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Exposure to benzophenones, parabens and triclosan among pregnant women in different trimesters

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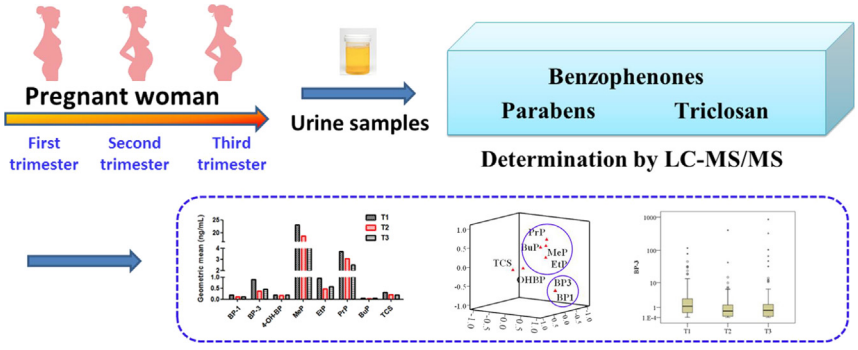
HIGHLIGHTS

- A total of 627 urine samples collected from 209 pregnant women were analyzed.
- Seven out of 11 target contaminants were detected at >50% frequency.
- There was significant correlation between BP-1 and BP-3 and between MeP and PrP.
- Levels of BP-1 and BP-3 were significantly higher in the first trimester than later stages.

GRAPHICAL ABSTRACT



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ABSTRACT

Humans are potentially exposed to many environmental pollutants, many of which may cause adverse health effects, especially to pregnant women and their fetuses. In this study, 11 environmental pollutants from three different chemical classes, including benzophenones, parabens and triclosan were measured in 627 urine samples collected from 209 pregnant women to evaluate exposure and trends as a function of pregnancy stage. Methylparaben (MeP), ethylparaben, propylparaben (PrP), butylparaben, 2,4-dihydroxybenzophenone (BP-1), 2-hydroxy-4-methoxybenzophenone (BP-3) and 4-hydroxybenzophenone were detected in >50% samples. The concentrations of BP-1 and BP-3 (Spearman's $r = 0.57$, $p < 0.01$) and those of MeP and PrP (Spearman's $r = 0.68$, $p < 0.01$) were found to be correlated. The urinary concentrations of BP-1 and BP-3 in the first trimester were significantly higher than those in the second or third trimester (Mann-Whitney U test, $p < 0.05$). These findings provide valuable information for improving the prediction of maternal exposure to these emerging pollutants and for assessing their potential health risks to the mother as well as the offspring.

1. Introduction

Due to the ubiquitous use of chemicals in homes, workplaces, public place installations, and other environments, humans are exposed to many environmental pollutants. These contaminants may alter one or more functions of the endocrine system and consequently cause

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adverse human health effects (WHO, 2012). In particular, human exposure to benzophenones, parabens and triclosan (TCS) is of significant concern (CDC, 2017). These chemicals are pharmaceuticals and personal care products (PPCPs) and have been frequently detected in environmental matrices such as surface water, sludge and soil (Camino-Sánchez et al., 2016), as well as in human biological samples (urine, human milk, plasma) (Cao et al., 2015; Ko et al., 2016).

In pregnant women, these pollutants and their metabolites may transfer to fetal across the human placenta (Valle-Sistac et al., 2016). Prenatal exposure to these compounds was reported to be associated with increased risk of diseases in neonates, such as adverse birth outcomes and allergic diseases (Geer et al., 2017; Zhou et al., 2017). Since pregnant women and their fetuses are vulnerable populations to endocrine disruption (Bergman et al., 2013), understanding exposure to these contaminants and the consequences in women during pregnancy is of paramount importance.

Urine is one of the most important pathways for excretion of environmental contaminants, and urinary concentrations have been often used as biomarkers of internal exposure (Ye et al., 2006). In a recent study, TCS was detected frequently in urine samples collected from pregnant women in Canada (Arbuckle et al., 2015a), with the geometric mean (GM) concentrations at 0.80 μg/L and 12.30 μg/L, respectively. The urinary concentrations of several environmental phenols were also monitored in pregnant women in the United States, the median concentration for 2-hydroxy-4-methoxybenzophenone (BP-3), TCS, methylparaben (MeP) and propylparaben (PrP) are 42.9, 15.6, 105.5 and 22.3, respectively (Mortensen et al., 2014).

Humans may be simultaneously and cumulatively exposed to a wide range of environmental pollutants, dictating the need for exploring their co-occurrence and interactions (Vo et al., 2015). In addition, the metabolism of chemicals may vary in pregnant women during the different gestation trimesters due to physiological changes (Abduljalil et al., 2012). However, most studies so far focus on only a specific group of compounds (Shirai et al., 2013) and the studies on pregnant women often use one-spot samples during pregnancy (Arbuckle et al., 2015a) or at delivery (Dereumeaux et al., 2016). There lacks a clear knowledge on exposure of pregnant women to environmental contaminants in different trimesters.

