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Co-exposure to polycyclic aromatic hydrocarbons and phthalates and their associations with oxidative stress damage in school children from South China

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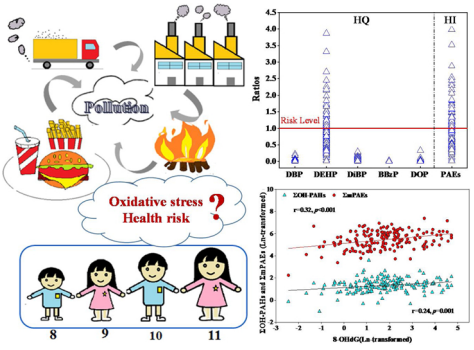
GRAPHICAL ABSTRACT



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ABSTRACT

Monohydroxylated polycyclic aromatic hydrocarbons (OH-PAHs), phthalate metabolites (mPAEs), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) in the urine of school children aged 8–11 years from Shenzhen, China were measured in order to investigate oxidative stress damage from co-exposure to PAHs and PAEs. The concentrations of OH-PAHs and mPAEs in urine were 0.36–36.5 (median: 3.86) and 9.48–1609 (median: 240) ng/mL respectively. Gender and age did not influence urinary concentrations of ΣOH-PAHs and ΣmPAEs, but geographical variations (i.e., urban versus suburban) were observed. Levels of 8-OHdG were positively correlated with urinary OH-PAHs and mPAEs, with correlation coefficients (r) varying between 0.160 and 0.365 ($p < 0.05$). OH-PAHs made a greater contribution to oxidative DNA damage than mPAEs when these two types of pollutants were present at the same concentrations. Human health risks were assessed using the hazard quotient and the hazard index for the cumulative risk of a complex of chemicals. The results demonstrated that risks from PAHs could be neglected, but that 29.5 % of school children may be subject to obvious health risks from PAEs, especially diethylhexyl phthalate.

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1. Introduction

Shenzhen is a city in China located on the eastern side of the Pearl River Delta. It is a Special Economic Zone and one of the most important industrial centers in China. Rapid economic growth and urban development in Shenzhen over the past 30 years have caused sharply increasing energy demands and massive annual gasoline consumption in this region, where air pollution has been aggravated. Liu et al. (2010) reported that airborne concentrations of polycyclic aromatic hydrocarbons (PAHs) in Shenzhen were significantly higher than at background sites in the Pearl River Delta. In addition, in our recent study (Lu et al., 2018a), we found that concentrations of atmospheric particulate-bound diethylhexyl phthalate (DEHP), a phthalate (PAE) compound, were higher in Shenzhen (59.9 ng/m^3) than in some European regions such as the Netherlands (median: 11.9 ng/m^3) and Paris (median: 5.2 ng/m^3) (Peijnenburg and Struijs, 2006; Teil et al., 2016). As reported, because PAEs are used in plastic food packaging, dietary intake was assumed to be a major source of human exposure (Muñoz et al., 2018).

PAHs are widely detected contaminants that originate from incomplete combustion of petroleum or fossil fuel and organic material (Wang et al., 2012). PAHs are well-known carcinogenic chemicals and have been prioritized as controlled pollutants in many countries. In human bodies, PAHs are metabolized into hydroxylated products, especially monohydroxylated PAHs (OH-PAHs), and then excreted in urine, mainly in the forms of glucuronide and sulfate conjugates (Klotz et al., 2011; Li et al., 2006). To assess human exposure to PAHs, urinary OH-PAHs have been widely used as biomarkers (Bortey-Sam et al., 2017; Wang et al., 2019).

Phthalates (PAEs) are well-known plasticizers that are widely used in plastics, cosmetics, and personal care products (Radke et al., 2018). They can easily migrate to food and the environment because they do not covalently bind to their host products (Hartmann et al., 2015; Münch et al., 2018). Following uptake, PAEs can be rapidly absorbed and metabolized through hydrolysis. Subsequently, the metabolites are oxidized and finally excreted in urine and feces (Hartmann et al., 2015). Many studies have found associations between children exposure to phthalates and adverse effects such as negative behavioral development and respiratory diseases (Boas et al., 2010; Bornehag and Nanberg, 2010; Wallner et al., 2016; Wang et al., 2018). High concentrations of DEHP metabolites were also observed to be significantly associated with autism and had negative impacts on the development of children's intelligence quotient (Factor-litvak et al., 2014; Testa et al., 2012). In addition, a DEHP metabolite, mono-(2-ethylhexyl) phthalate (mEHP), has been found to be possibly more toxic than its parent compound (Bamai et al., 2015). In the past ten years, di-iso-nonyl phthalate (DiNP) and DEHP were banned from use in child-care products in the European Union, the United States, and Japan because of their toxicity. Dibutyl phthalate (DBP) and benzyl butyl phthalate (BBzP) are also banned from cosmetics in the European Union.

To assess oxidative DNA damage in human bodies, 8-hydroxy-2′-deoxyguanosine (8-OHdG) is a useful biomarker. A number of studies have shown that occupational exposure to PAHs or DEHP can elevate the levels of 8-OHdG in urine (Wang et al., 2011; Wu et al., 2003). For example, Wang et al. (2011) observed significant positive correlations between urinary 8-OHdG levels in male workers working in waste plastic recycling and exposure to PAEs, and a history of exposure to PAEs was an independent risk factor for increased urinary 8-OHdG levels. A significant positive association between occupational PAH exposure and urinary 8-OHdG in diesel exhaust emission inspectors was found by Lee et al. (2012). However, there is only one report of human internal co-exposure to PAHs and PAEs, as monitored by their metabolites, OH-PAHs and mPAEs, respectively (Hou et al., 2019). The influence of co-exposure to PAHs and PAEs on 8-OHdG levels is still not well known. It is also unknown to what extent PAHs and PAEs contribute to oxidative DNA damage when human are co-exposed to these chemicals.

Therefore, the main objectives of this study were to: (1) investigate urinary concentrations of OH-PAHs and phthalate metabolites (mPAEs) among children attending four elementary schools in Shenzhen and their potential sources; (2) assess correlations between urinary concentrations of OH-PAHs (or mPAEs) and factors including age and gender of the participants and sampling region; (3) evaluate the relative contributions of the two types of contaminants to oxidative stress damage; and (4) estimate the associated human health risks from exposure to PAHs and PAEs as calculated from urinary concentrations of OH-PAHs and mPAEs, which are the metabolites of PAHs and PAEs respectively.

