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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),

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AZP conceived of the study, performed the statistical analysis and drafted the manuscript. NJP, SLM, KK, EFS participated in the study design. NJP, SLM, KK, EFS, LJS, and CP contributed substantially to editing the manuscript. All authors read and approved the final manuscript.

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.

Keywords

Benzophenone-3; Bisphenol A; Dichlorophenol; Intra-individual variability; Parabens; Reliability; Triclosan

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 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 neuro-development 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.

The sampling strategy depended on ovulatory status as follows. We sampled ovulatory cycles in the early follicular phase, at ovulation, and midluteal 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 μ L 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 μ L urine +80 μ L 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. Demographic characteristics were compared for the study participants. We determined Pearson correlation coefficients for the log-transformed and creatinine adjusted metabolite concentrations and were then mapped using Cytoscape (Shannon et al., 2003). We did not plot correlations between 0 and 0.2, for parsimony, positive correlations were depicted in green, negative in red and the thickness of the line indicates strength of correlation. We measured Spearman correlations between pairs of phenol and paraben concentrations 0–2 weeks, 2–4 weeks, and 4–6 weeks apart.

2.4.2. Reliability analyses—To estimate reliability of unstandardized and creatinine-standardized urinary phenols, we calculated the intraclass correlation coefficient (ICC), defined as the ratio of between-subject variance to total variance, with 95% confidence intervals using a linear mixed model with a random intercept from the `icc9` macro for SAS (Hankinson et al., 1995). ICC values close to 0 indicate little to no reproducibility while values close to 1 indicate perfect reproducibility, where most of the variance is attributed to differences between individuals as opposed to within-person differences. Values were log-transformed to account for non-normal distributions. Correlation coefficients were classified

according to the guideline proposed by Rosner: < 0.4 , poor; 0.4 to < 0.75 , fair to good; 0.75 , excellent (Rosner, 2000).

Surrogate category analysis was performed to determine if a single spot urine sample could adequately describe a woman's "true" category of exposure over two months. This approach enables us to ascertain the level of misclassification and to help infer the number of measurements needed to minimize measurement error (Hauser et al., 2004; Willett, 2012). This analysis was limited to 89 women who had 4 or more samples and was further restricted when we used two urine samples to predict the "true" level ($n = 67$), based on creatinine measurement availability.

First, we determined the geometric mean for creatinine-standardized, log-transformed urinary metabolite levels using all repeated measurements for each participant with at least 4 observations (89 women). This was considered the participant's "true" level of exposure. This "true" level was categorized as either in the top tertile or the bottom two tertiles, as metabolite levels were dichotomized at the 66.7th percentile. We calculated sensitivity, specificity, and the positive predictive value (PPV) of the top tertile of the surrogate measure in comparison to the top tertile of the "true" average measure for each chemical. The PPV may be interpreted as the probability of being classified as having average concentration in the top tertile given a high surrogate measure. We measured how well various combinations of samples predicted the "true" level of exposure. The following sample combinations were selected: all available samples, 1 sample per person (first visit sampled), 2 samples in the same month (two days approximately 2 weeks apart), and 2 samples in different months (two days approximately six weeks apart). These combinations of days were used to determine if the length of time between samples influenced misclassification. For example, the ability of an exposure measurement that involves only a single sample to predict the "true" high (> 66.7 th percentile) exposure category, which comprised four measures, was determined.

We examined the number and percent of women who remained in the same tertile of exposure for two months among those who had at least 4 available specimens by counting the number of times that a woman's concentration was in the same tertile for each phenol measurement (one, two, three or four). For example, if a woman remained in the lowest tertile of exposure across all four urine samples, her count was four. All analyses were conducted with SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. Results

In total, 143 women provided 3–5 urine samples ($n = 509$ samples) across two months. Women who participated in the study were largely younger than 25, non-Hispanic white, nulliparous and did not smoke cigarettes (Table 1). Unstandardized and creatinine-standardized concentrations of the measured phenol and parabens are presented in Table 2.

