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Urinary parabens in adults from South China: Implications for human exposure and health risks

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ABSTRACT

Parabens are a kind of preservatives widely used in cosmetic and personal care products and ubiquitously detected in the environment. However, little is known on human exposure to these chemicals. Our study mainly investigated the urinary parabens in adults from South China to evaluate the cumulative risk of paraben exposure. A total of 562 urine samples were collected from adult workers for the determination of methyl paraben (MeP), ethyl paraben (EtP), propyl paraben (PrP), butyl paraben, and benzyl parabens. High detection frequencies (≥98%) were observed for MeP, EtP, and PrP with median concentrations of 8.88, 5.11, and 1.44 μg/L, respectively. Urinary parabens was 4.5–46.2 fold higher in urine of females than those in males. Urinary MeP was associated with alcohol drinking and a history of tumor, while urinary PrP was negatively associated with education levels of the subjects. There were not significant associations between urinary concentrations of parabens and body mass index, which indicated that obesity was not associated with paraben exposure. Also, parabens did not correlate with human dietary habits. Although the total estimated daily intake (TEDI) of the major compound MeP and EtP in adult workers was lower than the acceptable daily intake (ADI), the TEDI of PrP exceed the ADI for a very few subjects, especially for females and low-educated ones, suggesting potential health risks.

1. Introduction

Parabens (named as esters of para-hydroxybenzoic acid), a kind of preservatives, are mainly used in pharmaceuticals and personal care products (PCPs). These esters include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and benzyl paraben (MeP, EtP, PrP, iPrP, BuP, iBuP, and BzP) (Błędzka et al., 2014; Nowak et al., 2018). Among them, MeP, EtP, and PrP are the most commonly used and often added to pharmaceuticals, and all kinds of cosmetics, lotions, and other PCPs together (Kim, 2018; Lu et al., 2014). The antimicrobial activity of parabens tends to increase with the alkyl substituent length (Kolatorova et al., 2018). Similar trends were also found for their estrogen activities. Parabens have been reported having estrogenic effects using *in vitro* and *in vivo* assays. For example, sperm production and serum testosterone levels can be significant influenced resulting in adverse effects in male rats by BuP and PrP via oral exposure (Xue and Kannan, 2016). Parabens may affect sperm quality (Adoamnei et al., 2018) and fecundity (Honda et al., 2018). Therefore, restrictions on the addition of parabens in commercial products have been applied. For example, the allowable parabens in cosmetic products are 0.4% and 0.8% for a single ester and mixtures of all parabens, respectively, in European Union (EU) countries (Buzek, 2009). In Denmark, the use of PrP and BuP in the products for children had been prohibited since 2011 (SCCS, 2011). However, they are still widely applied to a lot of products in many other countries, including China (Ma et al., 2018).

Because of the usage of parabens in the preservatives and PCPs, they can be discharged via domestic wastewater into aquatic systems. Although parabens are biodegradable in the environment, they are still found to be ubiquitously present in different environmental compartments, such as water, sediment, and wildlife, due to large amounts of

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usage and continuous releases (Błędzka et al., 2014; Haman et al., 2015; Honda et al., 2018; Xue and Kannan, 2016). MeP and PrP in Chinese rivers reached 1062 and 3142 ng/L, respectively (Peng et al., 2008). Concentrations of MeP, EtP, and PrP in soil and sediment from different areas of Spain were determined to be 6.35, 5.10, and 4.32 ng/g dry weight (dw), respectively (Núñez et al., 2008). Parabens were also detected with high frequencies in meat, vegetables, and canned food (Liao et al., 2013). In addition, parabens in indoor air were measured with a level of 21 ng/m^3 for MeP and 4.0 ng/m^3 for EtP (Rudel et al., 2003). Because of ubiquitous occurrence in the environment, parabens can enter human bodies via oral ingestion, dermal contact, and inhalation. High levels of parabens were reported in human blood and urine by several research groups (Adoamnei et al., 2018; Guo et al., 2014; Kim, 2018; Ma et al., 2016).

The Pearl River Delta is the most commercialized and industrialized region in South China. The average household income in this region is relatively high compared with most of other Chinese regions. A previous study suggested that the concentrations of urinary parabens were positively correlated with household income (Calafat et al., 2010). Parabens were frequently detected in river water and sewage from a wastewater treatment plant in the Pearl River Delta, indicating the extensive use of these chemicals there (Peng et al., 2008; Yu et al., 2011). However, data on human exposure to parabens and potential health effects in South China is rarely reported. The present study was carried out to investigate the parabens in the urine of workers from South China and to identify whether any association exists between paraben exposure and health effects. In addition, estimate human exposure doses and potential health risks were evaluated by using urinary parabens. To our best knowledge, this is the first study to investigate the associations between urinary parabens and potential health effects in South China.

