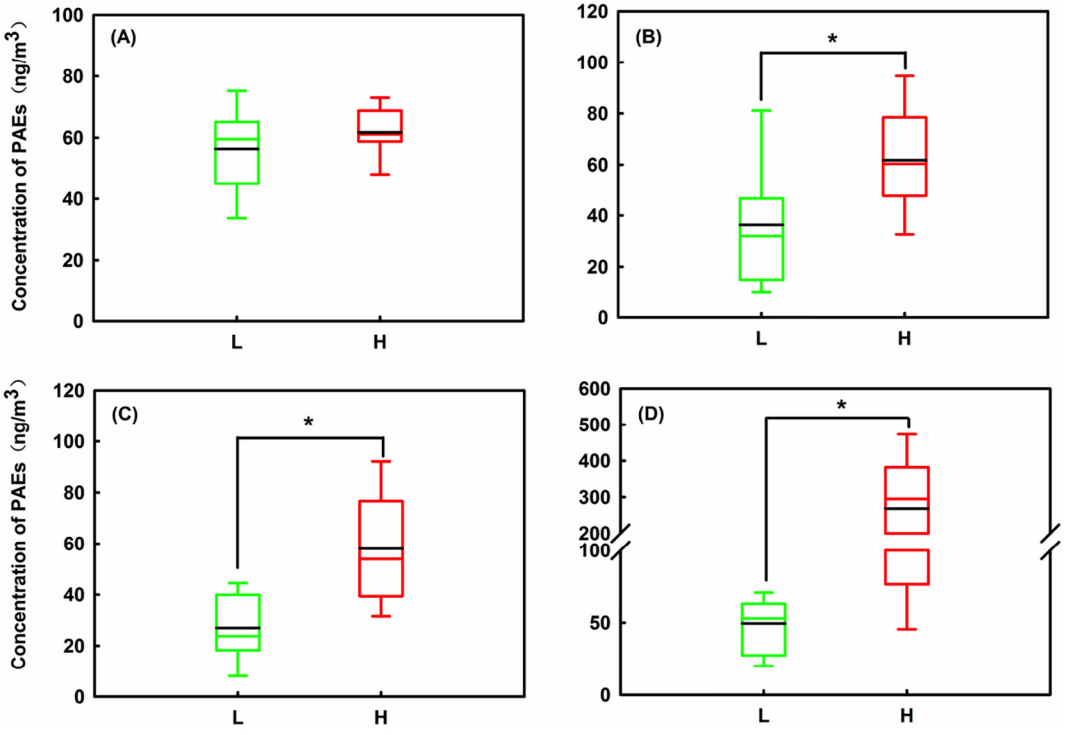

Fig. 2. PAEs concentrations (ng/m^3; sum of 14 PAEs) in $PM_{2.5}$ in cold season (Low temperature, L) and warm season (High temperature, H) in four cities of (A) Guangzhou, (B) Shanghai, (C) Beijing, and (D) Harbin between November 2015 and March 2017. Whisker boxplots showed the range between 25% and 75% percentiles. Colored and black lines in whisker boxes indicate the median and mean, respectively. Asterisks indicate statistically significant (p<0.05) higher concentrations in warm season than in cold season. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

change during warmer season and colder season in Guangzhou, suggesting that temperature is an important factor which can promote emissions of PAEs from building products, such as plastics and paints.

3.5. Verification of gaseous PAEs

Inhalation is the main route of exposure of humans to PAEs in air. Semi-volatile chemicals, such as poly brominated diphenyl ethers (PBDEs), PAHs and PAEs, in both indoor and outdoor airborne PAEs are present as both gas and particulate phases (Lyu et al., 2015; Sangiorgi et al., 2014). Thus, for achieving an accurate exposure data to the residents, it is necessary to determine the total concentrations of PAEs in both particle-bound and gaseous phases. In the present study, concentration of PAEs in the gas phase was estimated by the use of previously developed methods (Ma et al., 2014; Zhang et al., 2014) (Eqs. (4) and (5)).

