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Urinary phthalate metabolites and environmental phenols in university students in South China

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ABSTRACT

In China, university students have unique lifestyles compared with the rest of the youth population, as they are almost entirely isolated in campuses. The number of university students is large, and since students represent the future of human reproduction, exposure to environmental endocrine disruptors (EEDs) may have a large impact on society. In this study, levels of several EEDs, including phthalate metabolites, parabens, bisphenol A (BPA) and its analogues, triclosan (TCS), and benzophenone-3, were determined in 169 urine samples collected from university students in Guangzhou, South China. In addition, to further understand the potential sources of EEDs in their daily lives, a survey of students' lifestyles was conducted. Based on the urinary concentrations of EEDs and the survey results, daily exposure doses of target EEDs and their potential sources were investigated. Our results indicated that nine phthalate metabolites, three parabens, and BPA were ubiquitous (detection frequency > 60%) in the urine of university students. The concentrations of total phthalates (median: 99.4 $\mu g\,L^{-1}$) were orders of magnitude higher than those of total parabens (7.30 $\mu g\,L^{-1}$) and of other environmental phenols (0.40 $\mu g\,L^{-1}$). Significantly higher concentrations of phthalates, parabens, and TCS were found in female versus male students, partly due to the higher usage of personal care products (PCPs) by female students ($p < 0.05$). The estimated daily intakes (EDIs) of phthalates, parabens, BPA, and TCS were 0.46–1.35, 3.29–10.3, 0.007, and 0.67 μg/kg-bw/day, respectively. The EDIs of phthalates and BPA were much lower than those suggested by the European Food Safety guidelines (10, 50, and 50 μg/kg-bw/day for dibutyl phthalate, diethylhexyl phthalate, and BPA, respectively). Our results indicated that university students were widely exposed to EEDs, but at relatively low doses. PCP usage was the main reason for differences in levels of phthalates (especially diethyl phthalate) and parabens between male and female students in South Chinese universities.

1. Introduction

Phthalates and environmental phenols are widely used as solvents, plasticizers, preservatives, or as intermediates in numerous consumer products, such as polyvinyl chloride materials, personal care products (PCPs), pharmaceuticals, foodstuffs, and other products (Barusic et al., 2015; Guo et al., 2014, 2012; Jia et al., 2016). They have been detected in indoor dust, air, PCPs, food and drinking water, as documented in various papers (Guo and Kannan, 2011, 2013; Guo et al., 2012; Liao and Kannan, 2014). These chemicals, known as environmental endocrine disruptors (EEDs), may have potentially adverse effects on human health, and humans are exposed to them on a daily basis through inhalation, oral ingestion, and dermal absorption (Wittassek et al., 2011).

Several epidemiological studies have reported that exposure to phthalates or their metabolites may lead to reproductive and developmental toxicities (Hauser et al., 2016; Scinicariello et al., 2016), and that these substances may have positive relationships with obesity, headaches, coughing, and itching (Buckley et al., 2016; Kim et al., 2016). Like phthalates, parabens also act as a group of weak estrogenic and anti-androgenic chemicals (Soni et al., 2005). Inverse associations in concentrations between parabens and thyroid hormones were found in adults, and parabens were reported to be negatively associated with menstrual cycle length in women (Koeppe et al., 2013). Concurrently, 3,4-dihydroxybenzoic acid, a paraben metabolite, has also been associated with obesity and higher levels of this chemical were found in obese children than in non-obese children (Xue et al., 2015). In addition, recent studies have indicated that type 2 diabetes, hypertension, early microvascular diseases among middle-aged and elderly Chinese

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people, and wheezing in early life were associated with BPA exposure (Kim and Park, 2013; Spanier et al., 2012; Wang et al., 2015b). However, the potential biological mechanisms by which EEDs affect human health are not clear and those proposed by different studies are inconsistent. For instance, Reddy et al. reported that exposure to phthalates was associated with endometriosis, while another study concluded that no relationship existed between the two (Itoh et al., 2009; Reddy et al., 2006a, 2006b). In addition, one study reported a negative relationship between levels of urinary monoethyl phthalate and sperm motility in men, while no associations were found in another similar study (Joensen et al., 2012; Jonsson et al., 2005).

There is a diversity of biomonitoring data on human exposure to phthalates, parabens, and environmental phenols, including background exposure investigations for general or vulnerable populations, exploration of potential sources, and environmental epidemiologic studies of disease (Guo and Kannan, 2011; Guo et al., 2011; Lind et al., 2012; Xue et al., 2015). For example, studies have assessed phthalate exposure in children, babies, pregnant women, and in the general populations of many countries (Asimakopoulos et al., 2014; Axelsson et al., 2015; Bamai et al., 2015; Guo et al., 2011; Han et al., 2014; Kim et al., 2016). In addition to such studies, it is also essential to assess exposure levels of EEDs in the young population, such as in university students who will be important for societal development and human reproduction in the very near future. In China, the number of full-time undergraduate and graduate students in universities exceeded 33.8 million in 2014 (National Bureau of Statistics of China, 2014). Chinese university campuses are usually built in big cities, but are relatively isolated from the surrounding environment. Students have a unique lifestyle compared with the rest of the young population, e.g., staying in simply furnished dormitories or classrooms, eating in the school canteen together, having daily dermal contact with books and laptops, and using several varieties of PCPs. Therefore, university students may have a distinct fingerprint of EED exposure.