2. Materials and methods

2.1. Materials and reagents

Five paraben reference standards, including MeP, EtP, PrP, BuP, and BzP, were bought from Dr. Ehrenstorfer (Augsburg, Germany). Deuterated internal standards, including d_4-MeP, d_4-EtP, d_4-n-PrP, d_4-BuP, and d_4-n-BzP, were brought from CDN Isotopes (Quebec, Canada). KH_2PO_4 (HPLC grade, sodium acetate (NaAC), and glacial acetic acid (HAC) were obtained from Fisher Scientific (Houston, TX, USA). Methanol was brought from Merck (Darmstadt, Germany). β-glucuronidase/arylsulfatase (85000 β-glucuronidase units/mL and 7500 sulfatase units/mL) was obtained from Sigma (St. Louis. MO, USA). Bond Elut C_{18} solid-phase extraction (SPE) cartridges (500 mg/6 mL) were bought from Agilent (Santa Clara, CA, USA). Water was obtained by a Milli-Q water purification system made by Millipore Co., Ltd. (Billerica, MA, USA).

2.2. Study subjects and sample collection

A total of 562 workers (male: n = 550; female: n = 12) aged from 22 to 59 years old were recruited from a nuclear power plant in South China from 2013 to 2015. Under the direction of trained public health staff, all participants were required to fill out a questionnaire and signed an informed consent. The questionnaire included personal information, such as name, gender, age, weight, height, disease history, and dietary habits (Table S1). Generally, 50 mL first-voided morning urine were collected using pre-cleaned glass bottles with HCl (0.1 M) followed by pure water. Immediately after collection, urine samples was measured for specific gravity using a digital handheld refractometer (Atago, Bellevue, WA, USA) at room temperature to quantify urine dilution. The sampled urine were immediately stored at −20 °C, and sent to the laboratory using a box after dry ice added. The urine samples were stored at −20 °C before use.

2.3. Sample treatment protocols

Total parabens (free plus conjugated) were analyzed by following enzymatic deconjugation and SPE separation similar to the procedures reported by Ren et al. (2016). Briefly, an aliquot of 4 mL urine sample was transferred to a glass tube, buffered with 0.1 M hydrochloric acid after spiked with internal standards (0.25 ng for d_4-MeP; 10 ng for the others), and then followed by 0.1 M acetate (3.0 mL) for pH adjustment to 5.0. The sample was hydrolyzed further after adding 20 μL of β-glucuronidase/arylsulfatase, and incubated at 37 °C overnight for deconjugation. Finally, the sample was extracted and purified using a Bond Elut C_{18} SPE cartridge. The fraction containing parabens was concentrated to dryness under a gentle flow of nitrogen gas and stored in 400 μL using a mixture of methanol and water (1:1, v:v) at −20 °C before high performance liquid chromatography – tandem mass spectrometry (HPLC-MS/MS) analysis.

2.4. Instrumental analysis

Measurement of parabens was achieved on an AB Sciex Q-Trap 5500 MS (Applied Biosystems, Foster City, CA, USA) coupled with a 20A HPLC (Shimadzu, Japan). The HPLC-MS/MS conditions were similar to a previous report (Ren et al., 2016). Briefly, chromatographic separation was achieved on an Atlantis C_{18} column (2.1 × 150 mm, 5 μm, Waters, Ireland). A flow rate of 0.3 mL/min was set for the methanol and water mobile phases. The gradient elution program was set as follows: 0–2.5 min, 5% methanol; 2.5–4 min, 10% methanol; 4–8 min, 50% methanol; 8–12.5 min, 95% methanol; and finally 12.5–18 min, 5% methanol. The injection volume was 10 μL. The column temperature was set at 40 °C. The analysis of paraben compounds were carried using negative ionization multiple-reaction monitoring (MRM) mode.

2.5. Quality assurance and quality control (QA/QC)

To check potential contamination, procedural and solvent blanks were carried out during each batch of 12 urine sample analyses. The relative standard deviations (RSDs) were used to evaluate the method precision by calculating of repetitive analysis of standard solutions with concentrations of 1.0, 5.0, and 20.0 μg/L, respectively. The method accuracies were used by analyte recoveries. The intra- and inter-day precisions were assessed by analyzing the standard solutions six times within a single day and in six consecutive days, respectively. The limits of detections (LODs) were 0.02, 0.02, 0.01, 0.02, and 0.01 μg/L for Mep, Etp, PrP, BuP, and BzP, respectively. Calibration curves covering concentrations of 0.1–100.0 μg/L exhibited satisfactory correlation coefficients ($R^2 > 0.999$).