$$C_g = \frac{F/PM}{K_p} \quad (4)$$

$$\log K_p = m_r \log P_L^0 + b \quad (5)$$

In Eq. (4), C_g is the concentration of vapor phase PAEs (ng/m^3), F is the concentration of particle-bound PAEs, PM is the mass concentration of $PM_{2.5}$ (μg/m^3) according to the study (Chen et al., 2018). Kp (m^3/μg) is the gas-particle distribution coefficient, which can be calculated (Eq. (5)). In Eq. (5), values of $m_r = -0.0738$ and $b = -2.74$ were obtained from results of a previous study (Wang et al., 2008), and $\log P_L^0$ for DEP, DMP, DBP and DEHP were −0.56, −0.27, −1.8 and −4.72, respectively, which were obtained from the study for PAEs in ambient air of China (Ma et al., 2014).

Calculated gaseous concentrations of the four PAEs (Table S7) were significantly higher than concentrations in particle phase. Concentrations of gaseous DMP, DEP, DBP and DEHP were 9.8–12, 6.7–12, 6.8–10.7 and 3.5–6.9 times higher than the mean concentration in the particle phase, respectively. Similar trends were reported by the study of Ma et al. (2014) and Zhang et al. (2014), which demonstrates that PAEs were primary in the gas phase.

3.6. EDI, HQ and HI of PAEs

The EDI values of four PAEs were shown as mean value in Table 1. The total EDIs of the sum of the four PAEs of infants, toddlers, adolescents and adults were ranged from 22.3–52.2, 30.7–78.0, 19.2–49.5 and 9.3–23.5 ng/kg/d, respectively. Infants, toddlers, and adolescents experienced higher exposure to PAEs via inhalation, and their exposure level was 2–3.3 times higher than those of adults, which was mainly attributed to their smaller body mass. Among the four cities, the highest EDI was observed for Harbin, due to its higher concentrations of PAEs in particle and gas phases. EDIs for DMP and DEP were significantly less than those of DBP and DEHP in outdoor air of all cities. DBP and DEHP accounted for 23.1%–62.8% and 36.8%–76.7% of the total EDIs of four detectable PAEs in the four cities (Fig. 3). According to the EDI values of PAEs among four cities, DEHP was the most abundant PAEs in terms of exposure in Shanghai, Beijing and Harbin, while DBP was the abundant one in Guangzhou.

Maximum of HQs and HI values were 1.5×10^{-2} and 1.7×10^{-2} for children, and 1.0×10^{-2} and 1.2×10^{-2} for adult, respectively. The values were <1, indicating that hazards and risks were *di minimis* (Table 2). The HI values were calculated base on the levels PAEs metabolites in urine of children and adult, which found that 155 of 782 children and 43 of 108 adults had high HI values exceeding 1, and 54.8% of adult females had HI values exceeding 1 compared with 30.3% of adult males (Gao et al., 2016; Wang et al., 2015). This finding indicates that inhalation in outdoor may not be the main source of PAEs exposure, because it only contributed approximately 1% of HI value based on previous studies. As such, our study may underestimate the exposure dose of PAEs because the value of EDI was based on the concentration of $PM_{2.5}$ and did not include other exposure routes, such as ingestion and skin intakes.

3.7. Carcinogenic risk assessment for inhalation exposure to DEHP

DEHP has been reported to exhibit carcinogenic potency (Guyton et al., 2009) and there was no evidence of carcinogenic potencies for the other PAEs. Besides, previous study has indicated that by dividing the particulate-phase PAEs into four size ranges (<2.5, 2.5–5, 5–10 and >10 μm), PAEs in $PM_{2.5}$ turn out to be the most abundant, with the proportion of 72.6% (Song et al., 2015). Moreover, when inhaled by humans, $PM_{2.5}$ can penetrate deeper into the lungs and also be more retained, which can result in associated chemicals reaching circulation leading to adverse effects, indicating that it is necessary to assess the carcinogenic risk for inhalation exposure to DEHP which bound to $PM_{2.5}$. Thus, the LADD and ILCR were used to assess the carcinogenic risk for inhalation exposure to DEHP. The exposure dose and risk were quantitatively estimated for four age groups of infants, toddlers, adolescents and adults.