In the present study, 11 phthalate metabolites, six parabens, and 11 other environmental phenols (including nine bisphenol analogues, triclosan (TCS), and benzophenone-3 (BP-3), all containing two phenyl rings) were analyzed in 169 urine samples collected from students (who had already been living on campus for at least three months) at eight universities (all ranked in the Top 10 in Guangdong province) in Guangzhou, South China. Following this analysis, a questionnaire survey was carried out in order to further explore the potential sources of EED exposure, either in hard copy in classrooms or via a dedicated mobile phone application (APP) in the same universities to study the lifestyles of the students. The objectives of this study were as follows: 1) measure concentrations and profiles of phthalate metabolites, parabens, bisphenols, and other environmental phenols in university students; 2) investigate the potential sources of these EEDs; and 3) assess the daily exposure doses of these EEDs in university students in South China.

2. Materials and methods

2.1. Study population and sample collection

The target EEDs in the present study are metabolized in a short time, e.g., several hours, after entering the human body (Koch et al., 2005; Ma et al., 2013). In order to avoid the influence of chemical exposures from students' hometowns, urine samples were collected from volunteers in January 2016, immediately prior to the winter holidays, when the students had already lived on the university campus for at least three months. The first morning, urine was collected in a polypropylene tube, quickly transferred to a lab, and maintained at − 20 °C until analysis. A total of 169 urine samples, including those from 107 male and 62 female students (Table S1, "SI" designates figures and tables in the Supporting information thereafter) were collected from ten campuses of eight universities distributed in different districts of Guangzhou, South China (Fig. S1). Approvals for urine analysis were obtained from the Jinan University Review Board, Jinan University, China (2015-LSPK-029). After urine collection, a questionnaire survey of daily life of the students was carried out in October 2016 in the same universities. A similar questionnaire was answered in hard copy by students in classrooms or via a mobile phone APP, and a total of 702 completed and valid questionnaires were collected (169 by APP and 533 in hard copy) for final analysis.

2.2. Sample preparation and instrumental analysis

Three groups of EEDs were analyzed, including 11 phthalate metabolites (monomethyl phthalate (mMP), mono (3-carboxypropyl) phthalate (mCPP), monoethyl phthalate (mEP), mono (2-ethyl-5carboxypentyl) phthalate (mECPP), monoisobutyl phthalate (miBP), mononbutyl phthalate (mBP), mono (2-ethyl-5-oxohexyl) phthalate (mEOHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (mEHHP), monocyclohexyl phthalate (mCHP), monobenzyl phthalate (mBzP), and mono(2-ethylhexyl) phthalate (mEHP)), six parabens (methyl-paraben (MeP), ethyl-paraben (EtP), propyl-paraben (PrP), butyl-paraben (BuP), benzyl-paraben (BzP), and heptyl-paraben (HepP)), and nine bisphenol anologues ((bisphenol A (BPA), bisphenol S (BPS), bisphenol AF (BPAF), bisphenol AP (BPAP), bisphenol Z (BPZ), bisphenol G (BPG), bisphenol PH (BPPH), bisphenol BP (BPBP), and bisphenol F (BPF)), TCS, and BP-3.

Concentrations of the target EEDs in urine were determined with an isotope-diluted method (Iyer et al., 2018; Wang and Kannan, 2013). Briefly, urine samples were allowed to thaw to room temperature in the dark, and 0.5 mL of urine was transferred into a glass tube. Upon addition of 250 μL of ammonium acetate buffer (pH = 4.5), 50 μL of labeled internal standards (IS: phthalate metabolites (250 $\mu g\,L^{-1}$); parabens (200 $\mu g\,L^{-1}$), bisphenols (200 $\mu g\,L^{-1}$), TCS (200 $\mu g\,L^{-1}$), and BP3 (200 $\mu g\,L^{-1}$)), 50.0 μL of β-glucuronidase (Helix pomatia, β-glucuronidase/sulfatase) and 0.5 mL of HPLC-grade water, the sample was incubated at 37.0 °C overnight for deconjugation. All analytes were liquid-liquid extracted with ethyl acetate (3.0 mL) three times by shaking for 30 min. The combined supernatant was concentrated under a gentle stream of nitrogen to near-dryness and 0.5 mL of solvent (90% HPLC water/10% acetonitrile) was added for instrumental analysis. Urine creatinine levels and specific gravity were also determined. For creatinine estimation, 40 μL of thawed urine was diluted to 14 mL with water, and 50 μL of diluent and 750 μL of labeled internal standards were added. The instrumental analysis was conducted over two days. Specific gravity was determined using a digital handheld refractometer. Fifteen isotope-labeled chemicals were used as internal standards to quantify the concentrations of target EEDs and creatinine, including ^{13}C-MeP, ^{13}C-TCS, ^{13}C-BPS, ^{13}C-BPA, ^{13}C-mMP, ^{13}C-mEP, ^{13}C-mBP, ^{13}C-mBZP, ^{13}C-mCHP, ^{13}C-mCPP, ^{13}C-mECPP, ^{13}C-mEOHP, ^{13}C-mEHHP, D_4-miBP, and D_5-creatinine.