Correlations between chemicals ranged from weakly negative (-0.2) to strongly positive (0.8), but most were weakly positive (0.2 – 0.3) (Fig. 2). Among phenols, the strongest observed correlation was between BP-3 and BP-1. The strongest correlation between

parabens was between MeP and PrP. In particular, negative correlations were observed between BzP and BP-3; BP-3 and 2,4,5-TCP; 2, 5-DCP and 3,4-DHB; 3,4-DHB and BP-1; and 2,5-DCP and 3,4-DHB. BPA was the most isolated metabolite and was only correlated with BP-3. There was also evident separation between the paraben and phenol metabolite groups. Correlation with creatinine was highest for 4-HB (0.37), 3–4-DHB (0.24), 2,5-DCP (0.24), PrP (0.23), and TCS (0.22). Correlations were lowest for HeP (–0.04) and were positive for all other phenols and parabens. Spearman correlations ranged from –0.04 for 2,4,6-TCP to 0.74 for BP-3 and PrP (Table 3). Correlations for BPA taken 2 weeks apart were low (0.08) (Table 3).

We found high within-person variability relative to total variability for BPA (Table 4) both before and after creatinine correction (ICC = 0.04) for the phenols. 2,4,6-TCP had similarly high levels of within-person variability relative to total variability for unstandardized levels (ICC = 0.04) but was higher after creatinine correction, though still exhibited poor reproducibility (0.24). BP-3 had the lowest within-person variability relative to total variability (ICC = 0.67). BP-1 and TCS had fair to good reproducibility (ICC = 0.55–0.59). For the unstandardized paraben concentrations, the ICCs ranged from poor reproducibility of 0.11 for HeP to fair to good reproducibility of 0.62 for MeP.

The proportion of women who were correctly identified in the highest tertile from a single sample (sensitivity) ranged from 0.47 for 3,4-HB to 0.86 for BP-3 (Table 5). Sensitivity was highest for BPA when selecting two samples from different months (approximately 6 weeks apart) (0.73) and was lowest when selecting two samples from a single cycle (0.56), showing that either sampling strategy resulted in moderately good agreement but that timing measurements closer temporally (two vs. six weeks apart) gave lower sensitivity for correctly classifying higher exposure. BP-1, BP-3 and TCS had high sensitivity (> 0.7) for one or two samples. For parabens, sensitivity was highest using two samples from different cycles for BzP (0.89) and BuP (0.86). Sensitivity was lowest for most parabens when only a single observation per person was used to predict the highest category of “true” exposure.

Less than 10% of women had spot urine samples in the same tertile of exposure for all phenols and parabens, except for HeP (11%) (Table 6). Only 1% of women had the same tertile of urinary BPA concentration at all four samples. A greater proportion of women were in the same tertile of exposure for all four measurements for TCS (11%), EtP (13%), and HeP (11%).

4. Discussion

The main purpose of our study was to measure concentrations of phenols and parabens, characterize within-subject variability relative to total variability, and to ascertain the reliability of a single spot urine sample to estimate the exposure to these chemicals over a period of two months in reproductive-aged women. We found considerable within-subject variability relative to total variability in urinary BPA concentrations (ICC = 0.04, 95% CI: 0.01, 0.22), but reliability was fair to good for other chemicals. The highest creatinine-adjusted ICCs, which showed fair to good reliability, were found for BP-3 (0.67), BP-1 (0.59), TCS (0.57), and MeP (0.59) while the lowest ICCs, which exhibited poor reliability,

were found for BPA (0.04), 2,4,6-TCP (0.24), HeP (0.20), and 3,4-HB (0.21). The sensitivity of one spot urine to predict two-month average paraben and phenol exposure was moderate to fair to good for most chemicals analyzed (sensitivity range for a single sample: 0.47–0.86). We observed a slightly greater increase in prediction for two samples ~6 weeks apart (sensitivity range: 0.62–0.91) compared to two samples collected ~2 weeks apart (sensitivity range: 0.54–0.84) but results for one sample were similar (sensitivity range: 0.47–0.86).

A spot urine sample predicted the highest “true” category of most phenols and parabens moderately well (Table 5). These findings underscore the importance of collecting more than a single biospecimen for the analytes that had poor to good reliability, to characterize true exposure for those analytes at the lower range of sensitivity for analyses where correct categorization of exposure is important. Although BP-3, BP-1, TCS, 2,4-DCP, BuP, and PrP exhibited excellent reliability; measurement error from comparable levels of reliability can bias effect estimates (Perrier et al., 2016).