2. Materials and methods

2.1. Reagents and materials

The OH-PAH standards, including 9-hydroxyphenanthrene (9-OHPhe), 2-hydroxynaphthalene (2-OHN), 1-hydroxypyrene (1-OHP), 2-hydroxyfluorene (2-OHF), and 1-hydroxynaphthalene (1-OHN), were bought from Sigma (St. Louis, MO, USA). The 1-hydroxyphenanthrene (1-OHPhe) standard came from the University of Minnesota, and 2-hydroxyphenanthrene (2-OHPhe) and 4-hydroxyphenanthrene (4-OHPhe) were obtained from Dr. Ehrenstorfer (Augsburg, Germany). The 3-hydroxyphenanthrene (3-OHPhe) standard came from Cambridge Isotope Laboratories (Andover, MA, USA). Reference standards for mEHP, monomethyl phthalate (mMP), mono isobutyl phthalate (miBP), mono-*n*-butyl phthalate (mBP), and monoethyl phthalate (mEP) were bought from Accustandard (New Haven, CT, USA); monobenzyl phthalate (mBzP), monocyclohexyl phthalate (mCHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (mEHHP), mono-*n*-octyl phthalate (mOP), mono-(2-ethyl-5-oxohexyl) phthalate (mEOHP), mono-3-methyl-5-dimethylhexyl phthalate (iso-nonyl, mNP), and mono-3-methyl-7-methyloctyl phthalate (iso-decyl, mDP) came from Cambridge Isotope Laboratories (Andover, MA, USA). Fifteen isotopically labeled compounds used as internal standards were 8-OHdG-$^{15}N_5$ for 8-OHdG; 1-OHP-$^{13}C_6$, 3-OHPhe-$^{13}C_6$, 2-OHF-$^{13}C_6$, and 2-OHN-D_8 for OH-PAHs; and $^{13}C_2$-mEP, $^{13}C_2$-mEHP, $^{13}C_2$-mMP, $^{13}C_2$-mBP, $^{13}C_2$-mCHP, $^{13}C_4$-mEHHP, $^{13}C_4$-mEOHP, $^{13}C_2$-mNP, $^{13}C_2$-mOP, and $^{13}C_2$-mBzP for mPAEs. These internal standards were bought from Cambridge Isotope Laboratories (Andover, MA, USA).

Formic acid, methanol, and acetonitrile were purchased from Fisher Scientific (Houston, TX, USA), and β-glucuronidase/arylsulfatase (124400 β-glucuronidase units/mL, 36010 sulfatase units/mL) was bought from Sigma (St. Louis, MO, USA). Other analytical grade reagents were directly used without purification. C_{18} (ENVI, 500 mg/3 mL) and MAX (60 mg /3 mL) solid phase extraction (SPE) cartridges were obtained from Supelco (Bellefonte, PA, USA) and Waters (Milford, MA, USA), respectively.

2.2. Sample collection

The investigation was carried out in September 2015. Study subjects included 166 children (82 boys and 84 girls) aged 8–11 years from four elementary schools in Shenzhen (two from suburban regions, SZ01 and SZ02, and two in the central region of the city, SZ03 and SZ04) (Table S1; Fig. S1). The height and weight of each subject were measured and recorded. About 50 mL of spot urine sample was collected in a polyethylene bottle that had been cleaned with deionized water. To quantify the dilution of urine, the specific gravity of each urine sample was measured using a digital handheld refractometer (Atago, Bellevue, WA, USA). The collected urine samples were sent to the laboratory

immediately and stored at −20 °C for further analysis. The parents of each participant signed a consent form after being informed about the objectives and procedures of the present study. The studies were approved by the ethics committee of the School of Public Health (Shenzhen), Sun Yat-sen University.

2.3. Sample pretreatment and instrument analysis

The sample treatment for OH-PAHs and 8-OHdG was modified from a previously described procedure (Lu et al., 2016). In brief, a 5-mL urine sample was added to a glass tube, and 200 µL of a mixture of isotopically labeled internal standards including 2-OHN-D_8 and 2-OHF-$^{13}C_6$ at 100 µg/L, 3-OHPhe-$^{13}C_6$ at 10 µg/L, 1-OHP-$^{13}C_6$ and $^{5}N_5$ for 8-OHdG at 50 µg/L was spiked. The urine pH was adjusted to 5.0 with 0.1 M HCl, followed by addition of 1.5 mL 0.5 M acetate buffer (pH = 5.0). After 20 µL β-glucuronidase/arylsulfatase (124400 β-glucuronidase units/mL, 36010 sulfatase units/mL, from *Helix pomatia*) was added, the sample was hydrolyzed at 37 °C for 16 h avoiding light. The hydrolyzed samples were subsequently cleaned with a C_{18} solid phase extraction (SPE) cartridge. After sample loading at a flow rate < 1.0 mL/min, the cartridge was washed sequentially with 5 mL of deionized water and 5 mL of 30 % methanol. After the cartridge had dried completely, 4 mL of methanol were used to elute out the target analytes, and then the eluate was concentrated to 500 µL. The final solution was filtered with a 0.22-µm filter and stored at −20 °C until analysis.

The mPAE measurement in the present study was similar to a previously described protocol (Chen et al., 2019). Generally, a 1-mL sample was added to a centrifuge tube (10 mL), and then 20 µL of isotopically labeled internal standards including $^{13}C_2$-mMP, $^{13}C_2$-mEP, $^{13}C_2$-mEHP, $^{13}C_2$-mBP, $^{13}C_2$-mCHP, $^{13}C_2$-mBzP, $^{13}C_4$-mEHHP, $^{13}C_4$-mEOHP, $^{13}C_2$-mOP, and $^{13}C_2$-mNP, 20 µL of hydrolase, and 0.5 mL of ammonium acetate was spiked. After being shaken for 1 min, the urine sample was hydrolyzed at 37 °C for 90 min, cooled down to room temperature, and then 0.5 mL of concentrated ammonia water was added. The supernatant was transferred to a fully automated solid phase extractor after centrifugation. The MAX SPE cartridge was activated with 3 mL of acetonitrile and 3 mL of water, and then the sample was loaded, followed by water (3 mL) and acetonitrile (3 mL). The target analytes were eluted out with 3 mL of a mixture of acetonitrile: ethyl acetate (1:1, *v:v*) containing 3% acetic acid. The eluates were evaporated to dryness, and then the dry residue was re-dissolved in 1 mL of acetonitrile. Finally, the eluates were stored at −20 °C before analysis. The quality assurance and quality control are given in the Supporting Information.