All analytes including urine creatinine were analyzed using an AB-Sciex 5500 triple quadrupole mass spectrometer (ESI-MS-MS; Applied Biosystems, Foster City, CA) equipped with a Shimadzu Nexera-XZ LC system (Shimadzu Corporation Inc. Kyoto). The details of the reagents and instrumental analysis protocols are shown in Table S2-S3.

2.3. Quality assurance and quality control (QA/QC), and data analysis

For each batch of 25 urine samples, two blanks (with HPLC water instead of urine), two spiked blanks (with a known amount of each target analyte added into HPLC water instead of urine) and three matrix-spiked samples (with a known amount of each target analyte added into urine samples) were analyzed. The results of the QA/QC system are shown in Table S4. As shown, trace levels of mMP, miBP, mBP, mEHP, BPF, and BPA (respective average concentrations: 0.24, 0.86, 0.62, 6.76, 2.09, and 1.03 $\mu g\,L^{-1}$) were found in the blanks, and were subtracted from the final reported data. The detection limits of all analytes ranged from 0.2 to 0.5 $\mu g\,L^{-1}$, and samples with analyte concentrations below the detection limits were assigned zero values for the following analysis. The reported concentrations of analytes were not adjusted by creatinine or by urine specific–gravity, unless indicated otherwise.

Data analysis was conducted using SPSS (Version 22.0). As the concentration values of EEDs did not show a normal distribution, we primarily used non-parametric tests. Comparison of concentrations of EEDs between male and female students, and between different urban areas or campus locations, was performed by employing the Kruskal-Wallis H-Test and the Mann-Whitney *U*-Test, separately. Relationships among concentrations of target EEDs in students were examined by Spearman Correlation analysis. $P < 0.05$ was defined as statistically significant.

3. Results and discussion

3.1. Lifestyles of university students in South China

In the present study, 702 valid questionnaires were collected from university students living in different districts of Guangzhou, including 282 male and 420 female students. General information, such as PCP usage, eating habits, smoking habits, time spent in different areas on campus, sleep quality, etc. collated from our questionnaire survey are summarized in Table 1.

The incidence of current smokers in all students was low in our study (5.7%), accounting for 11% of male and 2% of female students. A significantly higher usage frequency for all PCP types was found in female compared to male students; shampoo usage was an exception (daily usage: 31% of female and 77% of male students). Plastic bags, paper cups, and disposable tableware were used frequently by all students and no significant differences were observed between male and female students. To our surprise, around 20% of college students ordered fast food (packaged in plastic or paper materials) 3–7 times or more per week. With the rapid development of dedicated APPs on mobile phones, ordering food online has become easy and convenient. We checked the mobile phones of over fifty students in classrooms randomly, and found such APPs on each of the phones. This observation indicated that the students who were surveyed were more likely to have contact with plastic or paper food containers. Furthermore, more than one quarter of the students reported poor sleeping habits, and 36 students (5%) presented with symptoms of endocrine disorders as confirmed by a doctor's diagnosis.

3.2. Occurrence of target EEDs in university students

Detection frequencies and concentration distributions of target EEDs are shown in Table 2. Phthalate metabolites were found in > 90% of urine samples except for mCHP (not detected, ND), mBzP (15%), and mEHP (66%). Among parabens, only MeP, EtP, and PrP were found in 81%, 58%, and 63% of samples, respectively, while others were detected rarely (ND-8%). Among environmental phenols, the detection frequencies of all bisphenol anologues were low (< 6%), except for BPA (59%); the detection incidences of BP-3 and TCS were 25% and 47%, respectively. These results revealed a wide exposure to phthalates, parabens, BPA, and TCS in university students in South China. The detection frequencies of BuP, BzP, HepP, and BP-3, and bisphenols, except BPA, were too low and were excluded from further analyses.

In addition, we also examined the levels of EEDs in student groups categorized by sex, urban district, and residence time. Except for those of bisphenol analogues, concentrations (creatinine-adjusted) of phthalate metabolites, parabens, and TCS were significantly higher in female than in male students ($p < 0.05$, Fig. 1); such differences were found for parabens only if concentrations were not creatinine-adjusted. No difference was found in levels of EEDs among other groups.

3.2.1. Phthalate metabolites

Concentrations of total phthalate metabolites (median/range: 99.4/3.62–698 $\mu g\,L^{-1}$) were generally orders of magnitude higher than those of parabens (7.30/ND-481 $\mu g\,L^{-1}$) and of other environmental phenols (0.40/ND-197 $\mu g\,L^{-1}$) (Fig. 1, Table 2). The concentrations observed in our study were lower than those in young adults from rural and urban areas across China who had recently begun attending university (median: 329 $\mu g\,L^{-1}$), or in school children from the Yangtze River Delta (median: 169 $\mu g\,L^{-1}$) as reported by other studies in China (Gao et al., 2016a; Wang et al., 2015a). In addition, the sum of frequently detected phthalates in our study (99.4 $\mu g\,L^{-1}$) was lower than that reported in young adults, children, or students in Korea (125 $\mu g\,L^{-1}$), Denmark (207 $\mu g\,L^{-1}$), Japan (189 $\mu g\,L^{-1}$), Sweden (136 $\mu g\,L^{-1}$), and Canada (146 $\mu g\,L^{-1}$) (Axelsson et al., 2015; Bamai et al., 2015; Frederiksen et al., 2010; Hartmann et al., 2015; Lee et al., 2013; Saravanabhavan et al., 2013) (Fig. 2).