2.6. Calculations and statistical analysis

To evaluate paraben exposure, the total estimated daily intakes of MeP, EtP, and PrP were calculated based on the following equation (Moos et al., 2016a):

$$\text{TEDI} = \frac{C \times R}{F \times BW} \tag{1}$$

where TEDI (μg/kg-bw/day) is the total estimated daily intake of a paraben compound from all exposure pathways; C (μg/L) is the urinary concentration of the paraben; R (L/day) is total urine volume for an adult per day; BW (kg) is body weight; and *F* (dimensionless) represents the urinary excretion factor of a paraben. In the present study, urinary excretion factors of 17.4, 13.7, and 10.2 were used for MeP, EtP, and PrP, respectively (Honda et al., 2018); A BW of 54.8 kg for females and 62.7 kg for males was used (Ma et al., 2013); and a total urine volume of 2 L/day was estimated for an adult (Moos et al., 2016a).

To assess the health risks of paraben exposure, the hazard index was calculated on the basis of the following equation:

$$HI = \frac{TEDI}{ADI} \quad (2)$$

where HI (dimensionless) represents the hazard index and an HI > 1 indicates potential health risks for human; ADI is the acceptable daily intake, which is assessed to be 10000 μg/kg-bw/day for the sum of MeP and EtP (JECFA, 1974), and 100 μg/kg-bw/day for PrP alone, derived from the no-observed-effect levels (Honda et al., 2018).

Statistical analyses were performed on an SPSS version 13.0. The concentration of a paraben was given in μg/L without creatinine adjustment. Creatinine concentrations depend on not only muscle masses, but also urine excretion volume (urine dilution factor) (Honda et al., 2018). Thus creatinine adjustment may introduce bias to the estimations of human exposure and risks. For Mep, EtP, and PrP, if a concentration measurement is below the limit of quantitation (LOQ), a half LOQ was used for statistical analysis because of their high detection frequencies (DFs > 50%). BuP and BzP were not included in statistical analyses due to low detection frequencies, unless specified otherwise. The statistical significance level was set at $p < 0.05$. Spearman's correlations were used to determine the relationships among paraben compounds. The associations between urinary paraben concentrations and various variables were analyzed by using the Jonckheere-Terpstra and Mann-Whitney *U* test.

3. Results and discussion

3.1. Concentrations of parabens in urine

The detection frequencies and concentrations (median, mean, percentile, and standard deviation) of the parabens are listed in Table 1. In a total of 562 urine samples, MeP, EtP, and PrP were observed with high frequencies (i.e., 99.6%, 97.9%, and 98.9%, respectively). BuP and BzP were detected in only 23.8% and 14.9% of urine samples, respectively. These detection frequencies were similar to those reported in Japanese pregnant women (Shirai et al., 2013), and populations from Korea (Kim, 2018) and the United States (Quirós-Alcalá et al., 2018). The high detection frequencies of parabens in urine indicated the ubiquitous occurrence of this group of emerging pollutants in nuclear workers.

The sum concentrations of five parabens ($\Sigma_5$parabens) were from 0.17 to 3273 μg/L with a mean and median concentration of 147 and 28.3 μg/L, respectively (Table 1). Among them, MeP exhibited the greatest concentrations (median: 8.88 μg/L), followed by EtP (median: 5.11 μg/L), and PrP (median: 1.44 μg/L). Wide ranges of concentrations (i.e., < LOD–1880, < LOD–3270, and < LOD–2300 μg/L for MeP, EtP, and PrP, respectively) suggest large variations of individual exposure to parabens.

To further understand the levels of paraben exposure in nuclear industry workers, a comparison of urinary parabens with the findings from previous studies was conducted (Table S2). In our study, the urinary MeP and PrP were lower than the data from Japan (Shirai et al., 2013), the United States (CDC, 2017), and several other western countries (Casas et al., 2011; Myridakis et al., 2015; Philippat et al., 2012). However, MeP and PrP concentrations in nuclear industry worker urine were comparable with those reported in Korean population (9.87 and 0.614 μg/L, respectively) (Kim, 2018) and Chinese young adults (4.63 and 3.17 μg/L, respectively) (Ma et al., 2013). For EtP, it urinary concentrations in nuclear industry workers were comparable with the data from other countries, such as Japan, Greece, France, and Tunisia (Jiménez-Díaz et al., 2016; Myridakis et al., 2015; Philippat et al., 2012; Shirai et al., 2013), while lower than the concentrations reported in Korean population (32.4 μg/L) (Kim, 2018). These comparisons indicate that paraben exposure in Chinese nuclear industry workers was overall low when compared with general populations from other regions.