As shown in Table S8, LADD value of DEHP of four cites were ranged from 1.0×10^{-6}-1.0×10^{-4} mg/kg/d, and stratified by age and ranking of exposure dose in a decreasing order where

Table 1
Estimated daily intakes (EDIs) of selected phthalate from air inhalation (mean value as ng/kg/d) in four cities of China.

City	Age group	DMP		DEP		DBP		DEHP		∑PAEs	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Guangzhou	Infant	0.120	0.116	ND	ND	19.02	18.43	11.14	10.79	30.28	29.34
	Toddler	0.188	0.180	ND	ND	29.83	28.48	17.47	16.67	47.49	45.33
	Adolescent	0.121	0.109	ND	ND	19.20	17.28	11.24	10.12	30.57	27.50
	Adult	0.056	0.053	ND	ND	8.893	8.459	5.507	4.953	14.16	13.47
Shanghai	Infant	0.019	0.018	0.047	0.046	6.973	6.738	23.13	22.35	30.16	29.15
	Toddler	0.027	0.026	0.068	0.066	9.958	9.649	33.02	31.99	43.07	41.74
	Adolescent	0.017	0.015	0.044	0.039	6.516	5.757	21.61	19.09	28.19	24.90
	Adult	0.008	0.008	0.020	0.020	3.123	2.938	10.36	9.744	13.51	12.71
Beijing	Infant	0.325	0.319	0.083	0.081	7.481	7.342	14.85	14.57	22.74	22.32
	Toddler	0.475	0.439	0.121	0.112	10.93	10.09	21.70	20.03	33.26	30.68
	Adolescent	0.312	0.275	0.079	0.070	7.178	6.321	14.25	12.55	21.81	19.21
	Adult	0.145	0.134	0.037	0.034	3.333	3.073	6.614	6.099	10.13	9.339
Harbin	Infant	0.074	0.072	1.757	1.717	21.44	20.94	28.88	28.21	52.15	50.94
	Toddler	0.110	0.105	2.628	2.507	32.05	30.58	43.19	41.20	77.97	74.40
	Adolescent	0.070	0.063	1.670	1.497	20.36	18.26	27.44	24.60	49.54	44.42
	Adult	0.033	0.032	0.792	0.762	9.665	9.300	13.02	12.53	23.51	22.62

ND: not detected.

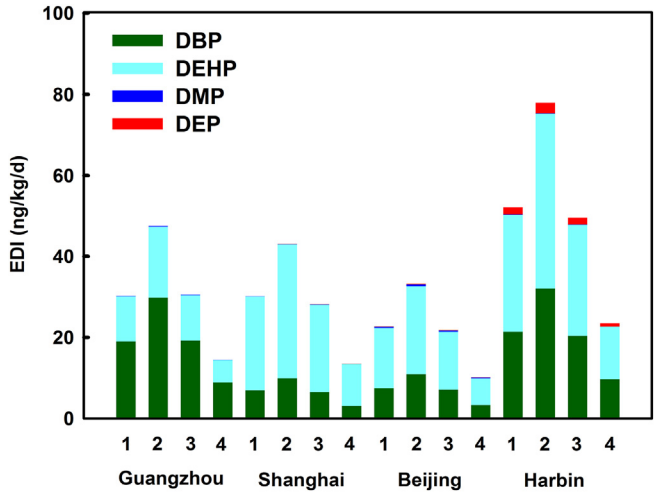

Fig. 3. Compositions of estimated daily intake (EDI) of phthalate in four age groups from four cities. 1: infant, 2: toddler, 3: adolescent, and 4: adult.

