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Predictors of Urinary Bisphenol A and Phthalate Metabolite Concentrations in Mexican Children

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Abstract

Exposure to endocrine disrupting chemicals such as bisphenol A (BPA) and phthalates is prevalent among children and adolescents, but little is known regarding important sources of exposure at these sensitive life stages. In this study, we measured urinary concentrations of BPA and nine phthalate metabolites in 108 Mexican children aged 8–13 years. Associations of age, time of day, and questionnaire items on external environment, water use, and food container use with specific gravity-corrected urinary concentrations were assessed, as were questionnaire items concerning the use of 17 personal care products in the past 48-hr. As a secondary aim, third trimester urinary concentrations were measured in 99 mothers of these children, and the relationship between specific gravity-corrected urinary concentrations at these two time points was explored. After adjusting for potential confounding by other personal care product use in the past 48-hr, there were statistically significant ($p < 0.05$) positive associations in boys for cologne/perfume use and monoethyl phthalate (MEP), mono(3-carboxypropyl) phthalate (MCPP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), and mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and in girls for colored cosmetics use and mono-*n*-butyl phthalate (MBP), mono(2-ethylhexyl) phthalate (MEHP), MEHHP, MEOHP, and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), conditioner use and MEP, deodorant use and MEP, and other hair products use and MBP. There was a statistically significant positive trend for the number of personal care products used in the past 48-hr and log-MEP in girls. However, there were no statistically significant associations between the analytes and the other questionnaire items and there were no strong correlations between the analytes measured during the third trimester and at 8–13 years of age. We demonstrated that

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personal care product use is associated with exposure to multiple phthalates in children. Due to rapid development, children may be susceptible to impacts from exposure to endocrine disrupting chemicals; thus, reduced or delayed use of certain personal care products among children may be warranted.

Keywords

Bisphenol A; phthalates; biomarker; children; personal care products; urine

1. INTRODUCTION

Bisphenol A (BPA) and phthalates are synthetic chemicals used in the production of a wide variety of consumer and medical products, and exposure to these chemicals has been documented worldwide (Hauser and Calafat, 2005; Vandenberg et al., 2007). In particular, urinary BPA and multiple phthalate metabolites have been measured in children across a variety of ages and in pregnant women where BPA and phthalates can cross the maternal-fetal placental barrier (Buckley et al., 2012; Vandenberg et al., 2007). Because exposure to these endocrine-disrupting chemicals is ubiquitous in children at various stages of development and trends for rates of endocrine-related diseases and disorders among children have increased, there is growing concern among scientists, physicians, governments, and the public that these chemicals may influence child development (Meeker, 2012).

The animal evidence suggests that BPA and phthalate exposures may influence development through the disruption of hormonally-mediated pathways (Lyche et al., 2009; vom Saal et al., 2007). These findings are supported by human epidemiology studies reporting associations between biomarkers of exposures to BPA and phthalates and endocrine-related outcomes, including shorter gestation (Cantonwine et al., 2010; Latini et al., 2003; Meeker et al., 2009; Whyatt et al., 2009), low birth weight (Chou et al., 2011; Zhang et al., 2009), changes in breast and pubic hair development (Frederiksen et al., 2012; Wolff et al., 2010), and changes in brain development (Braun et al., 2009; Cho et al., 2010; Engel et al., 2010, 2009; Kim et al., 2009), body mass index (Hatch et al., 2008; Teitelbaum et al., 2012; Trasande et al., 2012; Wolff et al., 2007), and reproductive and thyroid hormone levels (Boas et al., 2010; Chevrier et al., 2012; Main et al., 2006) during various stages in childhood and adolescence. However, epidemiology studies conducted in children beyond infancy have largely been cross-sectional in design, relying on data concerning current exposures. If current exposures to BPA or phthalates in children are associated with exposures occurring in the prenatal environment, cross-sectional epidemiology studies that report associations with health outcomes may reflect effects related to exposures occurring during childhood/adolescence or in utero or both (i.e. exposures at one time point could be a surrogate for exposures at the other time point). This is a topic yet to be reported in the literature, but is important for understanding the results of such studies and in the design of future studies.

