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Co-exposure and health risks of parabens, bisphenols, triclosan, phthalate metabolites and hydroxyl polycyclic aromatic hydrocarbons based on simultaneous detection in urine samples from guangzhou, south China[☆]

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs) and certain ingredients in personal care products, such as parabens, bisphenols, triclosan and phthalate metabolites, have become ubiquitous in the world. Concerns of human exposure to these pollutants have increased during recent years because of various adverse health effects of these chemicals. Multiple compounds including parabens, bisphenols, triclosan, phthalate metabolites (mPAEs) and hydroxyl PAHs (OH-PAHs) in urine samples from Guangzhou were determined simultaneously to identify the human exposure pathways without external exposure data combined with data analysis, and the toxicants posed the highest risk to human health were screened in the present study. The detection frequencies for the chemicals exceeded 90%. Among the contaminants, mPAEs showed the highest concentrations, followed by OH-PAHs, with triclosan present at the lowest concentrations. Mono-n-butyl phthalate, methylparaben, bisphenol A, and hydroxynaphthalene represented the most abundant mPAE, parabens, bisphenol, and OH-PAH compounds, respectively. The present PAHs are mainly exposed to human through inhalation, while the chemicals added to personal care products are mainly exposed to human through oral intake and dermal contact. The urine samples from suburban subjects showed significantly higher OH-PAH levels than the urine samples from urban subjects, and females had lower OH-PAH levels than males. Urinary concentrations of the analyzed contaminants were significantly correlated with age, body mass index, residence time, as well as the frequencies of alcohol consumption and swimming. Risk assessments based on Monte Carlo simulation indicated that approximately 30% of the subjects suffered non-carcinogenic risks from mPAEs and OH-PAHs, with mPAEs accounting for 89% of the total risk.

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Author statement

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1. Introduction

Personal care products (PCPs) are ubiquitous to contemporary daily life and contain a variety of synthetic chemicals, among which

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parabens, bisphenols, triclosan (TCS), and phthalates (PAEs) are widely added as plasticizers, antimicrobials, etc. (Husoy et al., 2019; Lu et al., 2018a, 2018b). For example, parabens represent an important class of preservatives in cosmetics (Ao et al., 2017). Moreover, bisphenol A (BPA), is produced in large quantities worldwide for use as a plasticizer in consumer products. Potential alternatives to BPA, namely, bisphenol S (BPS) and bisphenol F (BPF), are also added to polycarbonate plastics (Chen et al., 2018; Sanchis et al., 2019). TCS – which is used commercially due to its robust antibacterial properties – has been detected from various environmental media (Karthikraj et al., 2020), while PAEs are also common in numerous environmental matrices due to their extensive use as plasticizers or softeners in products including food packaging, care and medical products (Frigerio et al., 2020). In contrast to these intentionally added chemicals, polycyclic aromatic hydrocarbons (PAHs) are released during the incomplete combustion of fossil or biomass fuels as well as certain natural occurrences, e.g. volcanic activity, and have been widely detected in the environment and human bodies (Zhang et al., 2017, 2019). These chemicals have become a topic of concern because of their toxic properties.

Previous literature has reported adverse health impacts for the aforementioned chemicals, more specifically, endocrine disrupting properties, carcinogenicity, reproductive and developmental toxicity, and neurotoxicity, among others (Berger et al., 2019; Motorykin et al., 2015; Nagar et al., 2019; Shoaff et al., 2019; Yin et al., 2020). For example, a study in *C. elegans* revealed that parabens are endocrine disruptors that can subject organisms to oxidative stress (Nagar et al., 2019). BPA, along with its analogues BPS and bisphenol AF (BPAF), have been shown to exhibit reproductive toxicity (Yin et al., 2020). TCS has been associated with immune system disease and suggested to play an important role in cancer progression (Berger et al., 2019). Phthalate metabolites (mPAEs), e.g., mono (2-ethyl-5-hydroxyhexyl) phthalate (mEHHP) and mono-n-butyl phthalate (mBP), were linked to symptoms of depression, anxiety, and stress in both male and female university students (Xu et al., 2020). Concerning PAHs, they generally rapidly metabolize into hydroxy polycyclic aromatic hydrocarbons (OH-PAHs), which are then used as biomarkers of human exposure to PAHs. Assessments of the health risks of PAH exposure largely depend on the OH-PAHs, as the concentrations of these metabolites are positively related to cardiovascular diseases and other immune diseases (Motorykin et al., 2015).

The health risks associated with the aforementioned contaminants are becoming an increasingly relevant concern due to their widespread occurrence in the environment. These ubiquitous environmental contaminants are generally either excreted directly in the urine or metabolized. Therefore, urine is an excellent biomonitoring matrix, and numerous reports of contaminant concentrations in urine have been published to assess human exposure to the contaminants. These studies have mainly focused on sensitive populations, such as children, school students, pregnant women and their offspring, as well as workers with occupational exposure (Ashrap et al., 2018; Sanchis et al., 2019; Xu et al., 2020), although parabens, bisphenols, TCS, and mPAEs had been identified in urine samples from Saudi Arabia, Norway and the USA (Asimakopoulos et al., 2016b; Husoy et al., 2019; Villanger et al., 2020). Several Chinese studies have assessed exposure to various contaminants among pregnant women from central and southern China (Liu et al., 2019; Peng et al., 2020; Zhu et al., 2018). It is important to note that these chemicals – which are either intentionally or unintentionally added to products – can enter the human body via inhalation, ingestion, and dermal absorption (Berger et al., 2019; Lei et al., 2015). Hence, the urinary monitoring of a single compound, or one class of compounds, cannot reflect the

main source of exposure for the chemical(s). External exposure assessments from food, air, dust samples, and so on should be carried out to evaluate the main source(s) through which the general population is exposed to a certain chemical.

China is the largest PCP consumer and biomonitoring studies found that most people exposed to all these environmental chemicals (Lu et al., 2017). At present, few studies simultaneously detect all these chemicals and to identify which chemical resulted the highest health risk. Guangzhou, as a core engine city in Guangdong-Hong Kong-Macao Greater Bay Area, China's major strategic layout areas, is a highly commercialized and industrialized city. The main novelty of the present study is that these contaminants including parabens, TCS, bisphenols, PAEs and PAHs in a population from Guangzhou were simultaneously detected, and were used to identify the main human exposure pathways for the various toxic chemicals without the need for external exposure data, and screen which contaminants resulted the highest human health risk. Also, this was the first time that these contaminants were assessed in urine samples from the general population of Guangzhou, and the gathered information can be used to identify which contaminants present the highest health risk. The presented results will expand the knowledge base regarding the sources of the aforementioned contaminants and public exposure to multiple organic pollutants in southern China; as such, the results are a useful foundation for further research on the relationship between contaminants and human health.