3.2. Composition characteristics of urinary parabens and source implications

In urine, MeP appeared to be the predominant paraben compound, accounting for 57.1% of $\Sigma_3$parabens (MeP, EtP, and PrP), followed by EtP (33.2%), and PrP (9.7%). Our results were different from those in Korea (Kim, 2018) and the United States (Pycke et al., 2015). In Korea, EtP was the predominant paraben compound which accounted for more than half of $\Sigma_3$parabens. By contrast, MeP and PrP were the most abundant parabens in a United States study (Pycke et al., 2015). These may imply the applications of parabens and consequent environmental releases vary between regions, resulting in region-specific human exposure scenarios.

To understand exposure sources in the workers, the correlations among individual parabens were analyzed by Spearman's correlation analysis. A strong significant correlation was found between urinary MeP and PrP (r = 0.475, $p < 0.01$). Also, significant correlation between EtP and PrP (r = 0.261, $p < 0.01$) and between MeP and EtP (r = 0.291, $p < 0.01$) were observed, although there were relative weak correlations. Strong correlations were frequently reported between MeP and PrP, which might can attribute to their widely combined used in pharmaceuticals, PCPs, and food processing (Guo et al., 2014; Jiménez-Díaz et al., 2016; Kim, 2018). For example, Guo et al. (2014) found that MeP and PrP were the major paraben compounds in pharmaceuticals and cosmetics collected from Chinese markets. In addition, no significant correlation was found between urinary EtP and MeP from Japanese and Korea, which agreed with our data (Kim, 2018; Shirai et al., 2013). However, in contrast with our results, there were significant correlations between EtP and MeP in urine of German adults (r = 0.55, $p < 0.0001$) (Koch et al., 2014). In addition to the region-specific applications of parabens, other factors may influence compositional profiles in different populations, such as exposure pathways and life styles (Kang et al., 2016).

3.3. Urinary parabens correlated with demographic characteristics

The median (mean) total concentrations of urinary parabens were 26.7 and 270 (140 and 339) μg/L in males (n = 550) and females (n = 12), respectively (Fig. 1A), which indicated the significantly greater paraben exposure for females than males. Indeed, the median MeP, EtP, and PrP concentrations in female were generally 4.5–46.2 folders higher than those in males. The result is very similar to the findings from previous studies in which higher urinary parabens were

Table 1
Urinary concentrations (μg/L) of parabens for workers from a nuclear power plant in South China (n = 562).

Compounds	Median	Mean	SD	Min	Max	5th Percentile	95th Percentile	DF (%)
MeP	8.88	42.9	141	< LOD	1880	1.09	176	99.6%
EtP	5.11	68.4	241	< LOD	3270	0.54	343	97.9%
PrP	1.44	34.8	148	< LOD	2300	0.13	194	98.9%
BuP	1.35	9.9	29.8	< LOD	181	0.07	48.2	23.8%
BzP	1.26	5.99	22.4	< LOD	181	0.06	29.2	14.9%
$\Sigma_5$parabens	28.3	147	335	0.17	3273	2.59	785	

SD: standard deviation; DF: detection frequency.