Numerous studies concerning predictors of exposure to BPA and phthalates in adult men and women, including pregnant women have been conducted (Berman et al. 2009; Braun et al. 2011; Buckley et al. 2012; Carwile et al., 2009; Casas et al., 2013; Duty et al., 2005; He et al., 2009; Hines et al., 2009; Just et al. 2010; Kwapniewski et al., 2008; Li et al., 2013; Mahalingaiah et al., 2008; Meeker et al., 2012; Parlett et al., 2012; Romero-Franco et al., 2011; Zimmerman-Downs et al., 2010). However, in comparison, exposure predictor studies in children are much more limited in number and have considered a far less variety of BPA and phthalate sources. These child exposure predictor studies have been conducted in infants (Calafat et al., 2004, 2009; Green et al., 2005), toddlers (Sathyanarayana et al., 2008),

preschoolers (Casas et al., 2013), and school-aged children (Colacino et al., 2011; Li et al., 2013; Nahar et al., 2012). Additional, more comprehensive studies concerning predictors of BPA and phthalate exposure in children at all stages are needed to better inform targeted behavior modifications and policy for reducing exposures to these endocrine-disrupting chemicals.

In this study, the primary aim was to identify the determinants of urinary BPA and phthalate metabolite concentrations in 108 children from Mexico City, Mexico aged 8–13 years. A secondary aim of this study was to determine whether childhood and maternal-third trimester urinary concentrations are correlated in 99 mother-child pairs. This study considered a greater variety of BPA and phthalate sources than previous child exposure predictor studies and, to our knowledge, this is the first study to examine the relationship between BPA and phthalate exposures at these two time points.

2. MATERIALS AND METHODS

2.1 Study Participants

This study used data from the Early Life Exposure in Mexico to ENvironmental Toxicants (ELEMENT) project that was started in 1994 and consists of three sequentially-enrolled birth cohorts from Mexico City maternity hospitals (Gonzalez-Cossio et al., 1997; Hu et al., 2006; Surkan et al., 2008). The mission of ELEMENT is to examine the influence of environmental toxicant exposures on the development and future health of the fetus and infant. Across these three cohorts, 2098 mothers were recruited during the first trimester of pregnancy or at delivery and followed at 1, 7, and 12 months post-partum and at ages 2–5 years for their offspring ($n=1710$) depending on the specific study. Socio-demographic, dietetic, anthropometric, and biomarker (urine, blood, bone) measures were collected at each follow-up visit. Spot urine and blood samples were collected and archived from mothers and children at different stages, including pregnancy, as well. In 2010, a subset of these children was contacted again at ages 8–13 years ($n=250$) through their primary caregiver based on availability of archived biomarker measures, and data from the first available 108 children were included in this current study. Urine samples and questionnaire data from these children were used in this analysis, along with urine samples from their mothers collected during third trimester when available ($n=99$). The questionnaire was administered by trained study nurses and filled out by the children with assistance from their primary caregiver (i.e. proxy-assisted). The research protocols were approved by the Ethics and Research Committees of all participating institutions (National Institute of Public Health, National Institute of Perinatology, and University of Michigan).

2.2 Urinary BPA and Phthalate Metabolites

Total (free + glucuronidated) BPA and nine phthalate metabolites were measured in maternal and child urine samples by isotope dilution-liquid chromatography-tandem mass spectrometry (ID-LC-MS/MS) at NSF International (Ann Arbor, MI, USA). The nine phthalate metabolites included: monoethyl phthalate (MEP), metabolite of diethyl phthalate (DEP); mono-*n*-butyl phthalate (MBP), metabolite of di-*n*-butyl phthalate (DBP); mono-isobutyl phthalate (MIBP), metabolite of di-isobutyl-phthalate (DIBP); mono(3-carboxypropyl) phthalate (MCPP), metabolite of DBP and di-*n*-octyl phthalate (DOP); monobenzyl phthalate (MBZP), metabolite of butylbenzyl phthalate (BBZP); and mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), metabolites of di(2-ethylhexyl) phthalate (DEHP).