2.4. Instrumental analysis

OH-PAH analysis was carried out on a 20A high-performance liquid chromatograph (HPLC; Shimadzu, Japan) coupled with a Q-Trap 5500 mass spectrometer (MS/MS; Applied Biosystems, Foster City, CA, USA). A Phenomenex C_{18} reversed-phase column (4.6 mm × 250 mm, 5 µm) was used to separate OH-PAHs and 8-OHdG simultaneously. The column temperature was kept at 25 °C. The mobile phases (methanol and water) were set at a flow rate of 0.6 mL/min. Separation of mPAEs was achieved using a Shisheido ACR C_{18} column (2.0 mm × 150 mm, 3 µm). A binary mixture of solvent A (0.1 % acetic acid in acetonitrile) and solvent B (0.1 % acetic acid in water) was used as the mobile phase, and the flow rate was set at 0.2 mL/min. The gradient programs for the two types of compounds are given in the Supporting Information.

2.5. Data analysis

To evaluate human exposure risks, the total estimated daily intakes (TEDI; µg/kg-bw/day) of PAHs and PAEs were calculated on the basis of the following equation (Chen et al., 2018):

$$\text{TEDI} = \frac{C \times \text{V} \times \text{M1}}{f \times \text{BW} \times \text{M2}} \quad (1)$$

where TEDI (µg/kg-bw/day) is the total estimated daily intake of an

Table 1
Concentrations (ng/mL) of urinary OH-PAHs, mPAEs, and 8-OHdG in school children (n = 167) in Shenzhen, Guangdong Province, China.

Compounds	DF (%)	Mean ± SD	50th percentage	95th percentage	Range
2-OHN	99.4	1.95 ± 2.14	1.45	4.49	N.d.–22.1
1-OHN	67.5	0.86 ± 1.29	0.65	2.14	N.d.–11.0
2-OHF	98.8	0.58 ± 0.39	0.49	1.28	N.d.–2.84
2-OHPhe	100	0.25 ± 0.17	0.22	0.41	0.08.–2.05
1- OHPhe	86.1	0.29 ± 0.23	0.25	0.63	N.d.–1.74
9- OHPhe	54.8	0.10 ± 0.09	0.14	0.21	N.d.–0.29
4- OHPhe	52.4	0.10 ± 0.13	0.14	0.25	N.d.–1.12
1-OHP	75.3	0.44 ± 0.40	0.40	1.08	N.d.–2.33
Σ_8OH-PAHs		4.57 ± 3.55	3.86	9.24	0.36–36.5
mMP	98.8	41.4 ± 45.6	24.7	129	N.d.–238
mEP	83.7	2.86 ± 8.72	0.22	14.6	N.d.–58.0
mEHHP	100	51.5 ± 52.3	38.9	131	1.00–500
miBP	100	35.5 ± 36.4	25.3	85.4	3.35–264
mBP	99.4	80.5 ± 74.5	63.6	215	N.d.–479
mEOHP	100	46.3 ± 40.8	38.4	109	0.49–359
mBZP	96.4	1.51 ± 6.59	0.46	3.68	N.d.–80
mCHP	36.1	0.40 ± 1.40	N.d.	1.73	N.d.–15.1
mEHP	100	20.7 ± 30.1	11.1	64.3	0.63–266
mOP	99.4	28.9 ± 48.5	14.5	87.8	N.d.–501
mNP	76.5	0.57 ± 1.43	0.13	2.41	N.d.–12.1
miDP	61.4	0.08 ± 0.13	0.02	0.25	N.d.–1.00
Σ_{12}mPAEs		310 ± 240	240	759	9.48–1609
8-OHdG	100	14.4 ± 22.1	5.83	66.3	0.09–113

DF: detection frequency; N.d.: not detected; SD: standard deviation; 8-OHdG: 8-hydroxy-2′-deoxyguanosine; 1-OHN: 1-hydroxynaphthalene; 2-OHN: 2-hydroxynaphthalene; 9-OHPhe: 9-hydroxyphenanthrene; 1-OHP: 1-hydroxypyrene; 2-OHF: 2-hydroxyfluorene; 1-OHPhe: 1-hydroxyphenanthrene; 4-OHPhe: 4-hydroxyphenanthrene; 2-OHPhe: 2-hydroxyphenanthrene; 3-OHPhe: 3-hydroxyphenanthrene; mMP: monomethyl phthalate; mEP: monoethyl phthalate; miBP: mono isobutyl phthalate; mEHP: mono-(2-ethylhexyl) phthalate; mBP: mono-*n*-butyl phthalate; mCHP: monocyclohexyl phthalate; mBzP: monobenzyl phthalate; mOP: mono-*n*-octyl phthalate; mEOHP: mono-(2-ethyl-5-oxohexyl) phthalate; mEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate; mDP: mono-3-methyl-7-methyloctyl phthalate; mNP: mono-3-methyl-5-dimethylhexyl phthalate.

individual PAH or PAE compound; C is the urinary concentration (μg/L) of an individual OH-PAH or mPAE; V(L) is the urine volume excreted, and a volume of 1.28 L was used (Lu et al., 2018b); M_1 and M_2 (g/mol) are the molecular weights of a parent PAH or PAE and its corresponding metabolite respectively; BW (kg) is body weight; and f (dimensionless) represents the ratio of OH-PAH or mPAE excreted in urine to the total exposure dose (Anderson et al., 2001). In this study, the f-values of four PAH compounds including naphthalene (NAP), phenanthrene (PHE), fluorene (FLU), and pyrene (PYR) were 100 %, 11 %, 60 %, and 6.8 % respectively (Li et al., 2012), and for miBP, mEP, mMP, mBZP, mEHHP, mEOHP, mEHP, mOP, and mBP, the f-values were 70.3 %, 69 %, 69 %, 73 %, 14.9 %, 10.9 %, 6.2 %, 13 %, and 70 % respectively (Anderson et al., 2001; Dewalque et al., 2014; Gao et al., 2017; Wang et al., 2015).

To assess non-carcinogenic risk, the hazard quotient (HQ) was used (Lei et al., 2015; Wang et al., 2015), which is defined as the ratio of a chemical TEDI to the reference limit. In addition, the hazard index (HI) was determined to assess the cumulative risk of chemical exposure:

$$HQ = TEDI/RfD \quad (2)$$

$$HI = \sum_{i=1}^{n} HQ_i \quad (3)$$

where the reference doses (RfDs) were 20, 40, 40, and 30 μg/kg-bw/day for NAP, PHE, FLU, and PYR respectively and 100, 20, 100, 200, and 800 μg/kg-bw/day for DBP, DEHP, di-isobutyl phthalate (DiBP), BBzP, and dioctyl phthalate (DOP) respectively. All these values were derived from chronic oral exposure according to the United States Environmental Protection Agency (Wang et al., 2015). The HQ value of DEHP in the present study was calculated from the highest TEDI value of DEHP derived from its three metabolites of mEHHP, mEOHP, and mEHP based on the protection of human health. If the HQ or HI value was less than one (risk level), this meant that there was no obvious potential non-carcinogenic risk, and vice versa (Lei et al., 2015).