toddlers>infants>adolescents>adults, with the values of 3.1×10^{-7}-1.0×10^{-4}, 2.3×10^{-7}-7.0×10^{-5}, 1.9×10^{-7}-6.4×10^{-5} and 1.0×10^{-7}-3.2×10^{-5} mg/kg/d, respectively. Males were exposed to higher doses than females in all four cities, which might be due to the higher inhalation rate of males than females. The ILCR values of different age groups for four cities are ranged widely with a decreasing order as follows: adolescents (1.1×10^{-9}-3.8×10^{-7}) >adults (1.1×10^{-9}-3.4×10^{-7}) >infants (9.0×10^{-10}-2.8×10^{-7}) >toddlers (7.5×10^{-10}-2.4×10^{-7}) (Table 3 and Fig. 4). As specified by US EPA, within a 70-year lifetime, a one-in-a-million chance of developing cancer (ILCR = 10^{-6}) is considered to be "acceptable", and a lifetime, risk of additional cancer of one in ten thousand or greater (ILCR = 10^{-4}) is considered to be "serious". In the present study, the ILCR values for all age groups in four cities were all $<10^{-6}$, meaning that risks of cancers associated with inhalation of DEHP in both gaseous and $PM_{2.5}$ were acceptable. Nevertheless, it is noteworthy that the highest values of total 70-years ILCR in Shanghai and Harbin were 1.2×10^{-6} and 1.3×10^{-6}, which were slightly higher than the acceptable level of 10^{-6}. These results remind us that the cancer risk of DEHP in atmosphere in these cities should be paid much more attention. Higher ILCR values for adolescents and adults might be due to longer durations of exposure than the other two age groups. The study concern on the cancer risk assessment of PAEs in outdoor was very rare. Ma et al. (2014) proved that the carcinogenic risk value of PAEs exposure to people from Shanghai was $<10^{-6}$. However, in this study, we found that approximately 8% of ILCR value associated with inhalation of airborne DEHP were over the acceptable level in Shanghai. The main reasons were that when calculated cancer risk, the age susceptibility factor was taken into considered and we also used Chinese exposure parameters for evaluating the cancer risk of Chinese in the present study.

When carcinogenic risk associated with inhalation of DEHP in indoor air of China was assessed during a previous study, the values of ILCR for children and adolescents were several times higher than 10^{-6} (Pei et al., 2013). As we know, PAEs are not chemically bound to products and can be easily released into the indoor environment. The major sources of PAEs in indoor include plastic products, curtain, hand-wipes and decorated materials. Thus, DEHP concentration in indoor air is usually higher than that in outdoor (Saini et al., 2015; Tran et al., 2016; Zhang et al., 2014). In fact, people spent more time in indoor than in outdoor. Thus, the inclusion of indoor airborne of DEHP exposure may increase the cancer risk of DEHP exposure. Moreover, dietary, dust ingestion and

Table 2
Hazard Quotients (HQ) and Hazard Indexes (HI) Based on TDI (EFSA) and RfD (US EPA) for children and adult.