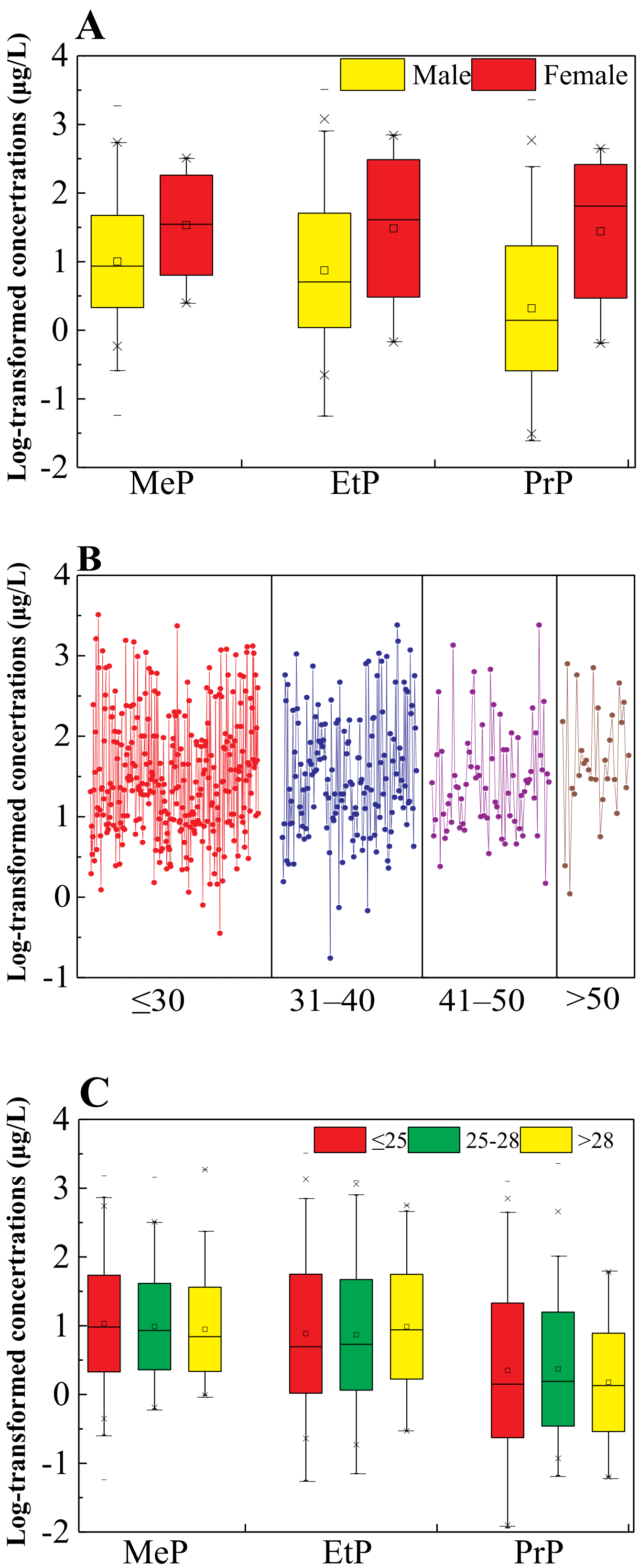

Fig. 1. Log-transformed urinary concentrations (μg/L) of parabens from a nuclear power plant workers in South China (A: MeP, EtP, and PrP in males and females; B: $\Sigma_3$parabens in urine with different ages; C: Comparison of MeP, EtP, and PrP by BMI). The solid lines of the box represent, from the bottom upward, the Q1 (25th percentile), Q2 (median or 50th percentile), and Q3 (75th percentile) values. Whisker caps denote the 10th and 90th percentiles.

observed in females from several Asian countries including China, the United States, and Greece (Honda et al., 2018; Kang et al., 2016; Ma et al., 2013). Higher usage frequencies of cosmetics and PCPs by females than males lead to greater paraben exposure in females (Biesterbos et al., 2013).

To analyze the age influence on urinary parabens, four subgroups, i.e., ≤30, 31–40, 41–50, and > 50 years old were divided and the results are shown in Fig. 1B. There were no significant correlations between age and urinary concentrations of Mep, EtP, and PrP. Similar results were also observed by Honda et al. (2018). This is probably due to rapid metabolism and elimination of parabens from human bodies, leading to no accumulation in tissues (Moos et al., 2016b). However, significant increasing trends of age-dependence were found for urinary MeP, EtP, and PrP from Korean (Kang et al., 2016; Kim, 2018), likely reflecting more usage of cosmetic and PCPs by older people and subsequent age-dependent exposure pattern (Błędzka et al., 2014). Therefore, the age influence on urinary parabens might mainly be attributed to the continuous, increased, or prolonged use of PCPs and cosmetics with age, although individual variations in pharmacokinetics and metabolic pathways as well as paraben bioavailability, might also effect the chemical accumulation in human bodies (Kang et al., 2016). The lack of age trend in our study may be due to the fact that most samples were from males, while males normally use much less cosmetics and PCPs than females.

Other socio-demographic characteristics were also analyzed to determine if they affect urinary paraben levels. In the present study, education levels were categorized into subgroups as “middle school or below” and “college or above”. Marital status was divided into single and married/divorced (Table 2). A significant association between urinary PrP and education level was observed with *p*-value of 0.025. The median urinary PrP concentration in workers with an education level of “middle school or below” is 4.19 times higher than those from the subgroup of “college or above”. Similarly, education level was positively associated with urinary concentrations of MeP as reported by Kang et al. (2016). By contrast, no association was found between urinary paraben concentrations and marital status (Table 2).