An in-house method was developed, which was a slight modification of the Centers for Disease Control and Prevention (CDC) Laboratory Procedure Manuals for phthalate

metabolites in urine (method no. 6306.03, revised: July 3, 2010) and BPA in urine (method no. 6301.01; revised: April 13, 2009) described elsewhere (Calafat et al., 2008; Silva et al., 2007). The methods were validated in accordance with Food and Drug Administration (FDA) Guidance for Industry: Bioanalytical Method Validation (2001). Samples underwent enzymatic deconjugation of glucuronidated species, online solid phase extraction, and analysis with a Thermo Scientific (Waltham, MA, USA) Vantage triple quadrupole mass spectrometer using multiple reaction monitoring in negative ionization mode. Urine sample online extraction was performed using a Thermo Scientific Cyclone-P (0.5 x 50 mm) turbulent flow extraction column followed by chromatographic separation using a Waters (Milford, MA, USA) Xbridge C18 5 μ m (3.0 x 150 mm) analytical column. BPA and phthalate metabolite calibration ranges utilized were based on CDC methods. The validated analyte calibration curve correlation coefficient (R^2) range was 0.985–1.000. The method accuracy (% nominal concentration) and precision (%RSD) were determined through six replicate analyses of analytes spiked at four different concentrations in aqueous and human urine across validation runs on three separate days (n=18) which reflects both the intra-day and inter-day variability of the assay. The accuracy (% nominal concentration) range across all analytes was 85.0 to 119% with precision (%RSD) range for both aqueous and urine quality control samples across all analytes being 1.3 to 10.8%. Specific gravity (SG) of the urine samples was also measured using a handheld digital refractometer (ATAGO Company Ltd., Tokyo, Japan).

BPA and phthalate metabolite concentrations below the limit of quantitation (LOQ) were assigned a value of LOQ divided by the square root of 2. For analyses concerning SG-corrected values, the following formula was used (Mahalingaiah et al., 2008; Nahar et al., 2012): $P_c = P(SG_p / (SG_i / I))$, where P_c is the SG-adjusted BPA or phthalate metabolite concentration (ng/ml), P is the measured urinary BPA or phthalate metabolite concentration, SG_p is the median of the urinary specific gravities for the sample (mothers: 1.108, children: 1.014), and SG_i is the urinary specific gravity for the individual. Urinary concentrations were corrected for specific gravity to adjust for variability in urine output (Pearson et al., 2009; Mahalingaiah et al., 2008).

2.3 Questionnaire

The questionnaire, which was adapted from questionnaires used in studies in adults (Duty et al., 2005; Meeker et al., 2013), was developed to capture information on potential BPA and phthalate sources to which the children may have been exposed. The questionnaire was separated into four sections: external environment, water use, food container use, and personal care product use. The external environment section contained yes/no questions about plastic/vinyl flooring at home and at school. In the water use section, the children were asked about the primary type of water consumed (tap water, filtered water, bottled/purified water, other), as well as the primary source of drinking water at home (municipal water, private well water, bottled/delivered water). The food container use section contained a yes/no question regarding foods microwaved on or in plastic containers or wrappers, and questions on the usual frequency of consuming foods microwaved on or in plastic containers or wrappers, canned foods, and canned beverages (<1 day/month, 1–3 days/month, 1–2 days/week, 3–5 days/week, >5 days/week, multiple times/day). The personal care product use section contained yes/no questions about the use of 17 different personal care products in the past 48-hr, in addition to questions on the usual frequency of using these personal care products (not at all, <once/month, 1–3 times/month, once/week, few times/week, every day). The questionnaire asked about the use of the following personal care products: aftershave, bar soap, cologne/perfume, colored cosmetics, conditioner, deodorant, finger nail polish, hair cream, hair spray/hair gel, laundry products, liquid soap, lotion, mouthwash, other hair

products (other than those listed), other toiletries (other than those listed), shampoo, and shaving cream.