Phthalate	HQ_{TDI}				HQ_{RfD}			
	Guangzhou	Shanghai	Beijing	Harbin	Guangzhou	Shanghai	Beijing	Harbin
Infant								
DEP	–	–	–	–	ND	0.0–5.4×10^{-7}	0.0–1.3×10^{-6}	0.0–9.1×10^{-7}
DBP	6.3×10^{-5}-7.7×10^{-3}	0.0–2.6×10^{-3}	0.0–5.4×10^{-3}	0.0–1.1×10^{-2}	6.3×10^{-6}-7.7×10^{-4}	0.0–2.6×10^{-4}	0.0–5.4×10^{-4}	0.0–1.1×10^{-3}
DEHP	9.0×10^{-5}-4.0×10^{-4}	7.1×10^{-5}-1.3×10^{-3}	2.3×10^{-5}-1.1×10^{-3}	4.3×10^{-6}-1.4×10^{-3}	2.3×10^{-4}-1.0×10^{-3}	1.8×10^{-4}-3.2×10^{-3}	5.8×10^{-5}-2.7×10^{-3}	1.1×10^{-5}-3.4×10^{-3}
HI	3.0×10^{-4}-8.1×10^{-3}	8.7×10^{-5}-3.9×10^{-3}	7.1×10^{-5}-5.9×10^{-3}	9.0×10^{-5}-1.3×10^{-2}	3.0×10^{-4}-1.8×10^{-3}	2.2×10^{-4}-3.4×10^{-3}	8.9×10^{-5}-2.8×10^{-3}	1.2×10^{-4}-4.1×10^{-3}
Toddler								
DEP	–	–	–	–	ND	0.0–7.7×10^{-7}	0.0–1.9×10^{-6}	0.0–1.4×10^{-6}
DBP	9.7×10^{-5}-1.2×10^{-2}	0.0–3.7×10^{-3}	0.0–8.0×10^{-3}	0.0–1.7×10^{-2}	9.7×10^{-6}-1.2×10^{-3}	0.0–3.7×10^{-4}	0.0–8.0×10^{-4}	0.0–1.7×10^{-3}
DEHP	1.4×10^{-4}-6.3×10^{-4}	1.0×10^{-4}-1.8×10^{-3}	3.2×10^{-5}-1.6×10^{-3}	6.3×10^{-6}-2.0×10^{-3}	3.5×10^{-4}-1.6×10^{-3}	2.5×10^{-4}-4.5×10^{-3}	7.9×10^{-5}-3.9×10^{-3}	1.6×10^{-5}-5.1×10^{-3}
HI	4.6×10^{-4}-1.3×10^{-2}	1.3×10^{-4}-5.5×10^{-3}	9.8×10^{-5}-8.6×10^{-3}	1.3×10^{-4}-1.9×10^{-2}	4.7×10^{-4}-2.8×10^{-3}	3.1×10^{-4}-4.9×10^{-3}	1.2×10^{-4}-4.1×10^{-3}	1.7×10^{-4}-6.2×10^{-3}
Adolescent								
DEP	–	–	–	–	ND	0.0–5.0×10^{-7}	0.0–1.3×10^{-6}	0.0–8.6×10^{-7}
DBP	5.9×10^{-5}-7.8×10^{-3}	0.0–2.4×10^{-3}	0.0–5.2×10^{-3}	0.0–1.1×10^{-2}	5.9×10^{-6}-7.8×10^{-4}	0.0–2.4×10^{-4}	0.0–5.2×10^{-4}	0.0–1.1×10^{-3}
DEHP	8.5×10^{-5}-4.1×10^{-4}	6.1×10^{-5}-1.2×10^{-3}	2.0×10^{-5}-1.0×10^{-3}	3.8×10^{-6}-1.3×10^{-3}	2.1×10^{-4}-1.0×10^{-3}	1.5×10^{-4}-3.0×10^{-3}	4.9×10^{-5}-2.5×10^{-3}	9.4×10^{-6}-3.2×10^{-3}
HI	2.8×10^{-4}-8.2×10^{-3}	7.4×10^{-4}-3.6×10^{-3}	6.1×10^{-5}-5.6×10^{-3}	7.8×10^{-5}-1.2×10^{-2}	2.9×10^{-4}-1.8×10^{-3}	1.9×10^{-4}-3.2×10^{-3}	7.6×10^{-5}-2.7×10^{-3}	1.0×10^{-4}-3.9×10^{-3}
Adult								
DEP	–	–	–	–	ND	0.0–2.4×10^{-7}	0.0–5.9×10^{-7}	0.0–4.1×10^{-7}
DBP	2.9×10^{-5}-3.6×10^{-3}	0.0–1.2×10^{-3}	0.0–2.4×10^{-3}	0.0–5.2×10^{-3}	2.9×10^{-6}-3.6×10^{-4}	0.0–1.2×10^{-4}	0.0–2.4×10^{-4}	0.0–5.2×10^{-4}
DEHP	4.2×10^{-5}-6.0×10^{-4}	3.1×10^{-5}-1.8×10^{-3}	9.6×10^{-6}-1.4×10^{-3}	1.9×10^{-6}-1.9×10^{-3}	1.0×10^{-4}-4.7×10^{-4}	7.7×10^{-5}-1.4×10^{-3}	2.4×10^{-5}-1.2×10^{-3}	4.8×10^{-6}-1.5×10^{-3}
HI	1.4×10^{-4}-4.2×10^{-3}	3.8×10^{-5}-2.9×10^{-3}	3.0×10^{-5}-3.0×10^{-3}	4.0×10^{-5}-6.9×10^{-3}	1.4×10^{-4}-8.3×10^{-4}	9.5×10^{-5}-1.5×10^{-3}	3.7×10^{-5}-1.2×10^{-3}	5.2×10^{-5}-1.9×10^{-3}

Value showed as minimum to maximum. "–" means no reference intake limit. ND: not detected.