3.4. Urinary parabens correlated with shift type, dietary habits, and health status

To further understand the factors influence on human exposure to parabens, the associations between urinary parabens and work shift, dietary characteristics, obesity, disease history, as well as other factors, were investigated. In the present study, the participants were divided into three groups on the basis of body mass index (BMI), i.e., underweight/normal weight (BMI ≤ 25), overweight (BMI ranges of 25–28), and obesity (BMI > 28) as defined by Chinese standard. Shift type was divided into day worker and night shift worker. Furthermore, to understand the relationship between operating hours and urinary parabens, 40 h per week was set as boundary dividing the operating hours. A history of hyperlipidemia or tumor was recorded as “Yes” or “No”. Other dietary characteristics were also dichotomized. The results are shown in Fig. 1C and Table 2.

There were not significant correlations between BMI and urinary concentrations of MeP, EtP, and PrP (Fig. 1C). The mean (median) $\Sigma_3$parabens of the three groups were 154 (median: 27.6), 124 (median: 27.9), and 120 (median: 23.4) μg/L, respectively. Consistent with our results, no significant correlations were found among Tunisian women and Spanish man (Adoamnei et al., 2018; Jiménez-Díaz et al., 2016). Different from our results, there were positive correlations between urinary MeP and PrP and BMI in Korean adults (Kang et al., 2016). However, Smith et al. (2012) reported lower MeP and PrP concentrations in obese people than those with normal BMI. According to a recent report, parabens were suggested to be deposited in adipose tissue (Quirós-Alcalá et al., 2018). There were studies indicated that parabens could play an important role in altering metabolism (Hu et al., 2013).

Table 2
Levels of parabens by demographic characteristics, dietary characteristics, and health status.

Groups	Numbers (percentage)	MeP			EtP			PrP			$\Sigma_3$parabens		
		Median	IQR	*p*	Median	IQR	*p*	Median	IQR	*p*	Median	IQR	*p*
Education													
Middle school or below	19 (3.4%)	21	30.2	0.865	7.2	20.1	0.719	5.82	21.2	**0.025**	29.6	123	0.650
College or above	543 (96.6%)	8.9	24.3		5	20.1		1.39	5.83		27.9	91.7	
Marital status													
Single	196 (34.9%)	10.9	31.1	0.110	5.1	18.9	0.640	1.39	6.83	0.317	28.7	118	0.280
Married/divorced	366 (65.1%)	8.17	21.5		4.95	20.5		1.43	5.6		27.2	76.2	
Shift type													
Day worker	480 (85.4%)	9.21	26.2	0.505	4.95	20.7	0.927	1.38	6.23	0.356	28.7	90.8	0.550
Operating hours (< 40 h)	148 (30.8%)	9.12	21.7	0.750	5.4	24.8	0.660	1.2	7.7	0.270	29.5	105	0.430
Operating hours (≥40 h)	273 (56.8%)	9.84	29.2		5.0	19.8		1.73	6.8		30.3	91.3	
Night shift worker	82 (14.6%)	6.8	17.1		6.43	17.8		1.69	6.63		22.7	65.2	
Operating hours (< 40 h)	23 (28.0%)	10.4	55.7	0.075	7.2	6.5	0.760	1.67	8.1	0.990	22.5	154	0.720
Operating hours (≥40 h)	33 (40.2%)	4.9	11.9		3.8	30.3		1.72	5.7		20.4	65.3	
History of hyperlipidemia													
No	530 (94.3%)	8.92	24.6	0.386	5.03	20.4	0.477	1.41	5.69	0.551	27.4	90.9	0.910
Yes	32 (5.7%)	8.09	22.9		4.51	15.0		1.63	11.7		34.2	108	
History of tumor													
No	550 (97.9%)	8.66	23.7	**0.045**	5.01	20.1	0.830	1.41	5.96	0.380	27.4	88.2	0.263
Yes	12 (2.1%)	49.2	89.6		5.07	21.2		2.59	41.2		54.8	333	
Smoking status													
Non-smoker	456 (81.1%)	8.77	24.2	0.665	4.52	20.2	0.182	1.38	5.83	0.896	27.3	89.3	0.830
Current smoker	106 (18.9%)	7.96	27.0		6.81	19.3		1.72	6.15		29.3	96.1	
Drinking Status													
Seldom-drinker	420 (74.7%)	9.93	26.4	**0.009**	4.93	21.0	0.463	1.52	6.58	0.437	29.1	109	**0.070**
Regularly-drinker	142 (25.3%)	6.89	15.0		5.47	19.6		1.2	6.07		23.2	74.7	
Eating meat frequency													
Less than daily	73 (13.0%)	10.3	36.4	0.172	5.65	24.1	0.433	1.37	9.02	0.725	35.0	124	0.240
Daily or more	489 (87.0%)	8.54	22.8		4.96	19.8		1.44	5.65		27.1	83.1	
Eating vegetables frequency													
Less than daily	22 (4.0%)	6.39	15.0	0.450	6.53	77.2	0.240	1.02	4.92	0.590	19.1	109	0.820
Daily or more	540 (96.0%)	8.97	25.9		4.89	19.9		1.48	6.36		28.2	87.1	

IQR: interquartile range.