Exposure to phenols and parabens primarily comes from use of personal care products and food consumption (Guo and Kannan, 2013; Liao et al., 2013; Liao and Kannan, 2014a; Moreta et al., 2015). Differences in urinary concentration reliability may stem from differences in exposure source. The measured concentrations of phenols and parabens in this study were similar to those observed among women in NHANES (data from 2005 to 2006 (Table 2)) (Cdc, 2009). However, the unstandardized levels for BP-3 and MeP were lower than NHANES, while 2,5-DCP and TCS levels were higher. Differences in the concentrations of BP-3 may be explained by variation in the use of sunscreens and cosmetics, perhaps driven by the location of the present study in upstate New York, as compared with a nationally representative population, which may be more likely to use sunscreen regularly due to climate differences across the country (Liao and Kannan, 2014b).

Reliability of BPA was similar to previous reports (ICC = 0.04), indicating that a single measurement is not adequate to approximate typical exposure. Previous studies in adults have found ICCs between 0.07 and 0.20 (Braun et al., 2011; Engel et al., 2014; Guidry et al., 2015; Jusko et al., 2014; Ye et al., 2011). Our results indicated greater reliability than previously reported for BP-3, similar for BuP and MeP, but slightly lower than reported for PrP (Guidry et al., 2015). While it is possible that our findings were driven by environmental contamination, it is unlikely to entirely explain these findings. One limitation of our approach is that we did not measure total and free levels of phenols, which was recommended as a method to evaluate environmental contamination (Guidry et al., 2015). There are additional aspects of the measurement process, including the analyst themselves, the apparatus used in measurement, and the reagent blank, which may be sources of contamination (Ye et al., 2013). Contamination by urine preservative or in the laboratory has been demonstrated (Longnecker et al., 2013). This can to some extent be mitigated by good laboratory practices, which include, among other elements, participating in external quality assessment programs (Ye et al., 2013). These practices were used in this laboratory, suggesting that environmental contamination was unlikely to be a primary factor (Vandenberg et al., 2014). The levels we observed were largely similar to those observed by other studies, and we would expect higher levels if contamination of phenols by external sources affected these samples.

When categories of exposure were considered, sensitivity was similar to studies of women seeking pregnancy. The sensitivity of a single sample to predict “true” exposure for BPA in the present study was 0.61. This was similar to a study of women attempting to become pregnant in Utah (sensitivity 0.59) (Cox et al., 2016). For BPA, sensitivity was also similar to a previous study in a fertility treatment-seeking population (sensitivity 0.60) (Braun et al., 2012). In contrast, one study found that a single BPA measurement predicted categories of exposure moderately well over a period of several months, albeit in a smaller fertility center cohort of women who were attempting to become pregnant (Mahalingaiah et al., 2007). Collectively, these findings suggest that multiple BPA measurements are needed to accurately classify categories of exposure. A limitation of this method is that it may tend to overestimate measurements since a limited number of measures contribute to the “true” exposure category and as such, may reflect an overestimate. This could imply that researchers could use fewer samples than would actually be necessary to adequately characterize categories of exposure.

The present study had several strengths, including the collection of multiple metabolite measurements in healthy women who were selected to minimize unmeasured confounding factors. Women were selected to be free of chronic disease, not on a special diet, not using medications for a chronic medical condition or oral contraceptives, not pregnant or breastfeeding within the past 6 months, and with a self reported BMI between 18 and 35 kg/m² at screening. To our knowledge, this is the first study to quantify the reliability of such a range of phenols and parabens, specifically including 4-HB, 3,4-DHB, 2,4,5-TCP, and 2,4,6-TCP and is among the largest studies available to date among reproductive-aged women not attempting to become pregnant. An additional strength was our consideration of multiple phenols and parabens. The inclusion of individuals who identified with race/ethnicities other than non-Hispanic white is another strength, as several previous studies among women of reproductive age were limited to non-Hispanic white participants (Braun et al., 2012; Townsend et al., 2013). Inclusion of premenopausal women who were not actively planning pregnancy is another unique aspect of our study. Given increasing population-wide concerns about chemicals in personal care products, women seeking pregnancy may alter their habits to attempt to avoid such exposure (Barrett et al., 2014; Dott et al., 2010; Marie et al., 2016; Than et al., 2005). Therefore, these findings are more generalizable than studies of women attempting pregnancy. The inclusion of all instrument-derived values as a proxy for LOQ is another study strength, as substitution strategies utilized in prior studies can contribute to bias (Schisterman et al., 2006). However, the study was limited to adjustment for creatinine without accompanying measurement of specific gravity. Creatinine is widely accepted as a method to adjust for variability in excretion but may not be ideal for substances that are glucuronidated in liver and subsequently eliminated in urine (Boeniger et al., 1993). Further, creatinine levels can be influenced by diet, activity patterns, urine flow, and muscle mass (Boeniger et al., 1993).