Table 3
The results of ILCR value ($\times 10^{-6}$) of four age groups and the total cancer risks of 70-years for all four cites.

City	Item	Infant		Toddler		Adolescent		Adult		70-years	
		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Guangzhou	Min	0.019	0.019	0.017	0.017	0.028	0.025	0.025	0.023	0.089	0.084
	Max	0.084	0.081	0.075	0.071	0.120	0.110	0.110	0.100	0.384	0.361
	Mean	0.046	0.045	0.042	0.040	0.067	0.060	0.059	0.056	0.214	0.201
	Median	0.044	0.043	0.039	0.038	0.064	0.057	0.056	0.053	0.202	0.190
Shanghai	Min	0.015	0.015	0.013	0.012	0.020	0.018	0.019	0.017	0.067	0.062
	Max	0.264	0.255	0.216	0.209	0.353	0.312	0.319	0.301	1.152	1.076
	Mean	0.096	0.093	0.079	0.076	0.129	0.114	0.117	0.110	0.420	0.393
	Median	0.062	0.060	0.051	0.049	0.083	0.073	0.075	0.071	0.271	0.253
Beijing	Min	0.005	0.005	0.004	0.004	0.007	0.006	0.006	0.006	0.022	0.020
	Max	0.221	0.217	0.184	0.170	0.303	0.266	0.266	0.264	0.973	0.917
	Mean	0.062	0.061	0.052	0.048	0.085	0.075	0.074	0.074	0.273	0.257
	Median	0.038	0.037	0.032	0.029	0.052	0.046	0.045	0.045	0.167	0.157
Harbin	Min	0.001	0.001	0.001	0.001	0.013	0.011	0.011	0.011	0.041	0.039
	Max	0.282	0.275	0.241	0.230	0.382	0.343	0.343	0.330	1.247	1.177
	Mean	0.120	0.118	0.103	0.098	0163	0.146	0.147	0.141	0.533	0.503
	Median	0.116	0.114	0.099	0.094	0.158	0.142	0.142	0.136	0.515	0.486

dermal intake have been proved to be three main routes of exposure to PAEs and inhalation route is accounted for a small proportion of total PAEs intake (Giovanoulis et al., 2017; Shi et al., 2012b; Wei et al., 2017). It should be noted that all the above exposure pathways are contributing to the DEHP exposure and risk of additional cancers, thereby the exposure risk of DEHP was under estimated to some extent. For instance, the carcinogenic risks of DEHP via the dietary route and dust ingestion ranged from 2.4×10^{-6} to 7.6×10^{-5} and 2.2×10^{-6} to 3.8×10^{-5} in Beijing and Guangzhou, respectively (C. Li et al., 2016; Wang et al., 2013). Meanwhile, the estimated daily dietary and water intake of DEHP were 1.6 μg/kg/d and 0.7 ng/kg/d, in Shanghai and Beijing, respectively (Guo et al., 2012; Li et al., 2018). Obviously, if all of the exposure pathways of PAEs are considered, the exposure risk of DEHP will be much more serious than what is now in the present study. In addition, toxic compounds, such as heavy metals and chlorinated compounds absorbed on the $PM_{2.5}$ play jointly with PAES in carcinogenicity. Taken together, although most of our evaluation results of ILCR were in an acceptable safe range ($<10^{-6}$), further investigations on the risk factors of DEHP in various exposure pathways are needed, and the potential of synergistic effect as well as the cancer risks between DEHP and other toxic compounds still need further assessment.