SPSS 22.0 was used for statistical analysis. The concentrations (mean, median, and range) of OH-PAHs and mPAEs for descriptive analyses were presented as ng/mL and adjusted by specific gravity. One-half of LOQ was assigned when the concentration was lower than the LOQ (GB 17378.2-2007, 2007GB 82-, 2007GB 17378.2-2007, 2007), and "not detected" (zero) was used when the concentration was lower than the LOD. Spearman nonparametric correlation was used to analyze the correlations among individual OH-PAHs and mPAE. The significance level was set at $p < 0.05$.

3. Results and discussion

3.1. Levels of OH-PAHs and mPAEs in urine

The detection frequencies and concentrations of urinary OH-PAHs and mPAEs in school children are shown in Tables 1 and S2. The detection frequencies were greater than 95 % for 2-hydroxynaphthalene (2-OHN), 2-hydroxyfluorene (2-OHF), and 2-hydroxyphenanthrene (2-OHPhe), between 67.5 % and 86.1 % for 1-hydroxynaphthalene (1-OHN), 1-hydroxyphenanthrene (1-OHPhe), and 1-hydroxypyrene (1-OHP), whereas they were 52.4 % and 54.8 % for 4-hydroxyphenanthrene (4-OHPhe) and 9-hydroxyphenanthrene (9-OHPhe), respectively. Detection frequencies of individual mPAE compounds ranged from 36.1% to 100%. These results are similar to those for OH-PAHs and comparable to the results from the other studies shown in Table S3 (Li et al., 2010; Liao et al., 2018; Liu et al., 2017; Lu et al., 2016; Oliveira et al., 2017; Rocha et al., 2017; Thai et al., 2015; Wang et al., 2018; Wu et al., 2017; Yang et al., 2017), suggesting ubiquitous exposure to these contaminants.

The concentrations of ΣOH-PAHs (the sum of the eight OH-PAH compounds) varied between 0.36 and 36.5 ng/mL (n = 166), with a median of 3.86 ng/mL. The highest median concentration was 1.45 ng/mL for 2-OHN, followed by 1-OHN (0.65 ng/mL). In the present study, 1-OHP (0.40 ng/mL) exhibited lower concentrations than 2-OHN, 1-OHN, and 2-OHF, although it is a commonly used biomarker for human exposure to PAHs (Hansen et al., 2008). Compared with urinary concentrations of OH-PAH in children from other regions (Table S4), the data obtained in this study from Shenzhen school children fell in the moderate range and were much lower than in those living near e-waste dismantling sites in Qingyuan (20 ng/mL) and in coke oven workers in Poland (155 ng/mL) (Campo et al., 2010; Lu et al., 2016).

The concentrations of ΣmPAEs (the sum of 12 mPAE compounds) varied between 9.48 and 1609 ng/mL, with a median of 240 ng/mL. The compound mBP exhibited the highest median concentration (63.6 ng/mL) among the mPAEs, followed by mEHHP (38.9 ng/mL) and mEOHP (38.4 ng/mL), whereas miDP and mCHP had the lowest urinary concentration (0.02 ng/mL and not detected, respectively). In the present study, the broad range of urinary mPAE concentrations suggested large variations between individuals in their exposure to PAEs. Compared with other studies (Table S5), children in Shenzhen overall exhibited higher urinary mPAE concentrations, indicating elevated exposure in the study region.

3.2. Composition characteristics and potential sources

The composition profiles of OH-PAHs are shown in Fig. 1A. The predominant isomer was 2-OHN, accounting for 42.7 % of the ΣOH-PAHs, followed by 1-OHN (18.8 %), ΣOHPhe (16.0 %), 2-OHF (12.8 %), and 1-OHP (9.7 %). The dominance of OHN (sum of 2-OHN and 1-OHN, accounting for 61.5 % of the total) suggested that naphthalene was the major contributor to children exposure to PAHs. In addition, significant and positive correlations ($p < 0.05$) were found among most OH-PAH compounds, with correlation coefficients (r) of 0.158–0.773, which

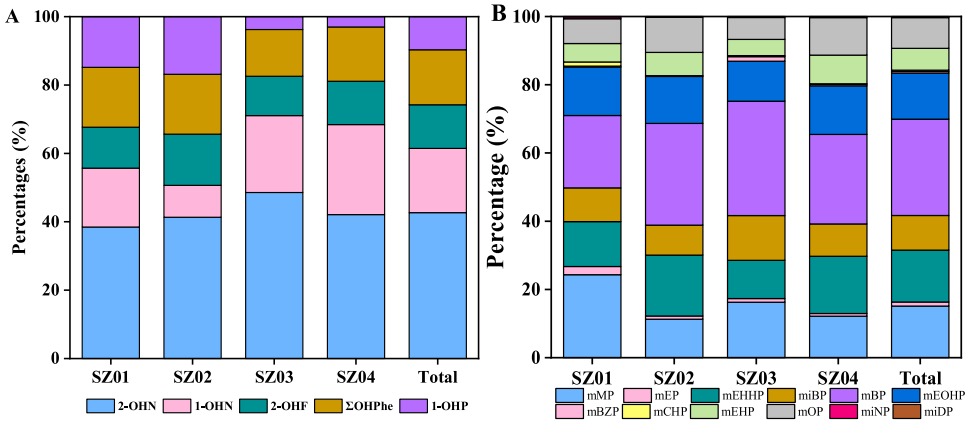

Fig. 1. Composition profiles of OH-PAHs and mPAEs in urine of school children from four sites in Shenzhen, China.

means that all the OH-PAH compounds were significantly correlated with total OH-PAHs (Table S6) and that the sources of PAHs were mostly related. Moreover, for low-molecular-weight OH-PAHs, the concentrations of 2-OHN, 2-OHF, 2-OHPhe, and 3-OHPhe correlated well with each other, indicating similar sources. The results further demonstrated that vehicle exhaust and petrochemical emissions might be important sources and that inhalation is an important route of exposure to PAHs for children in Shenzhen, China. As reported in the literature, naphthalene, the parent of 1-OHN and 2-OHN, is derived from incomplete combustion of biomass, fossil fuel emissions, and vehicle exhaust emissions (Peng et al., 2020; Thai et al., 2016). In addition, it should be noted that except for PAHs, carbaryl might have also been a source of 1-OHN (Dong et al., 2010; Phale et al., 2019).