Additionally, an *in vitro* study reported that adipogenesis can be promoted when exposure to parabens at concentrations similar to typical human exposure (Hu et al., 2013). All these findings indicate that the differences in pharmacokinetic may contribute to urinary paraben variations. They also suggested that personal individuals with varied BMI values have different paraben exposure profiles attribute to medications, PCPs, or food.

In the present study, no association was observed between paraben exposure and a history of hyperlipidemia. However, we found that a history of tumor was positively associated with concentrations of MeP ($p = 0.045$). The median concentration of MeP in workers who have suffered from tumor is 5.68 times higher than those without tumor history. Considering the limited data, it is difficult to draw a conclusion that paraben exposure is associated with a history of tumor. However, patient who had suffered from tumor need long-term intake of medicines. During pharmaceutical production, parabens are generally used as preservatives, they were detected in 97% of 100 commercial pharmaceuticals sampled from China (Ma et al., 2016). Therefore, tumor patients may be subjected to greater exposure due to medicine intake.

Interesting, the present study found a significant correlation between urinary MeP and alcohol drinking status ($p = 0.009$). Higher concentrations of parabens were observed in the urine samples of seldom-drinkers than regularly-drinkers. We hypothesize that alcohol drinking may induce certain metabolic enzymes, leading to elevated enzymatic metabolism of parabens. However, this requires additional studies to prove. No other dietary habits were found to be associated with urinary paraben concentrations. Actually, the mean dietary intake of parabens from foodstuffs for Chinese adults was reported to be approximately 1 μg/kg-bw/day (Liao et al., 2013), only accounting for 3.8% and 2.6% of the total TEDI (mean) for males and females in the present study. Thus, nondietary sources such as PCPs appear to be more important exposure sources of parabens for Chinese populations, although the influence of foodstuffs cannot be excluded.

Additionally, no significant association was observed between urinary parabens and shift type ($p = 0.50$) or operating time ($p = 0.75$ and $p = 0.075$ for Day and Night shift worker, respectively). It may imply that operating environment does not constitute an exposure source to nuclear power plant workers. In addition, no significant association was observed between urinary parabens and cigarette smoking. Different from our result, negative association between MeP levels and cigarette smoking were observed in general Chinese (Engel et al., 2014) and Korea population (Kang et al., 2016). This is probably because most non-smokers were females among their study populations.

3.5. Human exposure and risk assessment

To assess human exposure to parabens and the associated health risks, the TEDI of individual parabens and Mep + EtP (the sum concentrations of MeP and EtP) were calculated and the results are shown in Table 3. The median TEDIs of Mep + EtP was 63.1 and 2.58 μg/kg-bw/day for female and male workers, and PrP of 28.2 and 0.26 μg/kg-bw/day, respectively. The median TEDI values for MeP and PrP in the present male workers were greatly lower than the estimation (75.8 and 12 μg/kg-bw/day for MeP and PrP, respectively) for United States populations with ages greater than 6 years old (Calafat et al., 2010). A similar TEDI value of PrP was found between female workers and a Korean population (Kang et al., 2016).

The median TEDI value of Mep + EtP was approximately three orders of magnitude lower than 10000 μg/kg-bw/day, the ADI value. The 95th percentile TEDI value of PrP (56.2 μg/kg-bw/day) for male workers was approximately half of ADI. However, the 95th percentile TEDI value of PrP for female workers exceeds the value of ADI. The hazard index values of parabens for 562 nuclear workers were shown in

Table 3
Total estimated daily intake (μg/kg-bw/day) of parabens exposure to the workers and the comparison with other regions.

	This study						Other regions		
	Male workers			Female workers			The United States [a]		Korean [b]
	Mean	Median	95th Percentile	Mean	Median	95th Percentile	Mean	Median	Median
MeP	6.67	1.64	30.1	11.4	24.6	66.6	64.8	75.8	
EtP	7.55	1.07	77.8	18.0	38.4	134	–	–	
PrP	12.2	0.26	56.4	9.03	28.2	145	9.6	12.0	25.0
MeP + EtP	18.9	2.58	96.4	29.4	63.1	113	–	–	301

[a] Cited from the report by Calafat et al. (2010).
[b] Cited from the report by Kang et al. (2016).