The concentration comparisons reflected the relatively lower phthalate exposure for university students in South China, compared with that reported in other domestic or international studies. As is known, human exposure to phthalates is from ingestion, inhalation, or dermal absorption. In our previous studies (Guo and Kannan, 2011; Guo et al., 2014, 2012), we found that food was the most important source for high phthalate exposure, especially for DEHP, which was found at high concentrations in meat or meat products, soft drinks, cooking oil, and in seafood. In addition, phthalates in indoor dust and PCPs also contributed considerably to human exposure.

The relatively low exposure of phthalates in university students might be attributed to several factors. First, previous studies have demonstrated that plastic tableware may leak considerable phthalates into foodstuffs during production or storage (Balafas et al., 1999; Fierens et al., 2012). Since most students eat in dining halls with stainless steel tableware and the food is usually cooked in a highly controlled manner, phthalate exposure from food should theoretically be low in such students. Also, this hypothesis could be partly supported by the fact that phthalate concentrations in male students who may eat a larger quantity of food were lower than those in female students in our study, though no difference in eating habits was observed between these groups in our questionnaire survey. Second, lower concentrations of phthalates were found in the indoor dust of college students' dormitories than in regular houses (Li et al., 2016). Furniture and other plastic products which may contain high levels of phthalates are very limited in university dormitories in China (Li et al., 2016). The typical furniture in dormitories consists of bunk beds and desks. In addition, the windows and doors of the dormitories are always open in South China, and this may reduce the occurrence of phthalates in the indoor environment. Based on the results of our questionnaire survey, more than half of the university students reported that they stay in their dormitories for 10–14 h per day, so we assumed that they were subject to lower levels of phthalates via indoor air and dust than are other populations in offices or in houses. Finally, as indicated by several previous studies, PCPs were important sources for human exposure to phthalates, especially those from the use of body wash, sunscreen, perfume, face cream, body and hand lotion (which contains a large amount of DEP), and nail polish (large amount of DBP) (Gao et al., 2016a; Guo et al., 2014). However, the frequencies of usage of these PCPs in university students were low in our study, especially those of sunscreen (< 1 time per week for 97%/36% of male/female students), nail polish (99%/82%), perfume (97%/71%), and body lotion (91%/37%). Thus, exposure to phthalates from PCPs was relatively low for all students. Further, even with limited PCP usage, significantly higher total phthalate concentrations were found in female students versus those in male students in the present study ($p < 0.05$, creatinine-adjusted) (Fig. 1), consistent with the more frequent use of PCPs by female students than by male students. This data also confirmed that PCP usage has a high impact on phthalate exposure, in agreement with previous studies (Sakhi et al., 2017).

Table 1

The lifestyle characteristics of university students in South China (total number = 702, including 282 male students and 420 female students). (Percentage of male students/percentage of female students, %).

PCP usage		*Sunscreen*	*Shower gel*	*Shampoo*	*Facial cleanser*	*Body lotion*
	seldom	96.8/36.2 [a]	14.3/6.19	2.56/0.24	44.0/3.82	91.1/37.1
	1–2 times per week	2.28/26.9	9.69/4.05	6.59/3.82	13.4/5.25	4.96/20.2
	2–5 times per week	0.38/16.0	11.2/12.4	13.6/65.4	8.21/10.0	1.06/21.2
	every day	0.38/21.0	64.7/77.4	77.3/30.6	34.3/80.9	2.84/21.4
		Toner	*Face cream*	*Facial mask*	*Eye cream*	*Hand cream*
	seldom	86.8/14.0	91.8/29.8	93.6/20.2	98.2/56.7	94.0/44.1
	1–2 times per week	6.76/5.24	3.19/17.9	5.34/41.0	1.07/12.9	4.26/26.6
	2–5 times per week	3.20/11.0	2.13/14.1	1.07/31.0	0.36/10.5	0.71/13.6
	every day	3.20/69.8	2.84/38.2	0/7.86	0.36/20.0	1.06/15.7
		Liquid makeup	*Nail polish*	*Lipstick*	*Perfume*	*Feminine hygiene wash*
	seldom	99.3/60.2	99.6/82.4	99.6/40.4	97.2/71.0	98.6/77.0
	1–2 times per week	0.71/17.6	0.36/11.2	0.36/23.8	2.49/14.3	1.07/9.52
	2–5 times per week	0/11.4	0/3.33	0/25.3	0/7.38	0/4.52
	every day	0/10.7	0/3.10	0/10.5	0.36/7.38	0.36/9.05
Eating and drinking habits	*Order fast food*	seldom	25.5/23.1	*Use tableware (> 2 times per week)*	*Use plastic cups*	34.4/31.9
		< 3 times a week	52.1/55.5		*Use plastic bags at breakfast*	60.3/66.9
		3–7 times a week	16.4/13.8		*Use disposable tableware, lunch box*	62.1/56.2
		> 7 times a week	6.08/7.54			
		Bottled drinks	*Canned food*	*Biscuits*	*Instant noodles*	*Packaged fruit snacks*
	seldom	19.8/28.6	82.4/82.6	54.8/37.2	65.8/62.6	66.7/59.8
	1–2 times per week	45.4/44.0	15.0/12.6	37.4/43.5	28.1/31.0	24.9/23.2
	3–5 times per week	23.2/23.1	2.64/4.03	6.85/16.7	4.82/6.11	6.67/13.0
	> 5 times per week	10.6/4.27	0/0.76	0.91/2.53	1.32/0.25	1.78/4.07
		Sausage, ham	*Packaged meat snacks*	*Oyster oil*	*Milk*	*Seafood*
	seldom	61.6/61.1	70.9/64.7	80.4/76.4	20.7/16.9	35.7/30.5
	1–2 times per week	27.5/27.6	24.2/24.8	17.0/17.8	30.4/35.8	43.8/52.8
	3–5 times per week	8.73/8.18	3.96/9.21	2.62/4.71	33.9/32.8	19.6/16.2
	> 5 times per week	2.18/3.07	0.88/1.28	0/1.05	15.0/14.6	0.89/0.51
Time spent on campus	*Dormitories*		*Outside*		*Classrooms and offices*	
	< 10 h	33.9/24.1	< 1 h	15.7/15.8	< 5 h	38.4/38.9
	10–14 h	52.0/62.1	1–3 h	36.3/35.4	5–8 h	34.8/35.6
	15–20 h	12.3/12.8	3–6 h	22.9/15.8	> 8 h	26.8/25.5
	> 20 h	1.76/1.01	> 6 h	25.1/33.1		
Other habits	*Smoking*	11/2.14	*Endocrine disorders*	8.20/23.4	*Poor sleep*	25.5/29.5