The composition profiles of mPAEs are shown in Fig. 1B. Among them, mBP accounted for the greatest proportion (25.9 %), followed by mEHHP (16.6 %), mEOHP (14.9 %), mMP (13.3 %), miBP (11.4 %), mOP (9.3 %), and mEHP (6.7 %). The other metabolites accounted for less than 2% of the totals. There were significant and positive correlations ($p < 0.05$) among individual mPAEs, with most coefficients ranging from 0.154 to 0.999 (Table S7), indicating related sources of

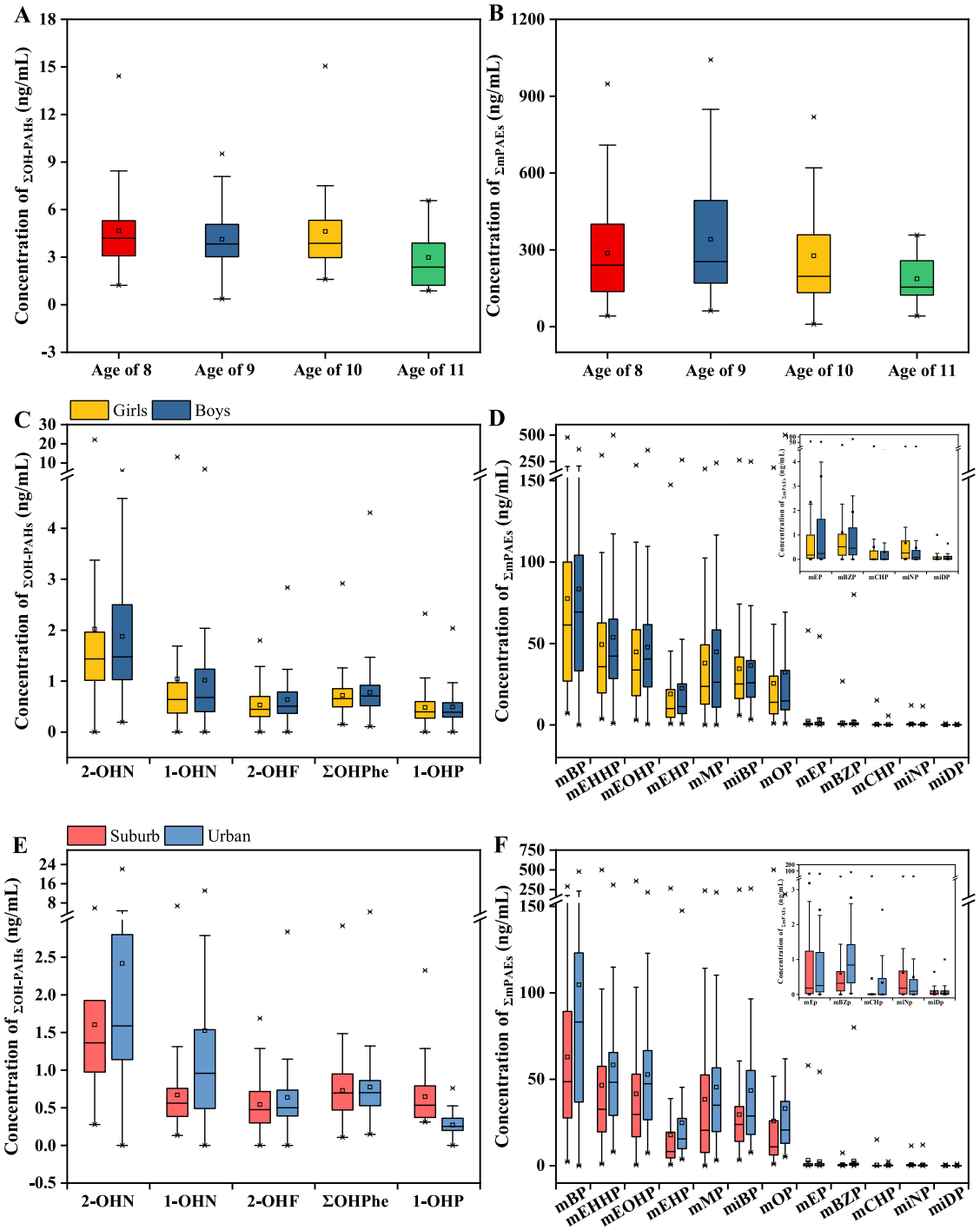

Fig. 2. OH-PAH and mPAE concentrations in urine of school children of different ages (A and B), genders (C and D), and at different sites (E and F). Horizontal lines within the box and the lower and upper limits of the bar indicate median, 25 %, and 75 % values, and the squares represent mean values. The whisker extends to the last observation within 1.5 times the interquartile range. The asterisks outside the whiskers represent the outliers.

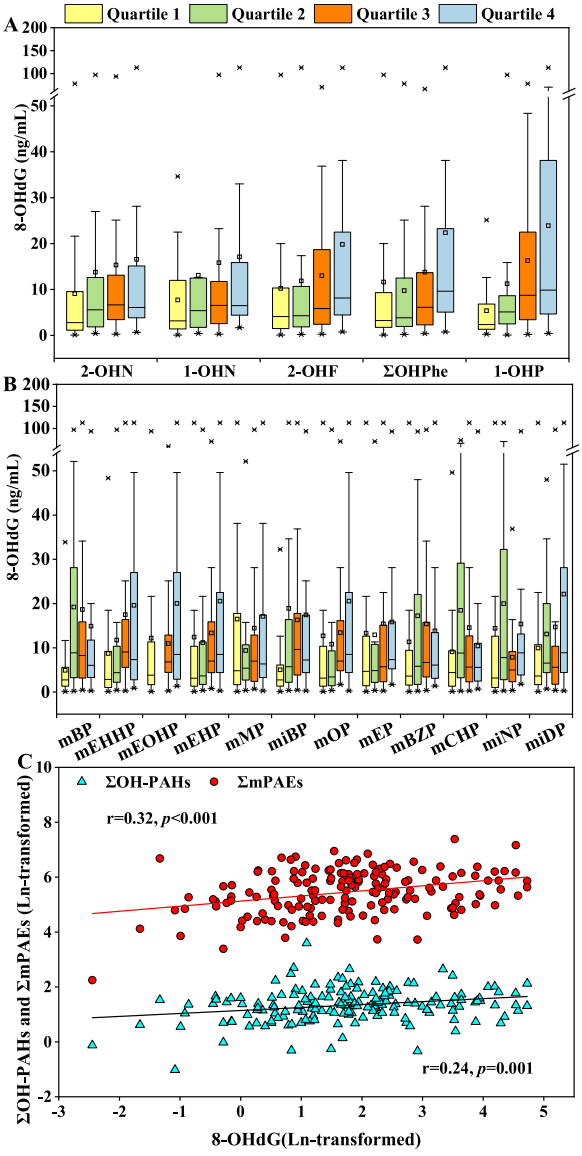

Fig. 3. Relationship between the concentrations of 8-OHdG with the levels of OH-PAHs (A) and mPAEs (B) stratified by 4 quartiles (quartiles 1, 2, 3, and 4 represent 25 %, 50 %, 75 %, and 95 %, respectively) and the correlations between the concentrations of ΣOH-PAHs and ΣmPAEs with 8-OHdG (C). Horizontal lines within the box and the lower and upper limits of the bar indicate median, 25 %, and 75 % values, and the squares represent mean values. The whisker extends to the last observation within 1.5 times the interquartile range. The asterisks outside the whiskers represent the outliers.

