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Variability and exposure classification of urinary phenol and paraben metabolite concentrations in reproductive-aged women

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ABSTRACT

Background: Human exposure to phenols and parabens is widespread. Within-person variability of urinary concentrations in healthy women is not well characterized.
Objectives: To characterize the variability of urinary phenol and paraben concentrations across two months and evaluate the ability of a single spot urine sample to characterize exposure.
Methods: 143 women provided 509 spot urine samples collected across two months of study (3–5 samples/woman). We measured urinary concentrations of 8 phenols: bisphenol A (BPA), benzophenone-3 (BP-3), benzophenone-1 (BP-1), 2,4-dichlorophenol (2,4-DCP), 2,5-dichlorophenol (2,5-DCP), 2,4,5-trichlorophenol (2,4,5-TCP), 2,4,6-trichlorophenol (2,4,6-TCP), triclosan (TCS); and 8 parabens and their metabolites (benzyl (BzP), butyl (BuP), ethyl (EtP), heptyl (HeP), methyl (MeP), propyl (PrP), 4-hydroxybenzoic acid (4-HB), 3,4-dihydroxybenzoic acid (3,4-DHB)). Biomarker variability was characterized using the intraclass correlation coefficient (ICC) and surrogate category analyses were conducted.
Results: ICCs ranged from very low for BPA (0.04) to moderate for BP-3, BP-1, TCS, BzP, and MeP (0.66, 0.58, 0.55, 0.54, and 0.62, respectively). Surrogate analyses suggested that BP-1, BP-3, TCS, 2,4-DCP, BuP, and PrP may be characterized by a single spot sample (sensitivity range 0.76–0.86) but that additional samples were necessary for BPA, HeP, 4-HB, and 3,4-DHB (sensitivity range 0.47–0.61).
Conclusions: Urinary phenol and paraben metabolite concentrations were variable across two months in healthy women but the degree of reliability differed by the specific biomarker. A small number of samples may sufficiently characterize typical concentrations for BP-3, BP-1, TCS, BuP, and PrP; but additional biospecimens may be necessary to characterize exposure for other compounds, including BPA.

1. Introduction

Phenols and parabens are chemicals that include some of the highest volume production chemicals in the world. Human exposure is nearly ubiquitous and comes from diet, personal care products, and pharmaceuticals (Guo and Kannan, 2013; Moreta et al., 2015). Although rapidly metabolized, the common detection of phenols and parabens in U.S. adults indicates exposure is nearly continuous (Calafat et al., 2010, 2008, 2007a, 2007b; Gerona et al., 2016; Harley et al., 2016; Jukic et al., 2016; Meeker et al., 2013; Mortensen et al., 2014; Smith et al., 2012). The primary source of exposure may vary by source population. Further, chemical half-life may influence variability. A

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growing body of literature have linked phenols and parabens with adverse health effects including ovarian toxicity, breast cancer, immune disorders, adverse birth outcomes, child behavior, and neurodevelopment outcomes (Karpuzoglu et al., 2013; Peretz et al., 2014; Rochester, 2013). Results have been inconsistent, however, which may be due to the inadequacy of a single measurement to characterize exposure.

Accurately capturing human exposure to phenols and parabens is important to ascertain their relationship to adverse health effects. The use of a single sample, often due to cost considerations, is a limiting factor in epidemiologic studies and is problematic when linking short-lived substances to health outcomes. Several studies on the variability of phenols and parabens are available (Braun et al., 2012; Engel et al., 2014; Guidry et al., 2015; Mahalingaiah et al., 2007; Meeker et al., 2013; Nepomnaschy et al., 2009; Reeves et al., 2014; Ye et al., 2011). However, findings are mixed and, to our knowledge, only one study included premenopausal women not actively attempting to become pregnant (Townsend et al., 2013). Two studies focused on women undergoing fertility treatment and captured samples prior to pregnancy (Braun et al., 2012; Smith et al., 2012). Due to increasing concerns about chemicals in personal care products, exposure patterns and behaviors may differ among women who are not attempting to become pregnant (Barrett et al., 2014; Dott et al., 2010; Marie et al., 2016; Than et al., 2005), as women seeking pregnancy may attempt to avoid such exposures. Differences in exposure by pregnancy status have been observed in representative US studies, as nonpregnant women had higher levels of BPA compared to pregnant women, supporting potential differences in exposure patterns for phenols (Woodruff et al., 2011).

Thus, the aim of our study was to measure concentrations of phenols and parabens over the course of two months, characterize reliability, and to conduct a surrogate category analysis to ascertain the reliability of a single spot urine sample to estimate exposure to these chemicals over time among a population of healthy reproductive age women not attempting to become pregnant.