2.4 Statistical Analysis

Data analysis was performed using SAS version 9.3 for Windows (SAS Institute, Cary, NC, USA). Distributions of BPA and phthalate metabolite concentrations uncorrected for SG at third trimester and 8–13 years of age were tabulated individually for boys and girls and compared between both sexes with Wilcoxon rank-sum tests. Spearman's rank correlation coefficients and the associated p values were calculated for boys and girls to evaluate the relationship between these two time points for SG-corrected BPA and phthalate metabolite concentrations. Median SG-corrected BPA and phthalate metabolite concentrations for both boys and girls collectively were tabulated and compared with Wilcoxon rank-sum tests between dichotomized categories of age, time of day when the urine sample was collected, and questions relating to the external environment, water use, and food container use. A similar analysis was performed for categories of personal care products used in the past 48-hr, except that we stratified on sex because we hypothesized that there were differences in personal care product use between sexes. We did not analyze the data concerning personal care product use frequency because the results of a sensitivity analysis demonstrated excellent agreement between product use in the past 48-hr and use frequency (data not shown). For all of the two-group comparisons, we only assessed those with $n \geq 5$ for both groups and we did not adjust the p values for multiple comparisons. We defined statistical significance as $p < 0.05$.

To assess whether there exists a trend between the total number of personal care products used in the past 48-hr and urinary concentrations of BPA and phthalate metabolites for boys and girls individually, four indicator variables were created (6, 7, 8, 9 products; reference group: ≤ 5 products) based on the distribution of responses and were regressed against log-transformed SG-corrected concentrations. Total number of personal care products used in the past 48-hr was also modeled as an ordinal variable to obtain the p value for the trend.

Many children in this cohort reported using more than one personal care product in the past 48-hr, and multiple personal care products may contain the same chemicals and thus share associations with the same urinary biomarkers. Thus, it is plausible that the statistically significant findings from the bivariate analysis could be confounded by the use of other personal care products. To enhance our confidence in the results of the bivariate analysis, a forward stepwise regression analysis (FSRA) was performed where variables corresponding to the use of personal care products in the past 48-hr were entered and retained in final models when $p < 0.15$. This cut point was chosen to permit the stepwise process enough flexibility so that personal care products with “suggestive” associations ($0.05 \leq p < 0.15$) would be retained in the final models. FSRA was performed for each urinary biomarker that had at least one statistically significant association that was identified in the bivariate analysis. Selected SG-corrected urinary biomarkers were log-transformed prior to performing the FSRA.

3. RESULTS

Table 1 shows the distributions of BPA and phthalate metabolite concentrations not corrected for dilution in urine samples ($n=99$) collected from mothers during the third trimester. Nearly all of the samples had detectable concentrations of the phthalate metabolites (0–4% $< \text{LOQ}$). The majority of samples also had detectable concentrations of BPA (24–31% $< \text{LOQ}$). Wilcoxon rank-sum tests comparing concentrations by analyte between mothers of boys and mothers of girls revealed no statistically significant differences.

Table 2 shows the distributions of BPA and phthalate metabolite concentrations not corrected for dilution in urine samples collected from boys ($n=53$) and girls ($n=55$) at 8–13 years of age. Similar to the third trimester urine samples (Table 1), a greater number of urine samples from boys and girls 8–13 years of age were above the LOQ for the phthalate metabolites (0–4% <LOQ) compared to BPA (11–13% <LOQ). Geometric mean (GM) concentrations for boys and girls 8–13 years of age were the highest for MBP rather than MEP, which was the case for the third trimester urine samples (Table 1). Except for MEP, GM urinary concentrations for boys and girls 8–13 years of age were higher compared to the third trimester urine samples from mothers of boys and girls (Table 1), respectively. Wilcoxon rank-sum tests comparing urinary concentrations by analyte between boys and girls 8–13 years of age revealed no statistically significant differences.

Table 3 shows the Spearman rank correlation coefficients comparing SG-corrected BPA and phthalate metabolite concentrations between the third trimester and 8–13 years of age. The results demonstrate that there were no strong or statistically significant correlations (absolute value range: 0.01–0.21) between these two time points.