2. Materials and methods

2.1. Chemicals and materials

The standards of TCS, parabens, including propylparaben (PrP), butylparaben (BuP), methylparaben (MeP), ethylparaben (EtP), and benzylparaben (BeP), and OH-PAHs, including 1-hydroxynthalene (1-OH-NaP), 2-hydroxynthalene (2-OH-NaP), 2-hydroxyfluorene (2-OH-Flu), 3-hydroxyphenanthrene (3-OH-Phe), 3-hydroxyfluorene (3-OH-Flu), 1-hydroxyphenanthrene (1-OH-Phe), 2-hydroxyphenanthrene (2-OH-Phe), 1-hydroxypyrene (1-OH-Pyr), 9-hydroxyphenanthrene (9-OH-Phe), 4-hydroxyphenanthrene (4-OH-Phe), and 3-hydroxybenzo(a)pyrene (3-OH-BaP), were bought from Dr. Ehrenstorfer (Augsburg, Germany). The standards of bisphenols, including BPA, BPAF, BPS, BPF, bisphenol Z (BPZ), bisphenol P (BPP), and bisphenol AP (BPAP), and mPAEs, including mEHHP, monoethyl phthalate (mEP), mono-methyl phthalate (mMP), mono(2-ethylhexyl) phthalate (mEHP), mono-n-octyl phthalate (mOP), mono-n-butyl phthalate (mBP), monoisobutyl phthalate (miBP), mono(2-ethyl-5-oxohexyl)phthalate (mEOHP), and monobenzyl phthalate (mBzP), were purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). The internal standards of d_3 -TCS, d_4 -n-BeP, d_4 -MeP, d_4 -n-PrP, d_4 -EtP, and d_4 -BuP were bought from CDN Isotopes, Inc. (Quebec, Canada), while the internal standards of d_7 -2-OH-NaP, d_9 -1-OH-Pyr, d_9 -2-OH-Flu, d_{11} -3-OH-Bap, $^{13}C_6$ -3-OH-Phe, $^{13}C_{12}$ -BPA, $^{13}C_4$ -mMP, d_4 -miBP, $^{13}C_4$ -mEP, $^{13}C_4$ -mBP, $^{13}C_4$ -mEHHP, $^{13}C_4$ -mEOHP, $^{13}C_4$ -mEHP, $^{13}C_4$ -mOP, and $^{13}C_4$ -mBzP were purchased from Cambridge Isotope Laboratories, Inc.

β -glucuronidase/arylsulfatase was obtained from Sigma Aldrich Corp. (St. Louis, MO, USA). KH_2PO_4 (HPLC grade), sodium acetate, and glacial acetic acid were purchased from Fisher Scientific (Waltham, MA, USA). Methanol, dichloromethane, and acetonitrile were purchased from Merck (Darmstadt, Germany). Oasis HLB solid-phase extraction (SPE) cartridges (500 mg/6 mL) were purchased from Waters Corp. (Milford, MS, USA).

2.2. Sample collection and preparation

A total of 480 first-voided morning urine samples representing the general population (male: $n = 240$; female: $n = 240$; ages from 5- to 77-years-old) were collected from four administrative districts of Guangzhou, south China in 2018 (Table S1). These four districts represented two urban areas (TH, $n = 120$; YX, $n = 120$) and two suburban areas (ZC, $n = 120$; HD, $n = 120$). The participants were required to fill out questionnaires and provide their informed consent before the samples were collected. Generally, 50 mL of urine was collected in a pretreated, frozen storage tube stored on dry ice. Immediately after collection, the samples were stored at -20°C and transported to the laboratory for analysis. The experiments were approved by the Ethics Committee of Guangdong University of Technology.

2.3. Sample analysis, quality assurance and quality control

TCS, OH-PAHs, parabens, and bisphenols were detected from the urine using an off-line analysis method based on a technique presented in a previous study (Lin et al., 2020), while mPAEs were detected from the urine using an on-line analysis method that was adapted from the approach presented by Heffernan et al. (2016). Both of the applied methodologies are described in detail in the Supporting Information, with the parameters used for instrumental analysis given in Table S2. To ensure the accuracy of the results, procedural and solvent blanks were incorporated into each batch of samples. The blank background of miBP, mBP, and mEHP were subtracted. mOP were not detected and therefore it was not reported in the present study. The method was verified based on the recovery rates of all the target compounds in urine samples containing standards and isotope-labeled standards. The intra- and inter-day precision of the method was assessed by analyzing the standard solution six times within a single day and on six consecutive days, respectively. The methodologies demonstrated satisfactory intra- and inter-day precision, as the relative standard deviations fell under 10%. The correlation coefficients of the calibration curves were more than 0.999 for all of the target compounds. The limit of detection (LOD) and limit of quantitation (LOQ) values for all of the target compounds are listed in Table S3.

2.4. Calculations and statistical analysis

In the investigation of the potential non-carcinogenic risks of the chemicals, a hazard quotient (HQ) was used to assess the health risks of a certain chemical and the hazard index (HI) was used to evaluate the total risk from multiple contaminants. Scores of $\text{HQ} > 1$ or $\text{HI} > 1$ indicate that the contaminant in question poses a potential health risk for humans. The calculations are given in the Supporting Information, and all of the associated parameters are listed in Table S4. Monte Carlo simulation was used to estimate the uncertainty and variability of health risks, which were applied as the input probability distributions. The HQ distributions for the general population were based on variation in the urinary concentration of a chemical, total urine volume for human per day, and human body weight parameters, with each parameter tested for logarithmic normal, Discrete uniform, and Weibull distribution through the Anderson-Darling to compare each empirical statistical distribution with the sample probability distribution. The 95% confidence interval for health risk was calculated in Crystal Ball© (Oracle, Redwood City, CA, USA) using 60,000 trials. Detailed information on the statistical distributions of the various parameters are shown in Table S5.

Statistical analyses were performed using SPSS version 13.0 software. If the concentration of chemical was less than the limit of

quantitative detection (LOQ), it was calculated as 1/4 LOQ when its detection frequency was less than 50%, while 1/2 LOQ was used when its detection frequency was more than 50%. Zero was used if the data of the chemical was below the limit of detection. Spearman correlations were used to determine the relationships among variances. The associations between the urinary concentration of a certain contaminant and the various variables were analyzed by using the Jonckheere-Terpstra and Mann-Whitney U tests. The statistical significance level was set at $p < 0.05$.

3. Results and discussion

3.1. Concentrations of the contaminants in urine

TCS, along with all of the studied parabens, bisphenols, mPAEs, and OH-PAHs, were detected in urine samples from urban (TH and YX) and suburban regions (ZC and HD), with the detection frequency for each class of contaminant generally exceeding 90% (Table 1). The detection frequencies of parabens (MeP, EtP, PrP, BuP, and BeP) in samples from the urban and suburban regions were 11.3%–90.0% and 9.6%–77.9%, respectively, with at least one of these compounds being detected in over 90% of the samples. The results indicated widespread human exposure to parabens in Guangzhou. The mean urinary concentrations of total parabens were 21.5 and 23.9 ng/mL in the urban and suburban regions, respectively. The predominant paraben detected from the samples was MeP, which demonstrated a mean urinary concentration of 13.7 and 15.3 ng/mL in the two regions, respectively. With the exception of BeP, urine samples from urban regions showed relatively lower concentrations of parabens than urine samples from suburban regions.

Bisphenols were detected in 90.4% and 97.9% of the samples from urban and suburban regions, respectively. The total concentrations ranged from <LOD to 215 ng/mL, with BPA being the most abundant analogue. The mean urinary concentrations of BPA were 12.9 and 8.59 ng/mL in urban and suburban regions, respectively, which were generally two orders of magnitude higher than the concentrations of other bisphenols. The results suggest that BPA is the most commonly used bisphenol in commercial products, although other analogues, such as BPS and BPF, are also used to some extent (Sakhi et al., 2018). TCS is an antimicrobial agent that is often added to PCPs. It was detected in 96.7% and 97.9% of the samples, with mean concentrations of 7.06 and 6.41 ng/mL, from urban and suburban regions, respectively. The general population of Guangzhou is more exposed to BPA, yet less exposed to TCS.