[a] 96.8% of 282 male students/ 36.2% of 420 female students seldom used sunscreen every week.

Among the 11 phthalate metabolites, concentrations of mBP (median: 26.2 $\mu g\,L^{-1}$) were the highest, followed by those of mECPP, mMP, mEP and miBP, mEOHP, and mEHHP, with median concentrations of 12.1, 10.4, 10.2 and 9.58, 4.50, and 2.24 $\mu g\,L^{-1}$, respectively. Concentrations of mEHP (1.01 $\mu g\,L^{-1}$) and mCPP (.82 $\mu g\,L^{-1}$) were the lowest (Fig. S2 and Table 2). The relative exposures were similar when concentrations were normalized by creatinine levels. The contribution of mBP to total phthalate metabolite exposure was the highest (34%), followed by that of the sum of metabolites of diethylhexyl phthalate (DEHP) (26%); the contributions of mMP, mEP, and miBP to total metabolite exposure were 14%, 13%, and 12%, respectively. The sum of mMP, mEP, miBP, mBP and metabolites of DEHP contributed about 98.9% of the total phthalate concentrations, which indicated that the participating students were primarily exposed to dimethyl ortho-phthalate (DMP), diethyl ortho-phthalate (DEP), dibutyl phthalate (DBP), di-iso-butyl phthalate (DIBP), and DEHP.

Similar to the present study, the reported urinary concentrations of mBP were also the highest among phthalate metabolites in Korean university students and Swedish young men (Axelsson et al., 2015; Lee et al., 2013) (Fig. 2); however, levels of miBP were reported to be the highest in similar studies conducted in Australia, Japan, and Germany. Among the phthalate metabolites, concentrations of mEP were the highest in Danish men and Canadian adolescents (Bamai et al., 2015; Frederiksen et al., 2010; Goen et al., 2011; Hartmann et al., 2015; Saravanabhavan et al., 2013) (Table S5). These results reflect the different characteristics of phthalate exposure in different countries and the broad exposure of DBP in Chinese populations.

3.2.2. Parabens

Methyl-paraben (MeP), PrP, and EtP were three dominant congeners, and their median concentrations were 2.44, 0.56, and 0.29 $\mu g\,L^{-1}$, respectively. Concentrations of the three parabens reported by other studies in China, India, U.S., Japan, and Korea also followed the same order (Table S5), indicating the extensive exposure to MeP and PrP in populations of these countries. Interestingly, concentrations of MeP in the present study (Geometric mean, GM: 6.17 $\mu g\,L^{-1}$) were two to three orders of magnitude lower than those of female students in Japan (206 $\mu g\,L^{-1}$), and also lower than those

Table 2
Concentration (μg L^{-1} (μg g^{-1} creatinine)) distribution of environmental endocrine disruptors in university students (n = 169), South China.