PAE exposure. Among DEHP metabolites, the present ratios of mEOHP and mEHP to mEHHP were 0.82 and 0.37 respectively according to linear regression (Fig. S2). According to literature data that give urinary excretion ratios of mEHHP (14.9 %), mEOHP (10.9 %), and mEHP (6.2 %), similar derived ratios of mEOHP and mEHP to mEHHP could be obtained, i.e., 0.732 and 0.416 respectively. The total amount of DEHP metabolites including mEOHP, mEHHP, and mEHP accounted for 37.4 % of total mPAEs (Fig. 1B). These biomarkers were the dominant metabolites, which may have been the case because DEHP is widely used in China (Liao et al., 2018; Yang et al., 2017). As mentioned earlier, DEHP is commonly added to plastic, and it can be released and transferred into food (Hartmann et al., 2015; Münch et al., 2018; Muñoz et al., 2018). The main sources of urinary mPAEs in children related to fast-food eating have been reported by several studies (Cullen et al., 2017; Zota et al., 2016). To the best of the authors' knowledge, many school children have lunch at school in Shenzhen, and the boxes for food are generally plastic. Therefore, food associated with PAEs might play an important role in urinary mPAE levels in school children, although higher concentrations in young children associated with more prevalent hand-to-mouth behavior and more time spent with toys and on the floor might also be suggested.

3.3. Factors influencing urinary OH-PAHs and mPAEs

Urinary concentrations of ΣOH-PAHs for different age groups are shown in Fig. 2A. The present study showed that 11-year-old children had the lowest mean concentrations of 3.90 ng/mL, which were lower than the other groups (mean: 4.32–5.02 ng/mL). However, there were no statistical differences in urine concentrations of OH-PAHs among the four age groups ($p > 0.05$). Similar result was also observed by Li et al. (2015a), although they reported significantly higher urinary ΣOH-PAH concentrations in younger children after creatinine normalization, which might be attributed to the age-dependent change in muscle mass and metabolism of children. As we know, PAHs are metabolizable compounds with excretion half-lives of approximately 1.4–33 h by urinary OH-PAHs after consumption of smoked salmon (Motorykin et al., 2015). Rapid metabolism prevents PAHs from accumulating in the human body. Thus, urinary ΣOH-PAHs are biomarkers to reflect the short-term exposure to PAHs for humans. In the present study, the subjects might have similar behavior habits. They spent most of their time in school and lived in the similar surrounding environments. Thus, their exposure doses of PAHs were similar and no significant differences among ages were observed. Similar results were observed for mPAE concentrations, i.e., there were no significant differences among the ages (Fig. 2B). The results likely suggest that age may not be an important factor influencing exposure of OH-PAHs and mPAEs in school children unless there are special exposure dose for a certain age.

Gender did not significantly influence urinary concentrations of OH-PAHs or mPAEs, as shown in Fig. 2C and D. A Chinese cross-sectional study among students aged 8–16 years old presented a similar result that no significant difference between genders was observed for mPAEs (Shen et al., 2015). By contrast, the U.S NHANES data and a study from Chongqing, China (Table S4) revealed higher levels of OHN in males than in females (CDC, 2015; Liu et al., 2017). However, there was a significant difference ($p < 0.05$) between the mean urinary concentrations of OH-PAH (4.05 vs. 5.29 ng/mL) in children from suburban and urban regions, especially for 1-OHN and 2-OHN (Fig. 2E). A similar significant difference ($p < 0.01$) was observed for mPAE (mean: 268 vs. 369 ng/mL), with higher exposure levels for urban children (Fig. 2F). The results suggested that children in urban regions suffer higher exposure to PAHs and PAEs.

3.4. Oxidative stress damage associated with OH-PAHs and mPAEs

With the exception of 1-OHN, 1-OHPhe, and 4-OHPhe, significant correlations were observed between urinary 8-OHdG concentrations and the concentrations of both individual OH-PAH compounds and ΣOH-PAHs. The coefficients (r) varied between 0.188 and 0.365 ($p < 0.01$), with that of 2-OHPhe being 0.161 ($p < 0.05$) (Table S6). To further understand the relationships between pollutants and the biomarker, the 8-OHdG concentrations were further stratified by the quartiles of individual OH-PAH compounds and ΣOH-PAHs (Fig. 3A). The results showed that urinary 8-OHdG levels increased from Q1 to Q4 quartile groups (p trend < 0.01), especially for total OHPhe and 1-OHP. This demonstrated a significant association between levels of 8-OHdG and OH-PAHs in children's urine. Similar results were also reported in several previous investigations (Chuang et al., 2003; Kuang et al., 2013; Sun et al., 2017). For example, a significant correlation between urinary 8-OHdG and OH-PAH levels was reported in Chinese coke oven workers (Kuang et al., 2013). Similarly, Chuang et al. (2003) found a remarkable correlation between urinary 1-OHP and 8-OHdG levels by

investigating 75 male community residents and 95 male taxi drivers. The studies indicated that 8-OHdG is a suitable biomarker to assess hazards from PAH exposure both for non-occupational and occupational populations.

Similarly, significant correlations were observed between the concentrations of 8-OHdG and of individual or total mPAEs, with correlation coefficients (r) of 0.16–0.315 ($p < 0.05$), except for mMP and mCHP (Table S7). Similarly to OH-PAHs, the 8-OHdG concentrations were also stratified by the quartiles of each mPAE (Fig. 3B). Urinary 8-OHdG levels were found to increase gradually from Q1 to Q4 quartile groups for most mPAE compounds (p trend < 0.01). Similar results have also been reported in the literature (Kim et al., 2018; Lin et al., 2017). For example, Wang et al. (2011) found that male workers in waste plastics plants who were subjected to long-term DEHP exposure had higher urinary concentrations of 8-OHdG than a control group. Lin et al. (2017) recruited 886 subjects aged from 12 to 30 years and found that urinary mMP concentrations were positively associated with an increase in urine biomarkers of oxidative stress damage. Epidemiological studies also suggested that exposure to PAEs had an indirect association with oxidative stress damage (Kim et al., 2018).