The chemicals of mPAEs were detected in all the samples. The detection frequencies of mBP were over 80% in samples representing both the urban and suburban regions. The concentrations of total mPAEs varied between < LOD and 1169 ng/mL (mean: 267 ng/mL) in urban samples and between 4.52 and 1410 ng/mL (378 ng/mL) in suburban samples. The mPAE with the highest prevalence was MBP, with mean concentrations of 137 and 209 ng/mL in the urban and suburban samples, respectively. The reported mPAE concentrations exceeded what has been reported for people residing close to e-waste sites in Guangzhou (Zhang et al., 2019) as well as pregnant women in Spain and the USA (Shin et al., 2019; Warembourg et al., 2019). The presented results indicate that residents in Guangzhou may be exposed to rather high levels of PAEs.

OH-PAHs were widely detected, with the detection frequencies for various species exceeding 99%. This result indicates that there is widespread exposure to PAHs among the general population in Guangzhou. OH-NaP exhibited the highest mean concentration, followed by 1-OH-Pyr, with both of these compounds widely used as biomarkers to assess human exposure to PAHs (Peng et al., 2020; Thai et al., 2016). Urinary concentrations of total OH-PAHs ranged

Table 1
Urinary concentrations (ng/mL) of parabens, bisphenols, TCS, OH-PAHs, and mPAEs among the general population of Guangdong, south China.

	Urban						Suburban					
	25%	50%	75%	Mean	Range	DF (%)	25%	50%	75%	Mean	Range	DF (%)
Parabens												
MeP	0.790	2.53	9.56	13.7	<LOD–291	90.0%	0.205	1.99	6.43	15.3	<LOD–296	77.9%
EtP	<LOD	0.207	2.81	4.28	<LOD–169	53.8%	<LOD	<LOD	1.37	4.80	<LOD–189	43.9%
PrP	<LOD	<LOD	0.947	3.23	<LOD–89.5	28.8%	<LOD	<LOD	<LOD	3.29	<LOD–190	24.6%
BuP	<LOD	<LOD	<LOD	0.249	<LOD–6.40	22.5%	<LOD	<LOD	0.542	0.487	<LOD–42.8	32.1%
BeP	<LOD	<LOD	<LOD	0.049	<LOD–1.96	11.3%	<LOD	<LOD	<LOD	0.044	<LOD–1.17	9.6%
∑Parabens	1.60	6.10	15.9	21.5	<LOD–298	95.8%	1.41	4.24	13.4	23.9	<LOD–503	92.5%
Bisphenols												
BPA	<LOD	3.88	14.5	12.9	<LOD–185	72.1%	0.312	3.47	9.56	8.59	<LOD–98.2	76.7%
BPAF	<LOD	0.012	0.048	0.037	<LOD–0.496	56.8%	<LOD	0.012	0.043	0.046	<LOD–1.18	64.2%
BPZ	<LOD	<LOD	<LOD	0.651	<LOD–59.0	12.9%	<LOD	<LOD	0.120	1.73	<LOD–79.0	27.9%
BPP	<LOD	<LOD	0.053	0.104	<LOD–3.46	43.8%	<LOD	<LOD	0.115	0.152	<LOD–6.71	47.5%
BPS	<LOD	<LOD	<LOD	0.034	<LOD–1.61	11.3%	<LOD	<LOD	<LOD	0.014	<LOD–0.814	7.1%
BPF	<LOD	<LOD	<LOD	0.009	<LOD–1.01	4.6%	<LOD	<LOD	<LOD	0.010	<LOD–1.29	4.6%
BPAP	<LOD	<LOD	<LOD	0.123	<LOD–12.7	2.9%	<LOD	<LOD	<LOD	0.182	<LOD–22.3	5.0%
∑Bisphenols	0.666	4.52	15.3	13.8	<LOD–215	90.4%	1.31	4.84	12.7	10.7	<LOD–99.9	97.9%
TCS												
	2.99	4.94	7.89	7.06	<LOD–178	96.7%	3.87	5.48	7.20	6.41	<LOD–81.7	97.9%
OH-PAHs												
2-OH-NaP	1.69	4.17	12.7	11.6	<LOD–97.8	91.3%	3.05	7.14	18.4	16.1	<LOD–158	90.8%
1-OH-Nap	1.14	4.94	16.0	14.7	<LOD–296	82.5%	1.96	6.53	20.9	18.7	<LOD–256	86.7%
2-OH-Flu	<LOD	<LOD	<LOD	0.572	<LOD–9.51	16.7%	<LOD	<LOD	1.12	1.63	<LOD–48.4	29.6%
3-OH-Flu	<LOD	<LOD	<LOD	0.378	<LOD–46.8	7.1%	<LOD	<LOD	0.261	0.961	<LOD–18.8	39.6%
2/3-OH-Phe	<LOD	0.026	0.202	0.129	<LOD–3.79	53.3%	<LOD	0.183	0.513	0.933	<LOD–77.2	73.3%
4-OH-Phe	<LOD	<LOD	0.082	0.161	<LOD–10.2	36.3%	<LOD	<LOD	0.232	0.552	<LOD–59.6	39.2%
1/9-OH-Phe	<LOD	<LOD	<LOD	0.123	<LOD–23.7	9.2%	<LOD	<LOD	<LOD	0.071	<LOD–2.15	21.3%
1-OH-Pyr	<LOD	0.297	0.475	0.361	<LOD–7.02	70.8%	0.177	0.477	0.950	1.03	<LOD–45.4	85.8%
3-OH-BaP	<LOD	<LOD	<LOD	0.283	<LOD–38.3	3.8%	<LOD	<LOD	<LOD	0.019	<LOD–1.66	6.7%
∑OH-PAH	4.98	12.7	31.7	28.3	<LOD–354	99.2%	7.97	21.3	42.7	40.0	<LOD–344	99.6%
mPAEs												
mMP	<LOD	14.3	29.6	17.4	<LOD–215	64.2%	<LOD	14.3	14.3	14.6	<LOD–136	62.5%
mEP	1.11	5.26	20.5	20.2	<LOD–232	76.3%	<LOD	1.11	14.5	14.2	<LOD–245	61.7%
mEHHP	<LOD	4.61	13.0	11.3	<LOD–300	67.9%	4.3	9.60	18.8	16.7	<LOD–212	94.2%
mEOHP	0.05	6.82	16.0	14.9	<LOD–315	75.0%	5.54	13.6	26.9	21.1	<LOD–178	94.6%
miBP	<LOD	<LOD	62.7	50.4	<LOD–386	46.3%	<LOD	24.3	108	63.7	<LOD–550	64.6%
mBP	21.6	89.4	221	137	<LOD–804	84.2%	65.6	153	310	209	<LOD–776	93.3%
mBZP	<LOD	<LOD	1.91	4.42	<LOD–81.2	29.6%	<LOD	7.92	33.6	21.2	<LOD–166	61.3%
mEHP	<LOD	3.21	15.1	10.9	<LOD–221	60.4%	7.05	13.8	23.0	17.2	<LOD–67.8	94.6%
∑mPAEs	80.0	190	373	267	<LOD–1169	99.6%	155	312	578	378	4.52–1410	100%