	No.	DF[a]	Range	Mean	GM	25th	Median	75th
mMP	168	99	ND[b]–61.5	11.9 (9.78)	9.03 (9.78)	5.54 (4.71)	10.4 (7.13)	16.2 (10.1)
mCPP	156	92	ND–6.43	1.10 (0.82)	0.89 (0.67)	0.45 (0.36)	0.82 (0.62)	1.30 (0.94)
mEP	169	100	0.27–386	29.8 (23.3)	11.2 (9.35)	4.40 (4.07)	10.2 (7.68)	23.8 (16.7)
mECPP	169	100	0.37–149	16.7 (12.8)	11.7 (9.78)	7.61 (6.37)	12.1 (9.86)	20.7 (14.8)
miBP	168	99	ND–188	13.8 (11.5)	8.19 (6.79)	4.20 (3.04)	9.58 (8.19)	17.7 (13.3)
mBP	169	100	0.39–408	45.0 (36.0)	22.6 (18.9)	9.85 (8.57)	26.2 (20.0)	59.7 (43.9)
mEOHP	152	90	ND–45.8	2.96 (2.65)	2.02 (1.56)	0.48 (0.31)	2.24 (1.64)	3.80 (3.65)
mEHHP	164	97	ND–94.2	6.14 (5.41)	3.58 (2.85)	1.19 (0.83)	4.50 (3.42)	7.75 (7.28)
mEHP	111	66	ND–24.4	2.22 (2.39)	2.03 (1.52)	ND (ND)	1.01 (0.64)	2.76 (2.34)
ΣPAEs[c]	169	100	3.62–698	130 (105)	92.3 (77.0)	56.5 (44.4)	99.4 (77.7)	170 (127)
$\Sigma_{\text{DEHP metabolites}}$[d]	169	100	0.48–249	28.0 (23.3)	19.0 (15.8)	11.5 (10.4)	22.3 (15.2)	35.2 (26.2)
MeP	136	81	ND–344	27.3 (22.1)	6.17 (5.12)	0.43 (0.26)	2.44 (2.24)	22.9 (19.4)
EtP	98	58	ND–110	6.21 (4.44)	2.27 (1.56)	ND (ND)	0.29 (0.21)	2.71 (2.21)
PrP	106	63	ND–183	8.73 (7.43)	3.30 (2.47)	ND (ND)	0.56 (0.38)	5.49 (3.78)
BPA	99	59	ND–12.7	0.71 (0.59)	0.79 (0.64)	ND (ND)	0.33 (0.22)	0.82 (0.71)
TCS	80	47	ND–273	4.13 (3.51)	NA (NA)	ND (ND)	ND (ND)	0.82 (0.85)

[a] DF: detection frequency (%); GM: geometric mean.
[b] ND = not detected; NA = not analyzed.
[c] ΣPAEs = total concentrations of eleven phthalate metabolites.
[d] ΣDEHP = total concentration of metabolites of DEHP (mECPP, mEOHP, mEHHP and mEHP).

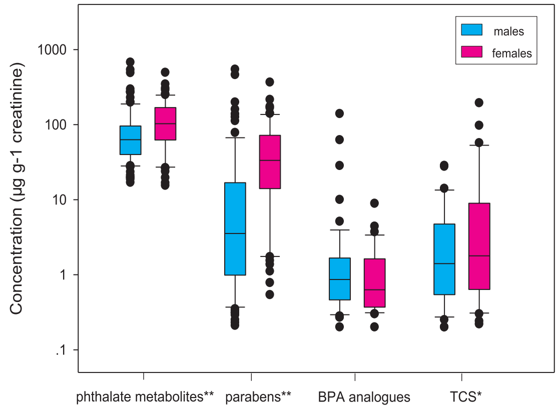

Fig. 1. Concentrations (μg g^{-1} creatinine) of phthalate metabolites, parabens, and other environmental phenols in university students in Guangzhou, South China. ("*" indicates that a significant difference in concentrations was found between male and female students. $*p < 0.05$, $**p < 0.01$).

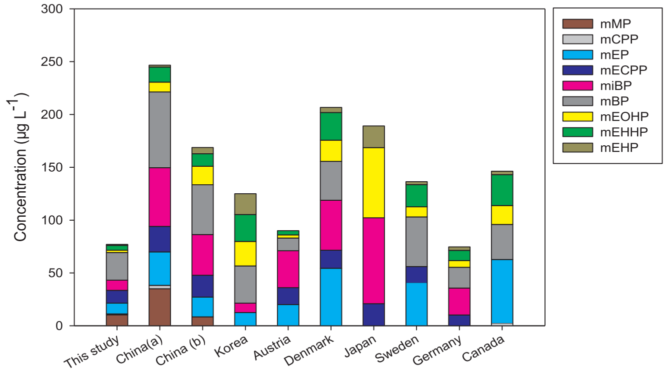

Fig. 2. Urinary concentrations (μg L^{-1}) of phthalate metabolites reported in different studies globally. (Data sources: China (a) (b): (Gao et al., 2016a; Wang et al., 2015a); Korea (a) (b): (Lee et al., 2013); Austria: (Hartmann et al., 2015) ; Denmark: (Frederiksen et al., 2010); Japan: (Bamai et al., 2015); Sweden: (Axelsson et al., 2015); German: (Goen et al., 2011)).

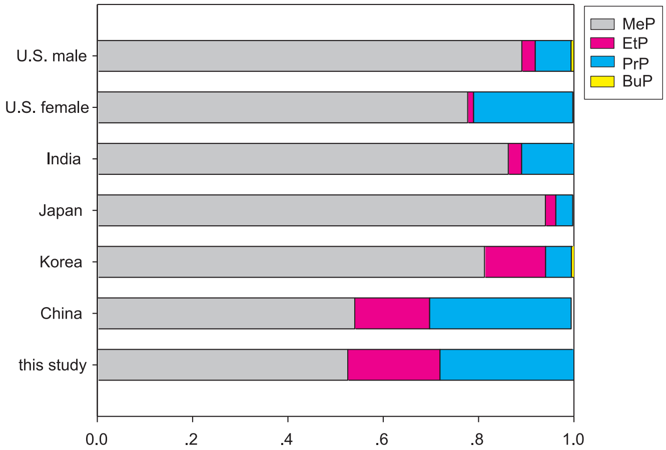

Fig. 3. Composition profiles of parabens in different studies globally. (Data sources: China: (Ma et al., 2013); U.S. male and female subjects: (Koeppe et al., 2013); India: (Xue et al., 2015); Japan: (Nishihama et al., 2016); Korea: (Kang et al., 2016)).

reported in Korea (86.8 μg L^{-1}); creatinine-adjusted data (GM: 5.12 μg g^{-1} creatinine) was also much lower in this study than reported for female (93.7 μg g^{-1} creatinine) and male (26.3 μg g^{-1} creatinine) subjects from the U.S. (Table S5). MeP, PrP, and EtP accounted for 52.6%, 28.1%, and 19.3 of the total urinary paraben concentrations, respectively (Fig. 3). The same distribution patterns were also found in the U.S., India, and Japan (Koeppe et al., 2013; Nishihama et al., 2016; Xue et al., 2015), with the contribution of MeP at > 75% (Fig. 3).