5. Conclusions

We demonstrated fair to good reliability for one urine sample to estimate exposure to several paraben and phenol metabolites over two months. Particularly for BP-3, BP-1, TCS, BuP, and PrP, a small number of samples may accurately classify categories of exposure. One

sample is not recommended for any of the phenols; as the highest ICC was BP-3 (0.67), indicating fair to good reliability. Our findings can be used to account for potential misclassification and for planning biospecimen collection in future studies of women not attempting to become pregnant.

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

Fig. 2.

Correlation map of log-transformed creatinine-corrected urinary phenol and paraben metabolite levels among reproductive-aged women (n = 89).

Table 1

Demographic characteristics of participating women (n = 143; 2005–2007).

Demographic factor	n (%)
Age (years)	
18–24	75 (52.4)
25–29	22 (15.4)
30–34	11 (7.7)
35–39	20 (14.0)
40–44	15 (10.5)
Body mass index (kg/m ²)	
<18.5	6 (4.2)
18.5 to < 25	87 (60.8)
25 to < 30	35 (24.5)
30	15 (10.5)
Race	
Non-Hispanic white	90 (62.9)
Non-Hispanic black	29 (20.3)
Other	24 (16.8)
Current cigarette smoker	6 (4.2)
Nulliparous	107 (77.0)

Distribution of phenol and paraben concentrations measured in spot urine samples from 143 premenopausal women (n = 509 samples) near Buffalo, New York.

Table 2

Analyte ^a µg/l	Geometric mean	Selected percentiles					NHANES ^b	
		5th	25th	50th	75th	95th	Geometric mean	
BPA	2.9	0.3	1.3	2.8	6.8	26.1	1.7	
BP-3	4.3	0.2	1.2	3.8	14.5	152.7	25.5	
BP-1	3.3	0.2	1.0	4.1	10.9	42.5	NA	
TCS	23.3	1.3	7.1	22.2	73.9	419.7	16.2	
2,4-DCP	0.9	0.1	0.3	0.8	2.0	9.5	0.8	
2,5-DCP	17.2	0.1	0.3	19.1	35.0	162.0	7.7	
2,4,5-TCP	0.08	0.01	0.04	0.08	0.1	0.3	NA	
2,4,6-TCP	0.3	0.1	0.2	0.3	0.5	1.2	NA	
BzP	0.01	0.002	0.003	0.004	0.02	0.2	NA	
BuP	0.3	0.002	0.02	0.5	2.3	17.9	0.9	
EtP	0.8	0.02	0.1	1.1	4.8	49.4	NA	
HeP	0.005	0.002	0.003	0.004	0.02	0.2	NA	
MeP	49.5	3.0	16.9	59.0	146.9	552.7	104.0	
PrP	12.5	1.0	3.6	15.1	48.6	202.4	20.4	
4-HB	414.4	77.5	190.2	389.1	890.7	2389.1	NA	
3,4-HB	279.4	20.4	108.4	344.8	826.0	2225.0	NA	
µg/g creatinine								
BPA	2.3	0.3	1.1	2.3	4.8	16.2	2.04	
BP-3	3.4	0.2	1.0	2.9	11.3	100.9	11.7	
BP-1	2.5	0.1	0.8	2.6	9.1	35.2	NA	
TCS	17.5	1.6	5.6	15.4	50.8	288.3	19.0	
2,4-DCP	0.6	0.07	0.2	0.6	1.6	7.2	1.03	
2,5-DCP	13.3	1.2	6.5	13.3	28.8	116.0	9.04	
2,4,5-TCP	0.06	0.01	0.03	0.06	0.1	0.3	NA	
2,4,6-TCP	0.2	0.03	0.1	0.2	0.5	1.6	NA	
BzP	0.008	0.001	0.002	0.005	0.03	0.3	NA	