DF: detection frequency; BPA: bisphenol A; BPAF: bisphenolAF; BPAP: bisphenol AP; BeP: benzylparaben; BPF: bisphenolF; BPP: bisphenol P; BPS: bisphenol S; BPZ: bisphenol Z; BuP: butylparaben; EtP: ethylparaben; MeP: methylparaben; MBP: mono-n-butyl phthalate; miBP: monoisobutyl phthalate; mBZP: monobenzyl phthalate; mEHHP: mono(2-ethyl-5-hydroxyhexyl) phthalate; mEHP: mono(2-ethylhexyl) phthalate; mEOHP: mono(2-ethyl-5-oxohexyl)phthalate; mEP: monomethyl phthalate; mMP: monomethyl phthalate; mPAEs: phthalate metabolite; OH-PAH: hydroxyl polycyclic aromatic hydrocarbon; OH-NaP: hydroxynaphthalene; OH-Flu: hydroxyfluorene; OH-Phe: hydroxyphenanthrene; PrP: propylparaben; TCS: triclosan; 1-OH-Pyr: 1-hydroxypyrene; 3-OH-BaP: 3-hydroxybenzo(a)pyrene.

from not detected to 354 ng/mL, with a mean of 40.0 ng/mL in suburban regions, which was higher than the mean value measured for urban regions (28.3 ng/mL). Noticeable variations in the measured concentrations of OH-PAHs are indicative of large inter-individual variation in the exposure to these compounds. The urinary concentrations of 1-OH-NaP, 2-OH-NaP, and 1-OH-Pyr reported in the present study are slightly higher than the concentrations observed among the American and Australian general population (Luderer et al., 2017; Thai et al., 2016), but several times that of mothers and their newborn children in the Ceske Budejovice (Urbancova et al., 2017), which suggests that the general population in Guangzhou is exposed to rather high levels of PAHs.

3.2. Composition profiles and source implications

As region, gender, or age did not impart significant effects on the urinary composition characteristics of different target compounds (Fig. S1), the composition patterns in all urine samples can be further discussed (Fig. 1). For parabens, MeP was the most abundant compound, accounting for 63.8% of total parabens, followed by EtP and PrP. A similar composition profile, i.e., MeP accounting for

more than half of total parabens, has been reported from China (Zhao et al., 2017), which could be explained by the widespread use of this compound, along with rapid excretion via urine because of the high hydrophilicity and low octanol-water distribution coefficient of MeP ($\log K_{ow} = 1.96$) (Lu et al., 2019; Yu et al., 2019). Similar results were also reported in publications from the United States and Japan (Nishihama et al., 2016; Pycke et al., 2015). However, EtP was the most abundant paraben in urine and break milk samples from Korea (Kim et al., 2018; Park et al., 2019), a finding which was mainly attributed to the widespread use of this compound in Korean PCPs (Jo et al., 2020). Therefore, the use of a specific paraben in widely used PCPs and the kinetics of elimination from the human body are the main factors underlying the paraben profile of urine.

Concerning bisphenols, BPA was the predominant analogue, accounting for an average of 87.4% of total bisphenols. Comparatively, bisphenol analogues other than BPA have rarely been detected in urine. Previous literature covering Korea, Hong Kong, China, and the United States has focused on BPA, BPS, and BPF concentrations in urine (Kang et al., 2020; Mendy et al., 2019; Zhao et al., 2018). For example, BPF and BPS were occasionally detected in urine samples from Australia (Heffernan et al., 2016), while BPP was found in the urine of Brazilian school students (Rocha et al.,

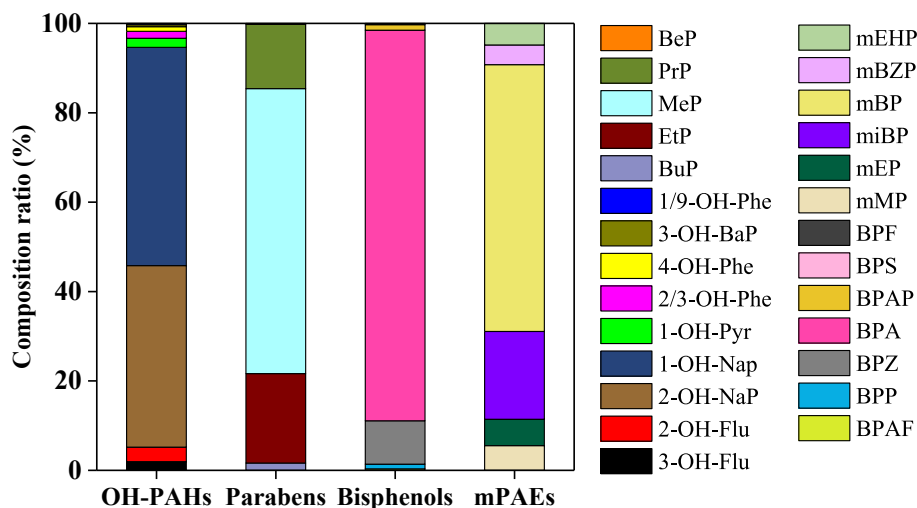


Fig. 1. Composition profiles of the parabens, bisphenols, mPAEs and OH-PAHs detected in urine samples from Guangzhou, south China.

2018). Although some studies have suggested a gradual increase in the use of other bisphenols, e.g., BPS and BPF, in various materials, BPA nevertheless remains the most commonly used bisphenol in industry (Sanchis et al., 2019). This would explain our result that BPA was the clearly dominant bisphenol analogue detected in urine samples.

For mPAEs, mBP was the most prevalent PAE metabolite (accounting for 59.7% of total mPAEs), followed by miBP and mEHP, which accounted for 20.0% and 4.83%, respectively, of total mPAEs. Similar results have been reported earlier, with the prevalence of these compounds in samples explained by the widespread use of the parent compounds due to excellent malleability (Henriksen et al., 2020; Li et al., 2020; Onipede et al., 2019; Zhang et al., 2018). In general, high molecular weight PAEs, such as di-n-butyl phthalate (parent compound of mBP) and di (2-ethylhexyl) phthalate (DEHP) (parent compound of mEHP), are generally used in PVC (polyvinyl chloride) floor, medical and food packaging materials. All of these PAEs are rapidly metabolized and excreted in the urine due to their very short biological half-lives (usually less than 24 h).

Two metabolites of naphthalene, 1-OH-NaP and 2-OH-NaP, were the two most prevalent OH-PAHs, accounting for 48.8% and 40.6% of the total OH-PAHs, respectively. Hence, total OH-NaP constituted about 90% of total OH-PAHs (Fig. 1), followed by 2- and 3-OH-Flu, which accounted for 3.22% and 1.96%, respectively, of total OH-PAHs. These composition distributions indicate that humans can metabolize PAHs, especially those containing naphthalene and fluorine, which usually exist in the air and are inhaled by humans. For example, both 1-OH-NaP and 2-OH-NaP arise from exposure to naphthalene, which is a byproduct of biomass burning, petrochemical emission, even vehicle exhaust (Peng et al., 2020; Thai et al., 2016). In addition, 1-OH-Pyr accounted for 2.03% of the total OH-PAHs. This chemical represents the biomarker most commonly used to assess human exposure to PAHs, and indicates excessive exposure to the burning of biomass fuels or traffic pollution (Chang et al., 2019). Therefore, the distribution profile of OH-PAHs in the analyzed urine samples suggests that inhalation might be an important route of exposure to the PAH isomers among the general population of Guangzhou.