Personal care products, and not food, have been suggested as the main source for human exposure to parabens (Ma et al., 2013; Soni et al., 2005). Our previous study found large amounts of MeP, EtP, and PrP in PCPs, exceeding 0.1% of the product weight (Guo and Kannan, 2013; Guo et al., 2014). The low levels of parabens in the present study, especially extremely low MeP levels compared with those reported from Japan, Korea, and the U.S., indicate the low usage of PCPs by university students in South China. The results of our questionnaire survey indicated that the variety of PCPs used daily by college students was limited, and only 70–80% female students used shower gels, facial cleansers, and face toner every day, while 65–80% of male students used shower gels and shampoos every day; other PCPs were infrequently used by all students (Table 1). However, we observed that the EtP levels were significantly higher than those of PrP in male students, and the opposite was true in female students. From our questionnaire survey, we found that most male students only used shower gels and shampoos, which may contain comparable or higher amounts of EtP than of PrP (Guo et al., 2014), and the frequencies of usage of other PCPs in male students were far lower than they were in female students (Table 1).

3.2.3. Bisphenol A and TCS

The concentration ranges of BPA and TCS were ND-12.7 μg L^{-1} and ND-273 μg L^{-1}, respectively. The concentration of BPA (GM: 0.79 μg L^{-1}) in the present study was one order of magnitude lower than that reported in general young adults in China (2.23 μg L^{-1}) (Gao et al., 2016b), and slightly lower than that in a defined Chinese population aged 21–31 years old in Shanghai (0.96 μg L^{-1}) (He et al., 2009). The BPA concentration in the present study was also lower than that reported in university students in Spain (2.30 μg L^{-1}), in teenagers in the U.S. (2.83 μg L^{-1}), and in children in India (5.8 μg L^{-1}) (Xue et al., 2015) (Table S5). Similar to that of high molecular weight phthalates, human BPA exposure occurs predominantly through dietary means, which accounts for about 70% of total BPA exposure, followed by ingestion and dermal contact with indoor dust (Gao et al., 2016b). The low levels of BPA in Chinese students, similar to those for phthalates, may result from their distinct lifestyle, which includes relatively clean food, indoor air, and exposure to dust containing low EEDs. For TCS, the geometric mean (GM) concentration in our study was also lower than that reported in Indian children (9.55 μg L^{-1}) (Xue et al., 2015), although one study reported the that the highest GM concentrations of TCS among eight Asian countries (including China, India, Japan, Korea, Kuwait, Vietnam and Saudi Arabia), Greece, and the U.S. (Iyer et al., 2018) were found in China (5.36 μg L^{-1}).

3.2.4. Relationships among target EEDs

The relationships among concentrations of target EEDs in students were examined by Spearman Correlation analysis (Table 3). The unadjusted or creatinine-adjusted concentrations of total phthalate metabolites, parabens, and bisphenol analogues correlated significantly with each other ($p < 0.01$), as well as with those of TCS ($p < 0.05$) The correlations among EEDs may indicate the same potential sources, and point to similarities in the living environment and lifestyles of university students.

We also checked individual phthalate metabolite concentrations, and significant correlations were found between concentrations of all metabolite pairs, except for those with mEP. Concentrations of mEP did not correlate with those of mECPP, mEOHP, mEHHP, or mEHP (all metabolites of DEHP). It is known that the primary source for human exposure to DEHP is diet (Guo et al., 2012), so our results may indicate another important source other than diet which substantially affected the concentrations of mEP in university students. We believe that the usage of PCPs was able to reasonably explain the observed data. On one hand, phthalates, parabens, and TCS were frequently detected in PCPs (Guo et al., 2014), so significant correlations were found among them. On the other hand, and more importantly, levels of DEP were higher than those of DEHP in most types of PCPs collected from China, thus even with limited usage, DEP in PCPs was able to affect concentrations of mEP in the study population (Guo et al., 2014).

Table 3
Spearman correlation coefficients among the concentrations of phthalate metabolites (non-corrected data/creatinine-corrected data), parabens, and other environmental phenols in university students in South China.

	me-phthalate	parabens	bisphenols	triclosan
me-phthalate	1	0.338**/ 0.330**	0.372**/ 0.401**	0.270**/ 0.237**
parabens		1	0.240**/ 0.198**	0.301**/ 0.272**
bisphenols			1	0.198*/0.193*
triclosan				1

Table 4
Estimated daily intake of environmental endocrine disruptors by university students in South China calculated based on urinary concentrations (GM, μg/kg-bw/day).