Fig. 2. The HI values of MeP and EtP were all less than unit. However, there are 15 workers with HI greater than one for PrP (Table S3). It is noteworthy that the number of subjects whose HI values for PrP greater than one is obviously higher in female group and in the group of "Middle school or below" (8.3% and 10.5%, respectively). This suggests that the potential risk of PrP exposure in females and low-educated people should receive additional concerns.

4. Conclusions

Parabens in urine from nuclear power plant workers were determined in our study. The high detection frequencies (≥98%) of parabens suggested their ubiquitous occurrences in human bodies. The urinary parabens in the study population were generally lower than or comparable to those reported from other regions. Differences in urinary parabens between genders were observed because of greater usage of cosmetics and PCPs by females. Alcohol drinking, education level, and a history of tumor, but not obesity, were found to be associated with urinary parabens. Estimation of human intake and exposure risks indicated potential risks of PrP exposure for female and low-educated workers. By contrast, no significant risks were estimated for our study populations with respect to MeP and EtP exposure.

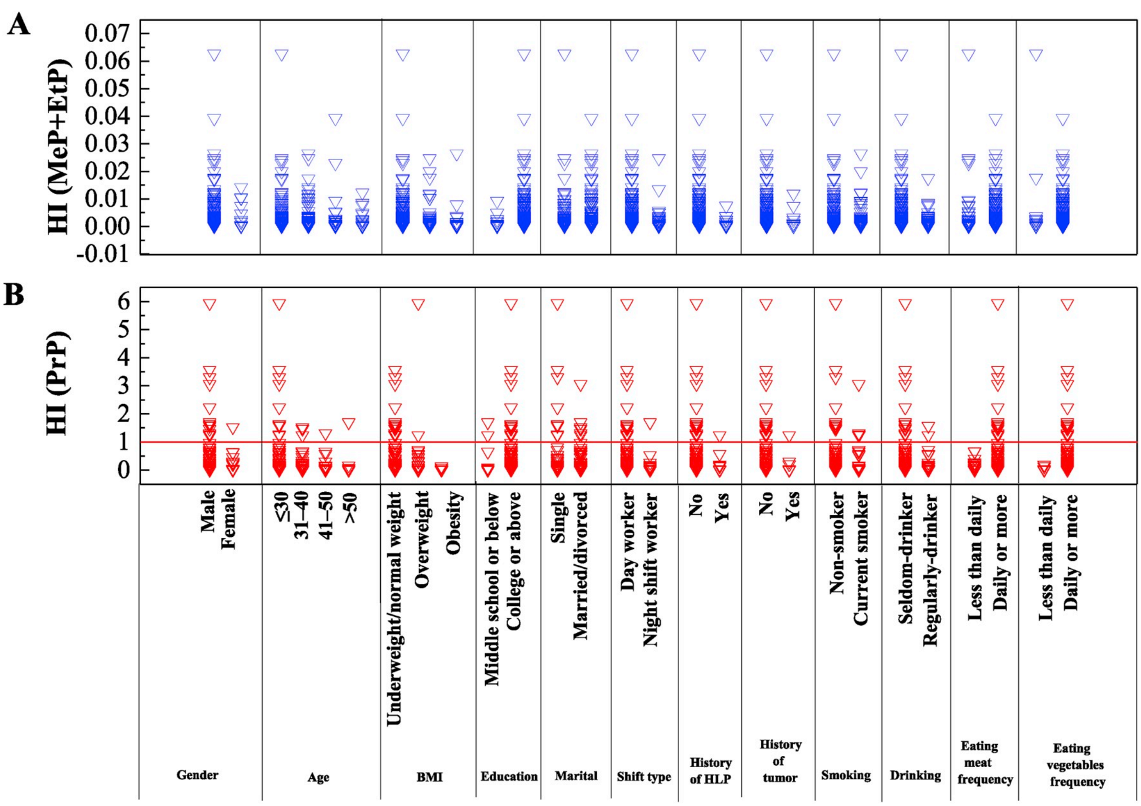

Fig. 2. Hazard index of parabens for nuclear power plant workers (A: the hazard index of MeP + EtP for workers; B: the hazard index of PrP for workers, and the red line represents risk level; HLP: hyperlipidemia). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ecoenv.2019.109419.

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