Analyte ^a µg/l	Geometric mean	Selected percentiles					NHANES ^b Geometric mean
		5th	25th	50th	75th	95th	
BuP	0.2	0.001	0.01	0.4	1.7	10.5	1.06
EtP	0.6	0.01	0.1	0.8	4.4	26.6	NA
HeP	0.004	0.001	0.002	0.004	0.008	0.02	NA
MeP	37.2	3.1	14.1	43.2	101.7	352.2	123.0
PrP	9.4	0.9	3.4	11.5	30.2	94.5	23.9
4-HB	316.4	58.4	151.4	318.4	692.5	1532.7	NA
3,4-HB	221.2	18.8	94.3	251.9	604.9	1529.2	NA

^a Bisphenol A (BPA), benzophenone-3 (BP-3), benzophenone-1 (BP-1), 2,4-di-chlorophenol (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), benzyl paraben (BzP), butyl paraben (BuP), ethyl paraben (EtP), heptyl paraben (HeP), methyl paraben (MeP), propyl paraben (PrP), 4-hydroxybenzoic acid (4-HB), 3,4-dihydroxybenzoic acid (3,4-DHB).

^b 2005–2006, females only.

Spearman correlation coefficients between urine samples by time interval between measurement, using uncorrected and creatinine corrected phenol and paraben concentrations in reproductive-aged women ($n = 143$).

Table 3

Analyte ^a	Time interval between samples (weeks) Rho (p value)							
	2	2-4	4-6	2	2-4	4-6	2	4-6
	Uncorrected				Creatinine corrected			
Number of sample pairs	103	95	55	86	76	44		
BPA	0.08 (0.41)	0.17 (0.11)	0.24 (0.07)	0.16 (0.14)	0.08 (0.48)	0.19 (0.22)		
BP-3	0.69 (< 0.01)	0.64 (< 0.01)	0.54 (< 0.01)	0.74 (< 0.01)	0.74 (< 0.01)	0.60 (< 0.01)		
BP-1	0.66 (< 0.01)	0.59 (< 0.01)	0.31 (0.02)	0.66 (< 0.01)	0.63 (< 0.01)	0.29 (0.05)		
TCS	0.60 (< 0.01)	0.56 (< 0.01)	0.45 (< 0.01)	0.58 (< 0.01)	0.59 (< 0.01)	0.52 (< 0.01)		
2,4-DCP	0.46 (< 0.01)	0.39 (< 0.01)	0.45 (< 0.01)	0.45 (< 0.01)	0.42 (< 0.01)	0.58 (< 0.01)		
2,5-DCP	0.39 (< 0.01)	0.28 (< 0.01)	0.39 (< 0.01)	0.48 (< 0.01)	0.45 (< 0.01)	0.22 (0.15)		
2,4,5-TCP	0.32 (< 0.01)	0.28 (< 0.01)	0.45 (< 0.01)	0.38 (< 0.01)	0.39 (< 0.01)	0.41 (< 0.01)		
2,4,6-TCP	0.11 (0.25)	0.005 (0.96)	-0.04 (0.78)	0.31 (< 0.01)	0.19 (0.10)	0.28 (0.06)		
BzP	0.57 (< 0.01)	0.54 (< 0.01)	0.65 (< 0.01)	0.59 (< 0.01)	0.44 (< 0.01)	0.54 (< 0.01)		
BuP	0.50 (< 0.01)	0.50 (< 0.01)	0.58 (< 0.01)	0.50 (< 0.01)	0.50 (< 0.01)	0.49 (< 0.01)		
EtP	0.32 (< 0.01)	0.43 (< 0.01)	0.58 (< 0.01)	0.32 (< 0.01)	0.40 (< 0.01)	0.47 (< 0.01)		
HeP	0.50 (< 0.01)	0.35 (< 0.01)	0.34 (0.01)	0.52 (< 0.01)	0.39 (< 0.01)	0.27 (0.07)		
MeP	0.59 (< 0.01)	0.55 (< 0.01)	0.61 (< 0.01)	0.61 (< 0.01)	0.39 (< 0.01)	0.27 (0.07)		
PrP	0.54 (< 0.01)	0.46 (< 0.01)	0.73 (< 0.01)	0.66 (< 0.01)	0.60 (< 0.01)	0.74 (< 0.01)		
4-HB	0.24 (0.02)	0.31 (< 0.01)	0.29 (0.03)	0.39 (< 0.01)	0.46 (< 0.01)	0.23 (0.13)		
3,4-HB	0.45 (< 0.01)	0.41 (< 0.01)	0.55 (< 0.01)	0.38 (< 0.01)	0.37 (< 0.01)	0.59 (< 0.01)		