2. Methods

2.1. Participants and study design

The study population was previously described in detail (Wactawski-Wende et al., 2009). Briefly, participants were free of known chronic health conditions and attended up to 8 clinic visits for up to two menstrual cycles of study. Mid-cycle visits were scheduled with the aid of a fertility monitor to improve capturing hormone variability around ovulation (Clearblue Easy Fertility Monitor; Inverness Medical, Waltham, Massachusetts) (Howards et al., 2009). This ancillary study included 143 of the original 259 participants, utilized stored fasting urine specimens collected at the University at Buffalo during morning clinic visits (Fig. 1). Prior to analysis, samples were stored at −80 °C and were not thawed prior to this study. Samples were collected in polycarbonate-free containers, which were not expected to be a source of phenol contamination.

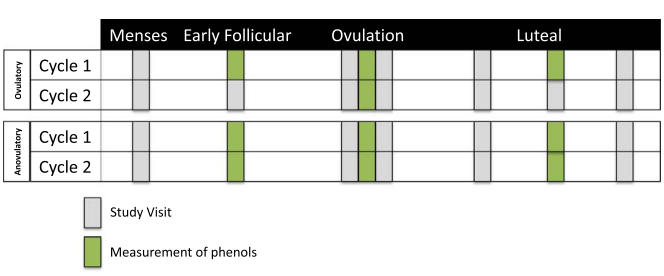

Fig. 1. Sampling strategy from stored urinary biospecimens for ancillary study of phenol and paraben metabolites in reproductive-aged women.

The sampling strategy depended on ovulatory status as follows. We sampled ovulatory cycles in the early follicular phase, at ovulation, and mid-luteal phase in cycle 1 and at ovulation in cycle 2. Anovulatory cycles were sampled in the early follicular phase, expected time of ovulation, and during the middle of the second half of the cycle of both cycles. Up to five samples per woman were selected. Sampling was also subject to biospecimen availability. Of the 143 women, 23 had anovulatory and 120 had ovulatory cycles (Lynch et al., 2014). Eleven percent of the participants had two samples, 27% had three samples, and 56% had four samples and the remaining 6% had five samples. The sub-study included 509 samples, comprising 72 anovulatory and 437 ovulatory samples. The University at Buffalo Health Sciences Institutional Review Board (IRB) approved the study and served as the IRB designated by the National Institutes of Health for this study under a reliance agreement. New York State Department of Health obtained IRB approval for sample analysis. All participants provided written informed consent.

2.2. Chemical analysis

Samples were thawed, aliquoted and shipped to the Wadsworth Laboratory (Albany, New York) where they were measured using high-performance liquid chromatography coupled with API2000 electrospray triple-quadrupole mass spectrometry (HPLC-MS/MS) to quantify environmental phenols and parabens (Asimakopoulos et al., 2014; Zhang et al., 2011). We determined limits of quantitation (LOQ) with the lowest point on the calibration curve and a nominal sample volume of 0.5 mL. Machine read values below the LOQ were used. The LOQ was 0.02 ng/mL for BPA (0.4% below), BP-3 (0.6%), TCS (0%), BuP (26.3%), BzP (74.7%), and HeP (98.8%); 0.05 ng/mL for MeP (0%), EtP (15.7%), PrP (2.9%), and BP-1 (0.8%); 0.5 ng/mL for 2,4-DCP (35.4%), 2,5-DCP (1.2%), 2,4,6-TCP (7.8%), and 3,4-DHB (0.4%); 0.08 ng/mL for 2,4,5-TCP (98.0%); and 0.2 ng/mL for 4-HB (0%). We implemented continual quality assurance and control processes in each batch and included a method blank, a spiked blank, and a pair of matrix-spiked sample duplicates. 43 specimens had <20 μL urine and creatinine measurement was impossible. Creatinine was measured using a Roche Cobas 6000 chemistry analyzer (Roche Diagnostics Inc., Indianapolis, IN) in 466 urine samples at the University of Minnesota Laboratory and urine samples were diluted 1:4 (20 μL urine +80 μL saline). The creatinine coefficient of variability was 1.5% at 96.6 mg/dL, 4.3% at 18.4 mg/dL. The limit of detection was 1 mg/dl.

2.3. Covariate assessment

Trained study staff measured height and weight to obtain body mass index (BMI) at the study enrollment visit using standardized protocols (Wactawski-Wende et al., 2009). Age, race, smoking, marital status, medical and reproductive history were obtained using questionnaires. More than 95% of participants had complete covariate data.

2.4. Statistical analysis

Unstandardized and creatinine-standardized values, resulting in absolute excretion units (ng/mg creatinine) were used.

2.4.1. Descriptive analyses

We computed the geometric mean and 5th, 25th, 50th, 75th and 95th percentiles for both unstandardized and creatinine-standardized phenol and paraben metabolite concentrations.