In a previous study, the principal component analysis (PCA) was used to investigate the exposure pathways of target compounds (Ding et al., 2019). In the present study, urine samples collected

from Guangzhou were used to evaluate the exposure pathways using the same method. Although the number of biomarkers included was limited, it still revealed valuable information, such as the identification of the major exposure pathways to several important compounds. As described in Table S6, it was found that three PCA factors are likely indicative of different exposure pathways including inhalation, oral ingestion, and dermal contact. In the present study, three factors (named PC1, PC2, and PC3) were extracted (Fig. 2), which covered 62.3% of the total variance (Table S6). PC1 (27.0%) included MeP, EtP, PrP, and mEP, with loadings of 0.922, 0.618, 0.899, and 0.857, respectively. All of these contaminants are widely used in PCPs, which indicates that people are mainly exposed to these chemicals via dermal contact. Although these compounds may also come from other exposure routes in the actual environment, compared with dermal contact, the loading scores in PC2 or PC3 were less than 0.5, representing only a less fraction for other exposure pathway. Therefore, PC1 could be explained the exposure pathway of dermal absorption.

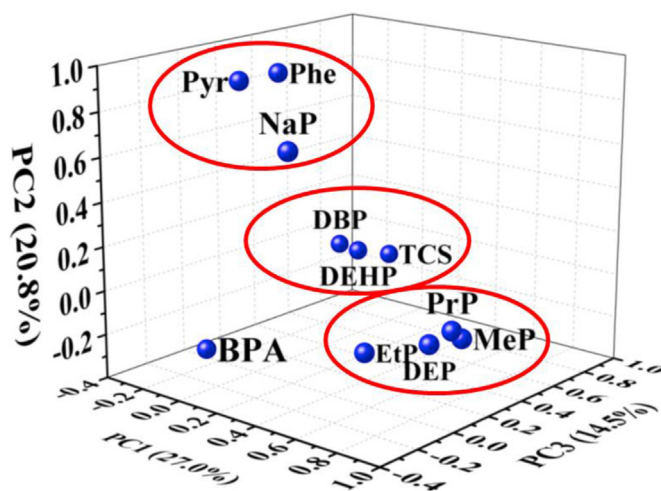


Fig. 2. Principal component analysis plot of the total estimated daily intake of parabens, bisphenols, TCS, mPAEs, and OH-PAHs. DBP: di-n-butyl phthalate (parent compound of mBP); DEHP: di (2-ethylhexyl) phthalate (parent compound of mEHP); DEP: diethyl phthalate (parent compound of mEP); Phe: 2-OH-Phe, 3-OH-Phe, 4-OH-Phe, 1-OH-Phe and 9-OH-Phe; NaP: 2-OH-NaP, 1-OH-NaP; Pyr: 1-OH-Pyr.

PC2 (20.8%) included OH-NaP, OH-Phe, and OH-Pyr, with loadings of 0.716, 0.903, and 0.922, respectively. All of these chemicals are PAH metabolites, with the parent compounds produced from the incomplete combustion of petrochemical fuels and bio-materials, which is particularly relevant for naphthalene. Compared with inhalation exposure, oral intake and dermal contact are much less. Hence, we suggest that residents of Guangzhou are primarily exposed to the present PAH isomers especially for naphthalene via inhalation. PC3 (14.5%) included mEHP, mBP, and TCS, with loadings of 0.615, 0.700, 0.771, respectively. As plasticizers, PAEs are generally added to food packaging and detected in food, while TCS is widely added to pharmaceuticals and toothpaste. Oral ingestion (especially dietary intake) has previously been considered the predominant exposure pathway for PAEs and TCS, although humans can also be exposed to mPAEs and TCS through dermal contact. The amount of dietary intake far exceeded the dermal contact as reported in the literature (Dong et al., 2017; Frigerio et al., 2020; Rodriguez-Carrillo et al., 2019). Additionally, PCA results also showed the low loading score of PC1 and PC2. Thus, PC3 represents the oral ingestion exposure pathway. Noteworthy, BPA was influenced by multiple exposure pathways (Fig. 2). Finally, it should be noted that there was still approximately 37% of the variance can't be explained by the three factors, although 63.2% of the variance were explained by the inhalation, oral ingestion, and dermal contact pathways (Table S6). Much more study are necessary.

3.3. Effects of demographic characteristics on urinary concentrations of contaminants

The stratified urinary concentrations based on region, gender, age, and body mass index (BMI) are shown in Fig. 3. Regional differences were observed for OH-PAHs and mPAEs. More specifically, suburban areas were characterized by significantly higher concentrations of these two classes of chemicals than urban regions ($p < 0.05$ and $p < 0.01$, respectively) (Fig. 3A). The result might be a reflection of the presence of numerous industrial production facilities (plastic and coating processing plants) in the suburban districts, including ZC and HD, of Guangzhou. This speculation is supported by the fact that ZC and HD showed significantly higher total industrial output values than the TH and YX urban areas (Table S7). Our results partly agree with previous research, as Afghan women living in rural regions showed significantly higher urinary levels of 1-OH-Pyr than women living in urban districts (Hemat et al., 2012). There was also a report that 1-OH-NaP may be metabolized from the carbamate insecticide carbaryl in gardening and agricultural settings (APVMA, 2014). Both of these results suggest that rural populations are more exposed to PAHs and PAEs, and would therefore show higher urinary levels of OH-PAHs and mPAEs, than urban populations. It should be noted that no regional differences in the urinary concentrations of parabens, bisphenols, or TCS were observed (Fig. 3A), although these compounds were present at slightly higher levels in the urban population than the suburban population.