^aBisphenol A (BPA), benzophenone-3 (BP-3), benzophenone-1 (BP-1), 2,4-dichlorophenol (2,4-DCP), 2,5-dichlorophenol (2,5-DCP), 2,4,6-trichlorophenol (2,4,6-TCP), triclosan (TCS), benzyl paraben (BzP), butyl paraben (BuP), ethyl paraben (EtP), heptyl paraben (HeP), methyl paraben (MeP), propyl paraben (PrP), 4-hydroxybenzoic acid (4-HB), 3,4-dihydroxybenzoic acid (3,4-DHB).

Table 4

Intraclass correlation coefficients (ICC) and 95% confidence intervals for concentrations of phenols and parabens in 143 premenopausal women (n = 509 samples).

Analyte ^a	Unadjusted Concentration ICC (95% CI) ^b (ng/mL)	Creatinine-adjusted concentration ICC (95% CI) ^c (ng/mg)
BPA	0.04 (0.01, 0.22)	0.04 (0.01, 0.25)
BP-3	0.66 (0.58, 0.73)	0.67 (0.60, 0.74)
BP-1	0.58 (0.49, 0.65)	0.59 (0.50, 0.67)
TCS	0.55 (0.47, 0.63)	0.57 (0.48, 0.65)
2,4-DCP	0.40 (0.31, 0.49)	0.38 (0.28, 0.48)
2,5-DCP	0.37 (0.28, 0.46)	0.33 (0.24, 0.44)
2,4,5-TCP	0.39 (0.30, 0.48)	0.36 (0.27, 0.46)
2,4,6-TCP	0.04 (0.01, 0.25)	0.24 (0.16, 0.35)
BzP	0.54 (0.45, 0.62)	0.48 (0.39, 0.58)
BuP	0.41 (0.32, 0.51)	0.39 (0.30, 0.50)
EtP	0.42 (0.33, 0.51)	0.38 (0.29, 0.48)
HeP	0.11 (0.05, 0.23)	0.20 (0.12, 0.32)
MeP	0.62 (0.54, 0.69)	0.59 (0.50, 0.67)
PrP	0.48 (0.40, 0.57)	0.46 (0.37, 0.56)
4-HB	0.33 (0.25, 0.43)	0.33 (0.24, 0.44)
3,4-HB	0.28 (0.19, 0.38)	0.21 (0.13, 0.33)

^aBisphenol A (BPA), benzophenone-3 (BP-3), benzophenone-1 (BP-1), 2,4-di-chlorophenol (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), benzyl paraben (BzP), butyl paraben (BuP), ethyl paraben (EtP), heptyl paraben (HeP), methyl paraben (MeP), propyl paraben (PrP), 4-hydroxybenzoic acid (4-HB), 3,4-dihydroxybenzoic acid (3,4-DHB).

^bUnadjusted concentration 509 measurements in 143 women.

^cCreatinine adjusted concentration 466 measurements in 143 women.

Table 5

Sensitivity for predicting women with the highest mean phenol and paraben levels (top 33%) and specificity for predicting women with lowest (bottom 66%) log-transformed creatinine-corrected mean phenol and paraben levels.