4. Conclusions

In the present study, LC-MS/MS was used, for the first time, to detect PAEs in airborne $PM_{2.5}$ from Guangzhou, Shanghai, Beijing and Harbin. DBP, DEHP, DEP and DMP were ubiquitous contaminants in outdoor air, and DBP and DEHP were the major PAEs in airborne $PM_{2.5}$ in urban air in China. Concentrations of the sum of the four detectable PAEs were significantly higher during the warmer season than colder season among all four cities. Concentrations of PAEs in Harbin were significantly higher than those in other cities where mean, maximum and minimum temperatures were greater. Studies are needed to determine sources of PAEs and airborne fine particles, especially $PM_{2.5}$, such

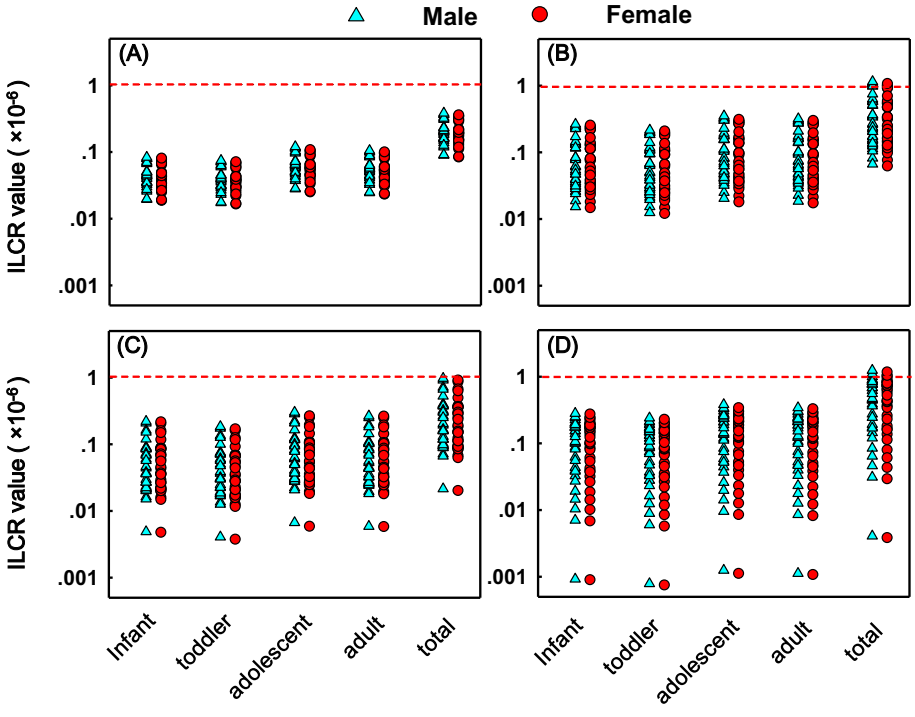

Fig. 4. The ILCR of four age groups and total cancer risks value ($\times 10^{-6}$) of phthalate in four cities. A: Guangzhou, B: Shanghai, C: Beijing, and D: Harbin.

information might help to take effective measures to improve air quality of China. Although the EDIs, HI and HQs of PAEs exposure to children were higher than those of adults, hazards and risks were less than reference values published by both US EPA and EFSA. The assessment for risks of additional cancers showed that 70-years ILCR values for inhalation of DEHP were above the target reference value given by US EPA (10^{-6}) in Shanghai and Harbin. Further studies are needed to focus on the air pollution of PAEs. Besides, given that other pathways such as dietary intakes and dust intakes also contributed to the health risk posed by PAEs, actual health risks from multi pathways should thus be taken into consideration using Chinese exposure parameters.

Acknowledgements

We thank the Public Welfare Program of National Health and Family Planning Commission of the People's Republic of China (No. 201402022), the Special Fund for Scientific Research in the Public Interest (No. 201309045) and the grant from the State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco Environmental Sciences (RCEES) of Chinese Academy of Sciences (KF2014-04) for this study. Prof. Giesy was supported by the Canada Research Chair Program of the Natural Sciences and Engineering Research Council of Canada. Although Dr. Tang was supported by the Start-up Funding from NIEH, China CDC, it has not been subjected to the peer and policy review from China CDC and therefore does not necessarily reflect the views of the China CDC and no official endorsement should be inferred.

Declaration of competing interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2019.133982.

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