However, it should be pointed out that 8-OHdG levels are the outcomes of exposure to a combination of different toxicants. Therefore, the relationships between 8-OHdG levels and total concentrations of the target substances were analyzed. In the present study, the natural logarithm-transformed concentrations of ΣOH-PAHs and ΣmPAEs were used, and multiple regression analyses were carried out. The results showed that urinary 8-OHdG concentrations exhibited a significant positive correlation with target concentrations (ΣOH-PAHs: $r = 0.24$, $p < 0.01$; ΣmPAEs, $r = 0.32$, $p < 0.01$) (Fig. 3C). To further understand the influence of OH-PAHs and mPAEs on 8-OHdG levels considering gender, age, and BMI, a multiple stepwise linear regression model was used. The model indicated that a one percent increase in concentrations of ΣOH-PAHs and ΣmPAEs could generate a 0.49 % ($p = 0.007$) and a 0.52 % ($p < 0.001$) increase in urinary 8-OHdG concentrations, respectively, with respective 95 %CI of (0.13, 0.85)% and (0.25, 0.79)%. In other words, when the urinary concentrations of ΣOH-PAHs and ΣmPAEs increased by 1 ng/mL, urinary 8-OHdG levels increased by 11.5 % (14.4 %) and 0.17 % (0.22 %) based on the mean (median) concentrations of ΣOH-PAHs and ΣmPAEs, respectively. These results suggest that exposure to ΣOH-PAHs could associate with 68.7 (66.5 based on median) times higher risks of DNA damage than exposure to ΣmPAEs based on mean concentrations.

3.5. Health risk assessments of children exposure to PAHs and PAEs

The TEDI values of PAHs and PAEs are summarized in Table 2. The TEDIs of PAHs ranged from 0.03 to 1.01 μg/kg-bw/day. The results were similar to those reported in Kuwait, Korea, and India, which ranged from 0.05–0.66 μg/kg-bw/day (Guo et al., 2013), although they were much lower than those from college students in Guangzhou (1.30–12.7 μg/kg-bw/day) (Li et al., 2015b). Among PAEs, DEHP exhibited the highest TEDI (mean: 14.8 μg/kg-bw/day), followed by DOP (mean: 12.7 μg/kg-bw/day) and DBP (mean: 5.71 μg/kg-bw/day). TEDI values of DEHP from both the United States (1.32 μg/kg-bw/day) and Belgium (3.37 μg/kg-bw/day) were lower than 4 μg/kg-bw/day (Dewalque et al., 2014; Marsee et al., 2006) and about 10–30 times lower than those in the present study. Therefore, overall, the TEDIs of PAHs in children from Shenzhen were comparable with children in other regions, but those of PAEs, especially for DEHP, were much higher than those from Belgium and the United States (Dewalque et al., 2014; Marsee et al., 2006).

In our previous study, EDIs of particle-phase PAEs in outdoor air were investigated in Shenzhen. Children (9–12 years old) had the highest "typical" and "high" EDIs of 0.03 and 0.11 μg/kg-bw/day of PAEs through $PM_{2.5}$ exposure respectively (Lu et al., 2018a), which were much lower than the estimates in the present study (86.7 and 217 μg/kg-bw/day). Guo et al. (2014) assessed a median exposure dose of PAEs through dermal application of personal care products in China at 0.76 μg/kg-bw/day. These results suggest that exposure to air and dermal contact does not constitute a main source of PAEs in children. Dietary exposure may be a more important source, as suggested by previous studies (Schettler, 2006).

The HQ and HI values of PAHs and PAEs based on RfD are shown in Fig. 4. The HQ values were far less than one for individual PAH compounds, which indicates that exposure to an individual PAH chemical does not pose a potential health risk for children (Dewalque et al.,

Table 2
Total estimated daily intake (TEDI, μg/kg-bw/day) of PAHs and PAEs estimated from urinary metabolite concentrations in school children from Shenzhen.

Compounds		Mean			50th			95th			Range		
Parent	Metabolite	All	Boys	Girls	All	Boys	Girls	All	Boys	Girls	All	Boys	Girls
NAP	2-OHN	0.07	0.07	0.07	0.05	0.05	0.05	0.18	0.18	0.16	0–0.56	0.01–0.23	0–0.56
	1-OHN	0.03	0.03	0.04	0.02	0.02	0.03	0.09	0.10	0.13	0–0.28	0–0.26	0–0.28
FLU	2-OHF	0.04	0.04	0.03	0.03	0.03	0.03	0.08	0.09	0.08	0–0.17	0–0.17	0–0.13
PHE	2-OHPhe	0.09	0.09	0.08	0.07	0.07	0.07	0.17	0.17	0.16	0–0.68	0–0.68	0.03–0.22
	1- OHPhe	0.10	0.10	0.09	0.08	0.09	0.09	0.21	0.21	0.19	0–0.58	0–0.58	0–0.37
	9- OHPhe	0.03	0.04	0.02	0.04	0.04	0.00	0.09	0.09	0.07	0–0.10	0–0.10	0–0.09
	4- OHPhe	0.03	0.03	0.03	0.04	0.04	0.04	0.08	0.08	0.08	0–0.34	0–0.14	0–0.34
PYR	1-OHP	0.26	0.26	0.20	0.22	0.23	0.14	0.69	0.62	0.67	0–1.69	0–1.69	0–1.30
PAHs	OH-PAHs	0.21	0.21	0.21	0.18	0.18	0.17	0.47	0.44	0.52	0.03–1.01	0.03–1.01	0.03–0.83
DEHP	mEHHP	14.4	15.4	13.5	11.1	15.4	13.5	36.2	42.1	34.5	0.24–77.4	0.24–77.4	1.14–54.2
	mEOHP	14.8	15.4	14.1	12.4	15.4	14.1	38.4	38.0	38.0	0.13–62.6	0.13–62.6	0.99–45.4
	mEHP	10.3	11.4	9.20	5.6	11.4	9.2	32.7	35.8	27.9	0.26–161	0.26–161	0.34–74.6
DiBP	miBP	2.63	2.69	2.57	1.93	2.69	2.57	6.75	5.28	6.84	0.21–22.3	0.21–22.3	0.44–18.0
DBP	mBP	5.71	5.81	5.62	4.43	5.81	5.62	16.9	17.0	15.4	0–29.5	0.14–25.3	0–29.5
BBzP	mBZP	0.10	0.07	0.14	0.03	0.07	0.14	0.27	0.27	0.21	0–5.18	0–0.66	0–5.18
DOP	mOP	12.7	14.6	10.9	6.50	14.6	10.9	37.9	41.7	32.1	0.35–267	0.35–267	0.46–86.0
PAEs	mPAEs	35.6	55.2	16.0	27.0	55.2	16.0	89.7	122	28.6	0.94–323	0.94–323	3.06–134