Analyte ^a	All samples n = 366 ^b			One sample/person n = 82 ^c			Two samples/person (~2 weeks apart) n = 62 ^d			Two samples/person (~6 weeks apart) n = 62 ^e		
	Sens	Spec	PPV	Sens	Spec	PPV	Sens	Spec	PPV	Sens	Spec	PPV
BPA	0.57	0.79	0.59	0.61	0.87	0.71	0.56	0.81	0.64	0.73	0.87	0.73
BP-3	0.82	0.91	0.83	0.86	0.91	0.83	0.79	1.00	1.00	0.90	0.93	0.86
BP-1	0.74	0.88	0.76	0.76	0.91	0.81	0.78	0.98	0.95	0.91	0.96	0.91
TCS	0.70	0.86	0.73	0.76	0.85	0.73	0.84	0.98	0.95	0.75	0.91	0.82
2,4-DCP	0.69	0.83	0.64	0.81	0.85	0.73	0.77	0.89	0.77	0.75	0.85	0.68
2,5-DCP	0.63	0.83	0.67	0.70	0.79	0.66	0.64	0.90	0.82	0.72	0.90	0.82
2,4,5-TCP	0.70	0.83	0.63	0.69	0.77	0.58	0.72	0.82	0.59	0.75	0.85	0.68
2,4,6-TCP	0.65	0.82	0.64	0.68	0.83	0.68	0.68	0.84	0.68	0.81	0.89	0.77
BzP	0.67	0.84	0.67	0.69	0.80	0.62	0.79	0.85	0.68	0.89	0.90	0.77
BuP	0.73	0.87	0.74	0.76	0.94	0.76	0.79	1.00	1.00	0.86	0.93	0.86
EtP	0.75	0.88	0.76	0.69	0.85	0.71	0.74	0.95	0.91	0.82	0.91	0.82
HeP	0.60	0.78	0.53	0.57	0.73	0.45	0.80	0.81	0.55	0.75	0.80	0.55
MeP	0.66	0.85	0.72	0.70	0.85	0.72	0.68	0.92	0.86	0.70	0.93	0.86
PrP	0.68	0.86	0.72	0.77	0.88	0.79	0.71	0.95	0.91	0.63	0.88	0.77
4-HB	0.59	0.81	0.63	0.53	0.71	0.52	0.65	0.88	0.77	0.69	0.90	0.82
3,4-DHB	0.53	0.78	0.59	0.47	0.81	0.58	0.54	0.82	0.68	0.62	0.85	0.73

^aBisphenol A (BPA), benzophenone-3 (BP-3), benzophenone-1 (BP-1), 2,4-dichlorophenol (2,4-DCP), 2,5-dichlorophenol (2,5-DCP), 2,4,6-trichlorophenol (2,4,6-TCP), triclosan (TCS), benzyl paraben (BzP), butyl paraben (BuP), ethyl paraben (EtP), heptyl paraben (HeP), methyl paraben (MeP), propyl paraben (PrP), 4-hydroxybenzoic acid (4-HB), 3,4-dihydroxybenzoic acid (3,4-DHB).

^bAll available samples used for prediction (n = 366 samples, 89 people).

^c82 women, 82 samples, one sample/person, early follicular phase of menstrual cycle.

^dSamples from one menstrual cycle: early follicular phase and mid-cycle in the same menstrual cycle (n = 67).

^eSamples from two different menstrual cycles: early follicular phase of menstrual cycle one and mid-cycle in the second cycle (n = 67).

Table 6Number (%) of women with spot urine samples in the same exposure tertile.^a

Analyte ^b	Number (%) of samples in the same tertile			
	None	Two	Three	Four
BPA	8 (9)	53 (62)	23 (27)	1 (1)
BP-3	8 (9)	35 (41)	37 (44)	5 (6)
BP-1	7 (8)	47 (55)	23 (27)	8 (9)
TCS	4 (5)	41 (48)	31 (36)	9 (11)
2,4-DCP	8 (9)	49 (58)	26 (31)	2 (2)
2,5-DCP	4 (5)	52 (61)	26 (31)	3 (4)
2,4,5-TCP	6 (7)	45 (53)	26 (31)	8 (9)
2,4,6-TCP	6 (7)	41 (48)	31 (36)	7 (8)
BzP	6 (7)	47 (55)	27 (32)	5 (6)
BuP	5 (6)	54 (64)	21 (25)	5 (6)
EtP	6 (7)	45 (53)	23 (27)	11 (13)
HeP	9 (11)	46 (54)	21 (25)	9 (11)
MeP	5 (6)	48 (56)	25 (29)	7 (8)
PrP	5 (6)	50 (59)	24 (28)	6 (7)
4-HB	6 (7)	48 (56)	24 (28)	7 (8)
3,4-HB	6 (7)	49 (58)	24 (28)	6 (7)

^aWomen with four urine samples (n = 85).^bBisphenol A (BPA), benzophenone-3 (BP-3), benzophenone-1 (BP-1), 2,4-di-chlorophenol (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), benzyl paraben (BzP), butyl paraben (BuP), ethyl paraben (EtP), heptyl paraben (HeP), methyl paraben (MeP), propyl paraben (PrP), 4-hydroxybenzoic acid (4-HB), 3,4-dihydroxybenzoic acid (3,4-DHB).