		Total	Sex	
			Male	Female
	DMP	0.46	0.43	0.52
	DEP	0.60	**0.49**[a]	**0.87**
	DBP	1.35	1.18	1.69
	DIBP	0.48	0.44	0.57
DEHP	mEHHP	0.68	0.64	0.76
	mEOHP	0.59	0.50	0.78
	mEHP	1.60	1.52	1.72
	MeP	10.3	**5.00**	**27.1**
	EtP	3.29	**2.14**	**6.25**
	PrP	5.56	**3.26**	**9.68**
	Σparabens	15.6	7.45	48.9
	BPA	0.007	0.008	0.007
	TCS	0.67	**0.52**	**0.97**

[a] Bold letters: significant difference between males and females.

To summarize, concentration levels of the target EEDs in university students in South China were lower than those reported in similar domestic or international studies, which may be attributed to the relatively "clean" living environment, controlled cooked food, and low usage of PCPs in universities in South China. The usage of PCPs (although of limited varieties) was an important source of the differences in concentrations of phthalates and parabens between male and female students (especially in the case of mEP).

3.3. Daily exposure and potential health risk of endocrine disruptors

Based on the urinary concentrations, simple steady-state exposure models (Supporting Information) were used to estimate daily intakes (EDIs, μg/kg-bw/day) of phthalates, parabens, BPA, and TCS for university students in South China (Table 4).

The respective EDIs (GM) of DMP, DEP, DBP, DIBP, MeP, EtP, PrP, BPA, TCS, and DEHP (based on concentrations of mEHHP, mEOHP, and mEHP) were 0.46, 0.60, 1.35, 0.48, 10.3, 3.29, 5.56, 0.01, 0.67, and 0.68–1.60 μg/kg-bw/day for university students in the present study. Higher EDIs of all target EEDs were found for female students than for male students, with statistical significances for DEP, MeP, EtP, PrP, and TCS (Table 4, $p < 0.05$).

Compared to other studies in China, the EDIs of DMP, DEP, DBP, DEHP, and BPA in the present study were lower than those of Chinese young adults from rural areas and cities (GM: 1.68, 2.14, 4.12, 1.26–2.98, and 0.065 μg/kg-bw/day). Particularly, the DIBP concentration (0.48 μg/kg-bw/day) in our study was more than seven times lower than that reported for young adults (3.52 μg/kg-bw/day) in the general population in China (Gao et al., 2016a, 2016b). Compared with global data, the EDI of DMP in our study was one order of magnitude lower than the value reported in Austria (median: 1.3 μg/kg-bw/day). The EDIs of DIBP and DEP were lower than those reported in Belgium (DIBP/DEP: 2.29/1.47 μg/kg-bw/day) and Austria (1.40/0.69 μg/kg-bw/day). The EDI of DBP was more than three times greater than that reported in Austria (0.44 μg/kg-bw/day) (Dewalque et al., 2014; Hartmann et al., 2015), while the EDIs of total parabens and TCS were lower than those reported in Greece (31.4 and 3.3 μg/kg-bw/day for parabens and TCS, respectively) (Asimakopoulos et al., 2014). These comparisons indicated that students in South China experienced a relatively high exposure to DBP, and a low exposure to DEP. In addition, our previous studies demonstrated that the general Chinese population is exposed to high levels of both DBP and DIBP (Guo et al., 2011); the present study indicates that sources of DIBP on university campuses is limited.

Generally, the EDIs of target EEDs for university students in South

China were lower than those specified by the European Food Safety Authorities (EFSA: DBP, DEHP, and BPA: 10, 50, and 50 μg/kg-bw/day), the U.S. Environmental Protection Agency (DEP, DBP, and BPA: 800, 100, and 20 μg/kg-bw/day), and the European Commission Scientific Committee (acceptable daily intakes of parabens for food: 0–10 mg/kg-bw/day) (CEC, 2007) guidelines, indicating low health risk from exposure to these EEDs. However, a small proportion of the students were still subject to potential risk. For example, the EDIs of DBP in 7 of 169 (4.1%) university students exceeded the TDI value as advised by the EFSA (10 μg/kg-bw/day) (EFSA, 2005a, 2005b, 2006), and all seven members of this subgroup were female students. Furthermore, as mentioned in our questionnaire survey, more than a quarter of the 702 student subjects reported poor sleeping habits, and 36 presented with symptoms of endocrine disorder diseases (confirmed by a doctor's diagnosis). Although no direct evidence was found, incidence of poor sleeping habits increased in direct proportion to concentrations and exposure doses of EEDs in female students in the present study; EED exposure may partly contribute to endocrine disorders in university students in South China.

Our research has some limitations. The number of urine samples was limited, and thus may not be representative of EED exposure experienced by all students in South China. In addition, the urine samples and questionnaires were unpaired, and were obtained from different sets of students. Although we analyzed the lifestyle habits of over 700 students to represent those of the 169 urine donors, this method may have led to some bias in determining occurrences or exposure doses of EEDs. However, as a pilot study, our data offers an opportunity to understand the exposure status of several emerging EEDs in university students in South China. Our findings show that, like the distinct living environment and habits, the occurrence of EEDs in these students is distinct compared with the rest of the young population in China. Our results also show that these students are exposed to low levels of EEDs, and female students experience a higher exposure than male students. Although food is generally considered to be the main source of phthalate exposure, we believe that for university students in the present study, PCP usage is the main reason for the differences in the exposure of phthalate metabolites and parabens (especially mEP) between female and male students.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2018.04.006.

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