The effect of gender on the urinary concentrations of various

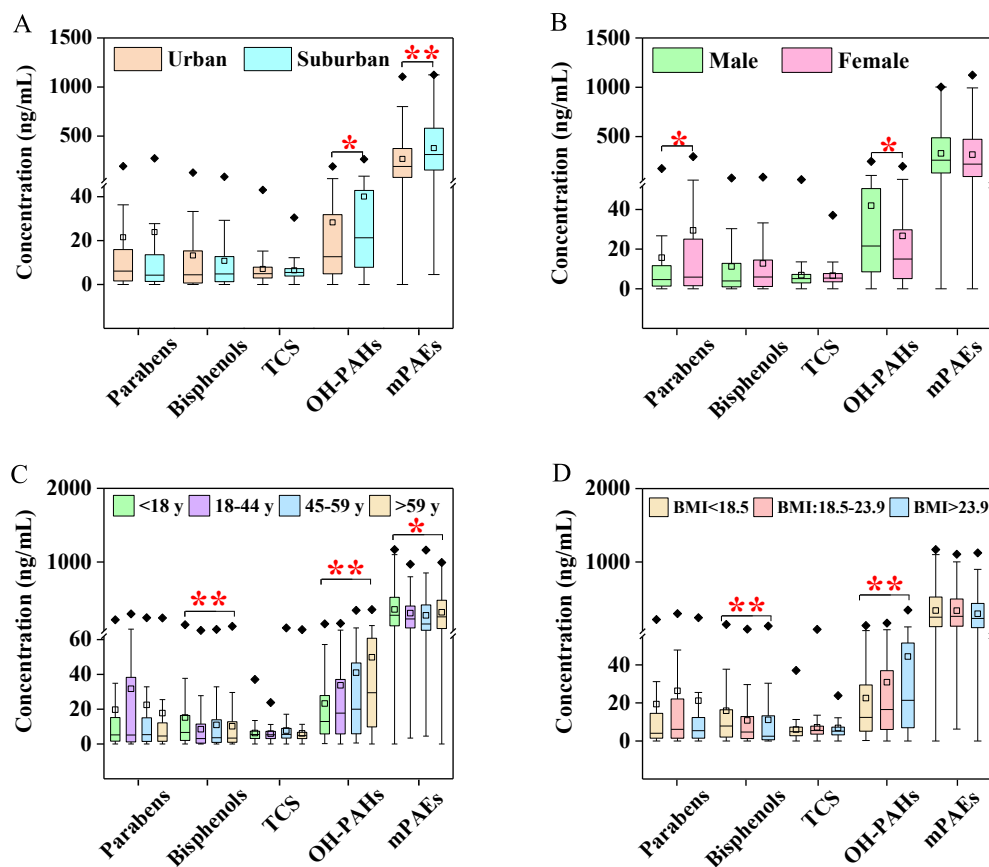


Fig. 3. Differences in urinary levels of parabens, bisphenols, TCS, mPAEs, and OH-PAHs based on demographic characteristics (A: region; B: gender; C: age; D: BMI). The lower and upper limits of the box denote the 25th and 75th quartiles, respectively, while the horizontal line within the box represents the median value. The length of the whiskers is 1.5 times the interquartile range, while the rhombus symbol denotes the 99th percentile. The small rectangular boxes represent average values and the star symbol means that there are significant differences between groups (*: $p < 0.05$; **: $p < 0.01$).

compounds is shown in Fig. 3B. The analyses revealed that females have higher urinary concentrations of parabens than males, with this difference especially strong for parabens ($p = 0.034$). This may be explained that the high concentrations of parabens have associated the high use frequency of PCPs based on the questionnaire (Table S8), for the parabens as main ingredients added in PCPs (Frederiksen et al., 2014; Rocha et al., 2018). The females in the present study reported longer mean shower times than males (8.8 h/month vs. 7.7 h/month), and also washed their hands and used repellents, disinfectants, toilet cleaners, and other PCPs more frequently than males. Therefore, female exposed to more parabens can be expected (Table S8). However, an opposite trend was noted for OH-PAHs and mPAEs, with the trend stronger for OH-PAHs. A higher incidence of smoking might one of the reason for the higher urinary levels of OH-PAHs in males than females ($p < 0.01$) because smoking is a recognized source of PAHs. According to the present study (Table S8), 70.0% of the male participants exposed to second-hand smoke more than once a week, which noticeably exceeded the corresponding results for females (54.6%). In addition, males reported consuming fried and grilled foods more often than females, and this may have also contributed to the increased PAH exposure among males (Table S8).

Different living habits may also affect human exposure to various contaminants based on the sub-parameters (Table S9). The effect of age on the concentrations of the studied chemical contaminants was analyzed (Fig. 3C). The results showed statistically significant differences among various age groups (including <18, 18–44, 45–59, and >59 years) for the urinary concentrations of bisphenols ($p < 0.01$), OH-PAHs ($p < 0.01$), and mPAEs ($p < 0.05$). The variability was likely due to the differences in distinct lifestyle habits (use of chemicals in consumer products or PCPs), behaviors, and metabolic capability among individuals. For example, the subjects smoking in the last 24 h accounted for the largest proportion between the ages of 18–59, and those drinking in the last 24 h was the largest for age of 45–59 (Table S9). Similarly, BMI-dependent differences were observed for bisphenols ($p = 0.002$) and OH-PAHs ($p = 0.001$), with the BMI > 23.9 group demonstrating the highest urinary concentrations (Fig. 3D). This result suggests that obese individuals are more susceptible to bisphenol and OH-PAH exposure than lower-BMI individuals (Ashrap et al., 2018). In addition, the BMI meaning of the degree of obesity, extremely related to human metabolism, such as lung function and cardiovascular metabolism. Several studies have proposed that obesity affected the exposure level of bisphenols and OH-PAHs in the human body (Lu et al., 2020; Mu et al., 2019; Poursafa et al., 2018; Wu et al., 2020). Therefore, differences in lifestyle, surrounding environment and metabolic capability can significantly influence human burden of the chemicals.

3.4. Other factors that influence urinary contaminant levels

To further investigate which factors influence the urinary levels of various contaminants, the associations between urinary concentrations and genetic disease, residential time, dietary characteristics, and certain lifestyle habits were analyzed. The results are listed in Table 2. The presence of genetic disease did not significantly impact the urinary concentrations of any of the analyzed contaminants ($p = 0.298$ – 0.845).

For the chemicals generally used in PCPs, significant differences between lifestyle factors and urinary contaminant concentrations were observed. For example, individuals who reported having used hair dye showed significantly higher median concentrations of parabens ($p = 0.002$) and TCS ($p = 0.030$) than individuals who did not use hair dye (disregarding having used hair dye when underage). Similar result was also observed for mPAEs. In contrast, the

participants who reported taking pills and taking nutrients had significantly lower levels of urinary mPAEs than the other participants ($p < 0.05$). In addition, individuals who had lived in Guangzhou less than 15 years showed significantly higher urinary concentrations of bisphenols than individuals who had lived locally for more than 15 years ($p = 0.001$), whereas an opposite trend was noted for OH-PAHs ($p = 0.007$). This suggests that the place of residence imparts an important influence on human exposure to bisphenols and OH-PAHs, although this factor should be studied in more detail.

Although inhalation is an important exposure pathway for PAHs, we also analyzed whether an individual's dietary habits, including taking pills, smoking, drinking, consuming barbecue and/or fried food, could expose them to PAHs (Table 2). Smoking and drinking significantly impacted the urinary concentrations of OH-PAHs ($p < 0.01$), although the urinary concentrations of OH-PAHs were not affected by the frequency of taking pills or consuming barbecue and/or fried foods ($p > 0.05$). The positive correlation between smoking and OH-PAH levels was not surprising because cigarette smoke contains PAHs as aforementioned, which is also consistent with inhalation being the main exposure pathway for the PAHs. In addition, many Chinese men smoke when they drink. Therefore, the high urinary levels of OH-PAHs in individuals who often drink may actually be a result of smoking rather than drinking. The effects of smoking and drinking habits on the urinary concentrations of various compounds have been studied before (Hoseini et al., 2018; Yu et al., 2019), although no significant correlation between urinary OH-PAHs and smoking frequency has been previously reported (Gaudreau et al., 2016). In addition, the frequency of swimming significantly impacted the urinary concentration of OH-PAHs ($p = 0.029$). In south China, many swimming pools are open-air. Therefore, those who swim often spend more time outdoors. The lower urinary levels of OH-PAHs observed in individuals who swam often (11.1 vs. 19.0 ng/mL in individuals who did not swim often) were consistent with lower median OH-PAH concentrations among individuals who were frequently outside (13.9 vs. 21.1 ng/mL in individuals who stayed indoors). The present study indicates that smoking and time spent in indoor environments are important factors influencing human exposure to PAHs.