In this study, 11 environmental pollutants were measured in urine from pregnant women in China at different trimesters during gestation to characterize the profiles of exposure as a function of pregnancy stages. To the best of our knowledge, this is the first study to simultaneously determine human exposure to the 11 target PPCPs in pregnant women in China during different trimesters.

2. Materials and methods

2.1. Study population and sample collection

This study enrolled pregnant women at different maternity hospitals in Wuhan, located in Hubei Province in central China. The study was approved by the ethics committees of the participating parties, including Tongji Medical College, Huazhong University of Science and Technology, and their affiliated hospitals. The 627 urine samples were collected from 209 pregnant women volunteers in 2014 and 2015. The participants were invited to finish a face-to-face interview before donating urine samples. The information included maternal demographic characteristics (e.g., maternal age) and socioeconomic characteristics (e.g., education, occupation, household income). The maternal pre-pregnancy body mass index (BMI) was calculated based on self-reported pre-pregnancy weight and height. All participants signed an informed consent form. Urine samples were provided by mothers from 12 to 16 gestation weeks (first trimester, T1), from 16 to 28 gestation weeks (second trimester, T2) and after 28 weeks (third trimester, T3), respectively. The samples were collected in polypropylene tubes and frozen at −80 °C until analysis.

2.2. Analysis of urinary environmental pollutants

2,4-dihydroxybenzophenone (BP-1), 2,2′,4,4′-tetrahydroxy benzophenone (BP-2), BP-3, 2,2′-dihydroxy-4-methoxybenzo-bpenone (BP-8), 4-hydroxybenzophenone (4-OH-BP), TCS (Irgasan), paraben target analyte mix solution and paraben internal standard mix solution were purchased from Sigma-Aldrich (St. Louis, USA). $^{13}C_6$-BP-3 and $^{13}C_{12}$-TCS were purchased from Cambridge Isotope Laboratories (Andover, MA, USA).

With the isotope labeled internal standards, urinary concentrations of five benzophenones, five parabens and TCS were measured by using an Ultimate 3000 Ultra-high performance liquid chromatography system (Dionex, Sunnyvale, CA, USA) coupled to a Thermo Scientific™ TSQ Quantiva™ Triple Quadrupole mass spectrometer (Thermo Scientific, San Jose, CA). The sample preparation procedure and LC-MS/MS parameters were referred to our previous study with some small modifications (Zhao et al., 2017). Briefly, 1 mL urine sample was incubated with β-glucuronidase at 37 °C overnight mixed with the internal standard solution (with the final concentration 20 ng/mL). After enzymatic hydrolysis, the solution was extracted for 3 times with 3 mL solvent (methyl tert-butyl ether/ethyl acetate (5/1, v/v) each time. The supernatants were combined and evaporated under nitrogen gas flow, and then reconstituted in 200 μL acetonitrile/water (6/4, v/v). Chromatographic separation was achieved on Thermo Scientific Betasil C_{18} column (2.1 mm × 100 mm, 3 μm) using a mobile phase gradient with water and acetonitrile (Table S1). The compounds were detected by negative-ion electrospray ionization mass spectrometry and multiple reaction monitoring mode (Table S2). The blanks and quality control (QC) samples were incorporated into each batch of samples. As reported in our previous work (Zhao et al., 2017), the limit of detection (LOD) of each compound ranged from 0.01 to 0.2 ng/mL. The calibration curves ranged from 1 to 50 ng for BP-3, from 1 to 100 ng for PrP and butylparaben (BuP) and from 0.5 to 50 ng for other targeted compounds, with good linearity ($R^2 > 0.99$). This method showed satisfactory accuracy, precision (intra- and inter-day) and recovery.

2.3. Statistical analysis

Compounds concentrations were expressed in the level of ng/mL and adjusted by specific gravity (SG), which was measured by a handheld digital refractometer (Atago, Tokyo, Japan). The urinary concentrations were adjusted using the following formula: SG-adjusted concentration (ng/mL) = unadjusted concentration (ng/mL) × [(SG_m − 1) / (SG_i − 1)](Weiss et al., 2015), where SG_i is the SG of the individual urine sample, and SG_m (1.012) is the median SG for the whole sample size ($n = 209$). For all statistical tests, the non-detectable concentration was accounted as a value equal to the LOD divided by the square root of 2 (Hornung and Reed, 1990). The sum of benzophenones molar concentrations (∑ benzophenones) was calculated by the sum of those of BP-1, BP-2, BP-3, BP-8, and 4-OH-BP, while the sum of parabens (∑ parabens) was calculated by the sum of those of MeP, ethylparaben (EtP), PrP, BuP and benzylparaben (BzP). The SPSS Statistics for Windows, version 18.0 (IBM, Armonk, NY, USA) was used for data analysis, such as percentile analysis, Spearman correlation analysis, Mann-Whitney *U* test and principal component analysis. The correlation analysis heat map was performed by MetaboAnalyst 3.0.

3. Results and discussion

3.1. Levels of environmental pollutants in urine

The socio-demographic characteristics of the participants in this study are given in Table 1. The 209 women had a mean age of 28.4 years, and 50.2% of them had a college degree. Only 13.9% of the women had a pre-pregnancy BMI over 24 kg/m^2. The mean birth weight of neonates was 3323.9 g and the mean birth length was 50.2 cm. Most