NAP: Naphthalene; FLU: Fluorene; PHE: Phenanthrene; PYR: Pyrene; DEHP: diethylhexyl phthalate; DiBP: di-isobutyl phthalate; DBP: dibutyl phthalate); BBzP: butylbenzyl phthalate; DOP: dioctyl phthalate; 1-OHN: 1-hydroxynaphthalene; 2-OHN: 2-hydroxynaphthalene; 9-OHPhe: 9-hydroxyphenanthrene; 1-OHP: 1-hydroxypyrene; 2-OHF: 2-hydroxyfluorene; 1-OHPhe: 1-hydroxyphenanthrene; 4-OHPhe: 4-hydroxyphenanthrene; 2-OHPhe: 2-hydroxyphenanthrene; 3-OHPhe: 3-hydroxyphenanthrene; mMP: monomethyl phthalate; mEP: monoethyl phthalate; miBP: mono isobutyl phthalate; mEHP: mono-(2-ethylhexyl) phthalate; mBP: mono-*n*-butyl phthalate; mCHP: monocyclohexyl phthalate; mBzP: monobenzyl phthalate; mOP: mono-*n*-octyl phthalate; mEOHP: mono-(2-ethyl-5-oxohexyl) phthalate; mEHHP: mono-(2-ethyl-5-hydroxyhexyl) phthalate; mDP: mono-3-methyl-7-methyloctyl phthalate; mNP: mono-3-methyl-5-dimethylhexyl phthalate.

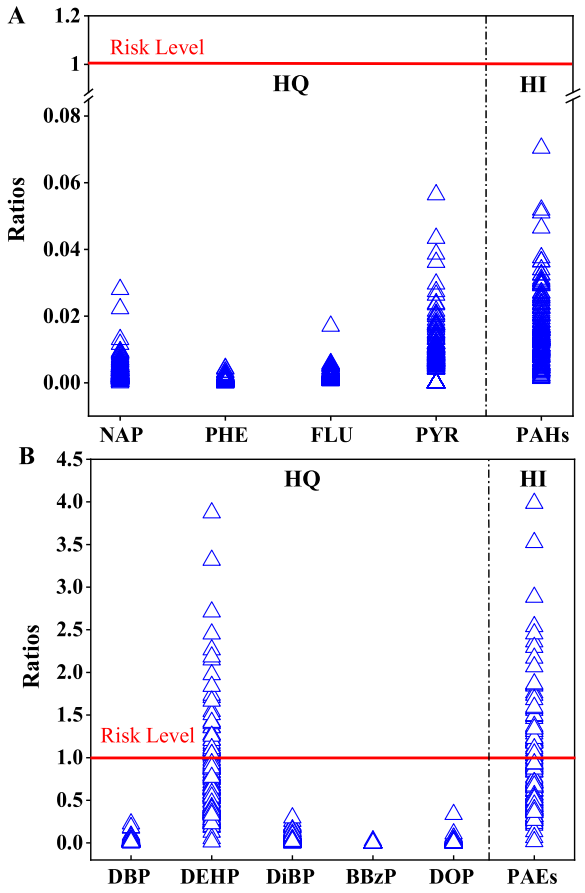

Fig. 4. Individual hazard quotients (HQ) and hazard indices (HI) of PAHs (A) and PAEs (B) for school children from Shenzhen, China.

2014). The cumulative risk of total PAHs as indicated by HI values was also less than one, suggesting that PAH exposure is unlikely to produce significant impact on children.

However, the HQ value of DEHP was greater than one in 39 children, accounting for 23.5 % of total subjects, and the HI values of PAEs in 49 children (29.5 %) were greater than one, indicating that some children from the study regions may be subject to potential health risks because of exposure to PAEs. These results were similar to findings from other regions in China. Wang et al. (2018) surveyed 782 children in Yuhuan County (Zhejiang Province), Haimen City (Jiangsu Province), and Minhang District (Shanghai City) and found that 155 (19.8 %) of the children showed an HI greater than one. In particular, 95 out of the 155 children with an HI greater than one were from Yuhuan, which is an industrial region with intensive consumer goods manufacturing activities. A study by Rocha et al. (2017) found that 98 out of 300 Brazilian children showed HI values greater than one. Approximately 25 % of Belgian children and 15 % of Danish adolescents and children were also reported to have HI values exceeding one (Calafat et al., 2011; Søeborg et al., 2012). All these results demonstrated that investigation of PAEs is urgently needed and that more actions should be taken by government. For example, in China, there are many regulations and limiting standards for PAE use in products. However, for some products used indoors, such as floor, wallpaper, and other products, there is no relevant limiting standard in China. PAEs are also added to products as plasticizers in some new industries, and limiting standards for the chemicals in these products need to be set. Although many products are not directly in contact with the human body, the widespread use of PAEs in products and their release into the environment can lead to high environmental levels of PAEs, which are harmful to human beings. Beyond controls on the use of PAEs in some products, the invention of low-toxicity or non-toxic substitutes for PAEs is also an important alternative.

4. Conclusions

OH-PAH and mPAE concentrations in the urine of children from elementary schools in Shenzhen were measured in this study. The high detection frequencies of OH-PAHs and mPAEs indicated ubiquitous occurrence of these contaminants and associated human exposure. Gender and age did not significantly influence children exposure to OH-PAHs and mPAEs, but geographical location did. 8-OHdG levels were significantly correlated with urinary OH-PAHs and mPAEs. Statistical analyses suggested significant associations between oxidative DNA damage and OH-PAHs (or mPAEs) and revealed that the risk of DNA damage from exposure to OH-PAHs was over 65 times higher than from exposure to mPAEs at the same concentration. However, estimates of HQ and HI suggested that although PAHs are unlikely to induce significant health risks because of their low concentrations, children in Shenzhen could be subject to elevated health risks from exposure to PAEs.

CRediT authorship contribution statement

Yingxin Yu: Methodology, Writing - review & editing. **Mengmeng Peng:** Formal analysis, Writing - review & editing. **Yanlin Liu:** Methodology. **Jinjing Ma:** Investigation. **Ning Wang:** Data curation. **Shengtao Ma:** Formal analysis. **Nannan Feng:** Formal analysis. **Shaoyou Lu:** Supervision.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jhazmat.2020.123390.

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