3.5. Human health risk assessment

To assess the potential health risks of the contaminants, non-carcinogenic risks were estimated using the HQ value and cumulative health risk (HI) of multiple contaminants using addition method of the individual HQ value (Du et al., 2014). The HQ values for TCS, parabens, bisphenols, OH-PAHs, and mPAEs were 0 – 5.0×10^{-4} , 0 – 0.74 , 0 – 0.18 , 0 – 1.06 and 0 – 8.17 , respectively. The mean HQ values of these compounds were 0.21×10^{-4} , 0.012 , 0.008 , 0.076 and 0.76 , respectively (Fig. S2). The mean HI value was 0.86 , which did not exceed the safe risk level, whereas a portion of the population was exposed to health risks. To further evaluate the non-carcinogenic risks of multiple compounds, Monte Carlo simulations were performed based on the simulated accumulation curve of $\lg(\text{HQ})$ (Fig. 4A). The results demonstrated that 0.4% and 26.7% of the 480 participants had been exposed to levels of OH-PAHs and mPAEs that constituted a health risk ($\lg(\text{HQ}) > 0$). Among the studied contaminants (Fig. 4B), mPAEs accounted for 89% of the total risk, and were hence the predominant health risk, followed by OH-PAHs (8.9%). The present results indicated that the relevant health authorities should pay more attention to the potential health risks of PAE exposure.

The health risks were then investigated in more detail, i.e., the effects of age, gender, region, and BMI on health risk were analyzed. The results revealed that parabens pose a larger threat to females

Table 2
Effects of demographic characteristics, dietary characteristics, and health status on urinary concentrations (ng/mL) of parabens, bisphenols, TCS, OH-PAHs, and mPAEs.

Group	Number (percentage)	Parabens			∑Bisphenols			TCS			OH-PAHs			mPAEs		
		Median	IQR	<i>P</i>	Median	IQR	<i>p</i>	Median	IQR	<i>p</i>	Median	IQR	<i>p</i>	Median	IQR	<i>p</i>
Genetic illness																
NO	281 (61.9%)	5.28	14.4	0.698	4.60	12.9	0.845	5.10	4.48	0.426	18.4	36.0	0.298	244	377	0.387
YES	173 (38.1%)	5.29	13.3		4.43	12.0		5.43	4.00		17.6	27.8		258	378	
Residence time																
≤15	115 (28.6%)	5.06	13.7	0.848	7.01	13.2	0.001**	5.41	4.50	0.665	13.9	23.3	0.007**	273	393	0.352
>15	287 (71.4%)	5.43	3.95		3.20	2.51		5.22	2.00		21.1	14.6		228	339	
Taking pills																
NO	396 (82.5%)	5.10	14.2	0.723	4.94	12.8	0.210	5.27	4.17	0.524	16.6	31.7	0.540	258	370	0.044*
YES	84 (17.5%)	5.60	10.5		2.82	12.0		5.54	4.73		20.0	29.0		187	322	
Taking nutrients																
NO	439(91.5%)	5.06	13.6	0.805	4.49	12.5	0.057	5.28	4.36	0.936	18.5	31.9	0.162	256	368	0.022*
YES	41(8.5%)	6.01	13.4		7.50	11.9		5.42	4.30		10.5	20.0		189	381	
Smoking																
NO	422 (87.9%)	5.20	14.1	0.295	4.71	12.9	0.595	5.27	4.31	0.793	15.6	28	0.000**	245	375	0.865
YES	58 (12.1%)	5.09	9.21		4.02	12.4		5.44	4.84		44.4	77.7		260	287	
Drinking																
NO	458 (95.4%)	5.10	13.6	0.971	4.67	13.1	0.960	5.35	4.46	0.969	16.6	29.0	0.000**	251	370	0.160
YES	22 (4.6%)	5.36	10.1		4.54	10.9		4.99	2.28		54.3	91.4		183	236	
Consuming barbecue food																
Less frequently	272 (56.7%)	5.27	13.6	0.864	4.32	12.2	0.652	5.20	4.63	0.790	19.0	33.1	0.300	228	349	0.263
More frequently	208 (43.3%)	4.98	13.8		5.13	13.5		5.36	3.94		16.5	28.0		274	390	
Consuming fried food																
Less frequently	122 (25.4%)	5.86	13.2	0.882	4.14	12.5	0.712	4.87	4.37	0.265	16.6	34.4	0.866	223	356	0.155
More frequently	358(74.6%)	5.04	13.7		4.71	12.9		5.40	4.36		18.2	30.9		254	385	
Using hair dye																
NO	158 (53.7%)	3.75	9.87	0.002**	3.92	10.2	0.065	5.11	4.55	0.030*	22.5	46.4	0.205	182	314	0.022*
YES	136 (46.3%)	6.81	35.0		4.46	13.6		5.53	4.23		19.0	29.2		260	366	
Washing hands																
Less frequently	392 (81.7%)	5.05	12.2	0.529	4.94	13.6	0.977	5.43	4.31	0.358	19.9	34.1	0.111	246	380	0.832
More frequently	88 (13.8%)	5.29	14.6		4.60	12.1		5.14	4.19		16.13	27.3		254	295	
Swimming																
Less frequently	239 (49.8%)	4.95	13.4	0.702	4.38	13.3	0.061	5.37	4.15	0.625	19.0	32.3	0.029*	246	351	0.828
More frequently	241 (50.2%)	4.99	15.8		7.66	12.7		4.83	5.17		11.1	22.7		251	381	

IQR: interquartile range; TCS: triclosan; OH-PAH: hydroxyl polycyclic aromatic hydrocarbon; mPAEs: phthalate metabolite; *: $p < 0.05$; **: $p < 0.01$.

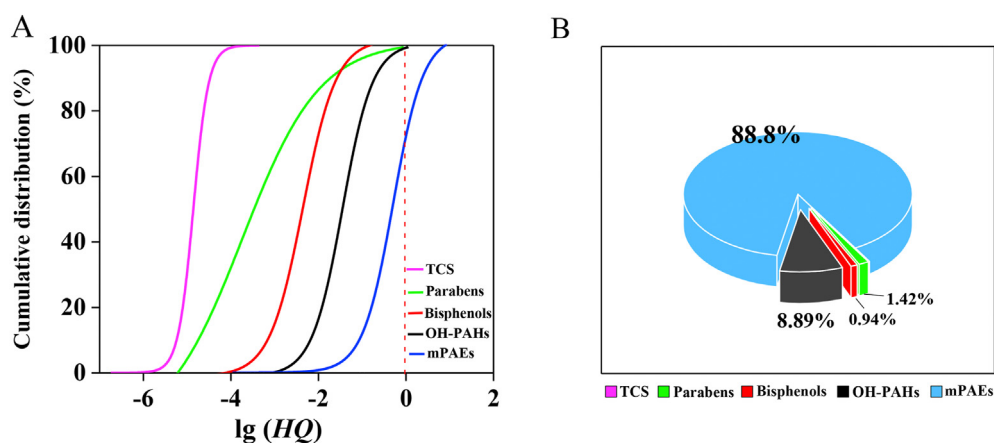


Fig. 4. A: Monte Carlo simulation of the hazard quotient (HQ) for multiple compounds based on urinary concentrations among residents of Guangzhou, China. B: relative contributions of various compounds to the estimated HQ (the proportion of TCS is close to 0).

than males across most age groups, especially 5–8-year-old children and 18–44-year-old adults ($p < 0.05$) (Fig. 5A). A similar dynamic was observed for both bisphenols and TCS, with females between the ages of 12–14 and 18–44 at more risk than males in the same age group. However, an opposite trend was observed for OH-PAHs (Fig. 5B), particularly for males over the age of 15 years, which can be explained by males over the age of 15 years being more susceptible to smoking than females. No significant health risk differences were found between females and males for mPAEs. Region and BMI also contributed to the potential health risks

(Fig. 5C and D). The risk posed by OH-PAHs was affected by region ($p < 0.01$), while the risk posed by bisphenols was affected by BMI. Both region and BMI have a significant influence on the health risk associated with mPAEs ($p < 0.01$). For smokers and non-smokers, there was no significant difference in health risks, shown in Fig. S3. Overall, none of them exceed the risk value, except for a smoker.

It is important to discuss several uncertainties that could have affected the risk assessment results. Firstly, the lack of reference dose (RfD) values for BuP, BeP, and the BPA homologues, along with

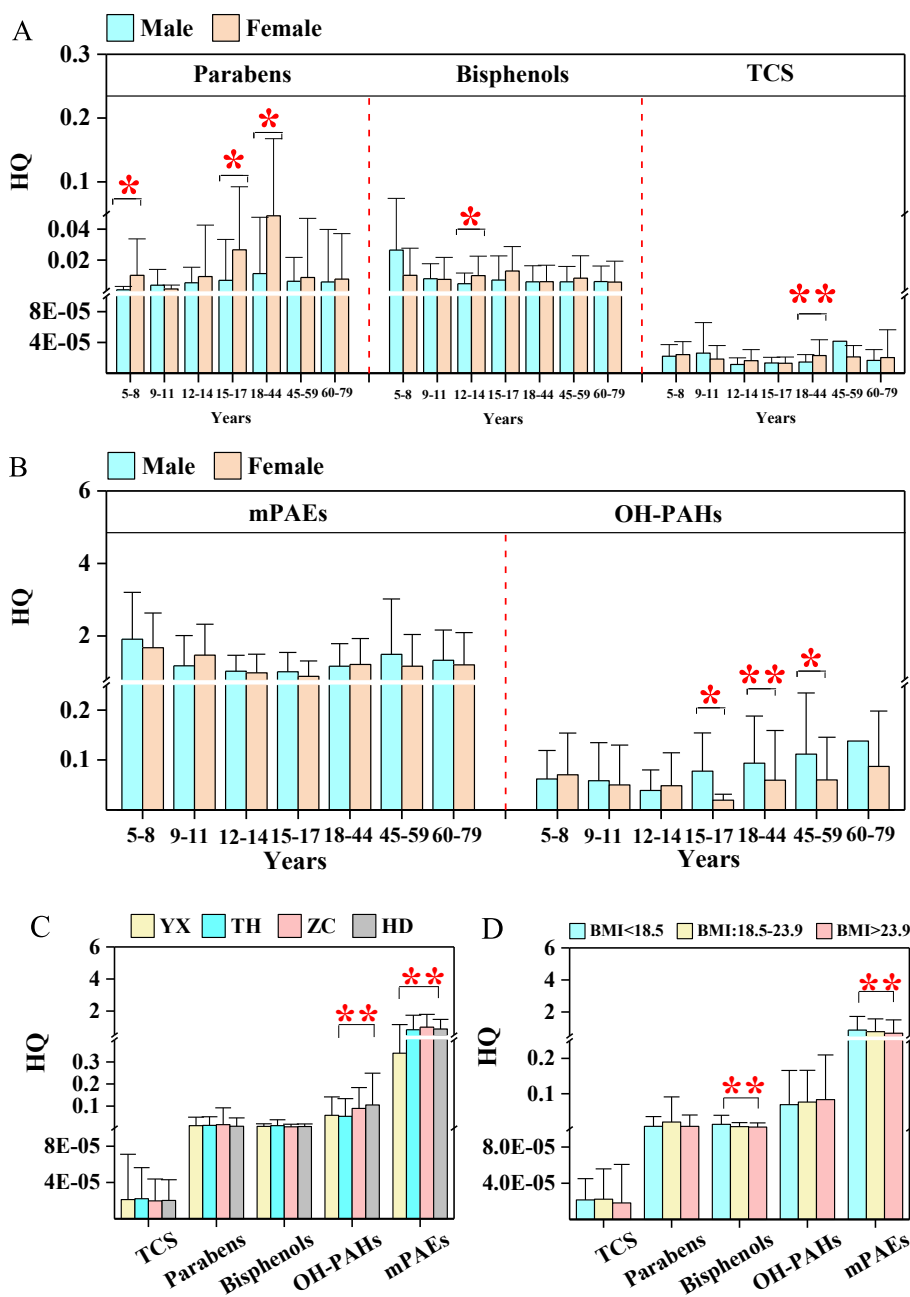


Fig. 5. A: Differences in the hazard quotient (HQ) of parabens, bisphenols, and TCS between males and females representing various age groups; B: Differences in the HQ of mPAEs and OH-PAHs between males and females representing various age groups; C: HQ differences between different regions; D: HQ differences based on BMI value. Star symbols indicate significant differences between groups (*: $p < 0.05$; **: $p < 0.01$).

extremely low concentrations and detection frequencies for 3-OH-BaP, means that these chemicals were not included in the HQ measurements as the results would have underestimated the health risks of these compounds. Secondly, the RfD reflects the highest daily exposure rather than appreciable risk over a lifetime. Hence, the non-carcinogenic health risks presented in this study may be overestimates because of conservative exposure assumptions. In addition, other references such as the tolerable daily intake and reference dose for anti-androgenicity were also used in the literature for the health risk assessment, which might result different risk values than those by using RfD. Finally, the present assessment of the health risk posed by multiple contaminants attempted to take into account the interactions between various

contaminants, as simply adding the risks of each compound could add a fair level of uncertainty to the estimation.

4. Conclusions

The simultaneous detection of OH-PAHs and contaminants found in PCPs from urine samples representing the general population of Guangzhou indicated that these compounds (parabens, bisphenols, TCS, mPAEs, and OH-PAHs) are now ubiquitous in human bodies. Regional and gender differences in the levels of contaminants were observed, with OH-PAHs being more prevalent in suburban than urban samples, and compounds added to PCPs (more specifically, TCS and bisphenols) being more prevalent in

females than in males. In addition, lifestyle choices and habits, such as drinking, smoking, swimming, and personal cleaning can significantly influence human exposure to various ubiquitous contaminants. Combining the simultaneous detection of multiple contaminants from urine with PCA analysis can be used to determine the main exposure pathways for distinct substances. The present health risk assessments revealed that 26.7% of the subjects suffered obvious non-carcinogenic risks from exposure to the studied contaminants, with PAEs posing the largest risk. Considering the significant health risk associated with PAEs, further research should focus on elucidating the main pathways through which humans are exposed to this class of compounds.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2020.115990>.

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