Table 4 shows the results for SG-corrected urinary analyte concentrations of dichotomized categories of personal care product use in the past 48-hr stratified by sex. Wilcoxon rank-sum tests revealed that there were no statistically significant differences in concentrations of BPA or MBZP by self-reported use of any personal care products in the past 48-hr for boys or girls. However, boys that used cologne/perfume in the past 48-hr had significantly higher concentrations of MEP (medians: 135 vs. 49.5 ng/ml, $p=0.007$), MCP (medians: 2.6 vs. 1.7 ng/ml, $p=0.009$), MEHHP (medians: 57.1 vs. 38.4 ng/ml, $p=0.03$), and MEOHP (medians: 25.7 vs. 16.5 ng/ml, $p=0.01$) compared with non-users. Boys that used lotion in the past 48-hr also had significantly higher concentrations of MEHP compared with non-users (medians: 9.8 vs. 6.7 ng/ml, $p=0.02$). For girls, users of colored cosmetics in the past 48-hr had significantly higher concentrations of MBP (medians: 246 vs. 101 ng/ml, $p=0.02$), MEHP (medians: 17.3 vs. 7.2 ng/ml, $p=0.001$), MEHHP (medians: 102 vs. 46.0 ng/ml, $p=0.005$), MEOHP (medians: 40.0 vs. 21.9 ng/ml, $p=0.01$), and MCP (medians: 141 vs. 71.9 ng/ml, $p=0.009$) compared with non-users. Significantly higher concentrations of MEP were found in girls that used conditioner (276 vs. 51.8 ng/ml, $p=0.001$) or deodorant (medians: 147 vs. 46.4 ng/ml, $p=0.003$) in the past 48-hr compared with those that did not, respectively. Girls that used other hair products (other than conditioner, hair cream, hair spray/gel, or shampoo) in the past 48-hr had significantly higher concentrations of MBP (medians: 293 vs. 101 ng/ml, $p=0.02$), MIBP (medians: 22.0 vs. 12.0 ng/ml, $p=0.008$), and MCP (medians: 4.5 vs. 2.3 ng/ml, $p=0.03$) compared with non-users.

Wilcoxon rank-sum tests for data not stratified on sex revealed no statistically significant differences for SG-corrected BPA or phthalate metabolites in the urine of 8–10 year-olds vs. 11–13 year-olds, or in urine collected in the morning vs. the afternoon (data not shown). There were also no statistically significant differences in SG-corrected urinary analyte concentrations for dichotomized categories of plastic/vinyl flooring at home or at school, primary type of water consumed (bottled/purified water vs. other), primary source of drinking water at home (bottled/delivered vs. other), microwaving foods on or in plastic containers or wrappers, or frequency (<1–2 days/week vs. 1–2 days per week) of consuming microwaved foods on or in plastic containers, canned foods, or canned beverages (data not shown).

Figure 1 shows a positive trend ($p=0.0002$) for the number personal care products used in the past 48-hr and log-transformed SG-corrected MEP concentrations in girls. Beta coefficients for the regression model were 3.73 (5 personal care products, reference group), 0.52 (6 personal care products), 0.89 (7 personal care products), 1.52 (8 personal care

products), and 1.89 (9 personal care products). Taking the antilog of the log-MEP value for each group revealed that the expected urinary MEP concentration on average for girls that used 5, 6, 7, 8, and 9 personal care products in the past 48-hr was 41.7, 70.1, 101, 191, and 276 ng/ml, respectively. There were no statistically significant trends for the number of personal care products used in the past 48-hr and concentrations of MEP for boys and any of the other analytes for boys or girls.

The statistically significant associations identified in the bivariate analysis also remained statistically significant in the FSRA, except for MEHP and lotion use in boys, and MIBP and MCPP and use of other hair products in girls (data not shown).

4. DISCUSSION

In this study, we measured total concentrations of BPA and nine phthalate metabolites (MEP, MBP, MIBP, MCPP, MBZP, MEHP, MEHHP, MEOHP, MECPP) in spot urine samples collected from 108 Mexican children aged 8–13 years and mothers of 99 of these children during the third trimester. Urinary concentrations of BPA and the phthalate metabolites between these two time points were not correlated. After adjusting for potential confounding by other personal care product use in the past 48-hr, we found that use of cologne/perfume (MEP, MCPP, MEHHP, MEOHP) in the past 48-hr in boys and colored cosmetics (MBP, MEHP, MEHHP, MEOHP, MECPP), conditioner (MEP), deodorant (MEP), and hair products other than hair spray/gel, shampoo, conditioner, and hair cream (MBP) use in the past 48-hr in girls were statistically significant positive predictors of urinary phthalate metabolite concentrations. In girls only, there was a statistically significant positive trend between the number of personal care products used in the past 48-hr and urinary concentrations of log-MEP as well. Taken together, our results suggest that personal care product use in Mexican boys and girls are potentially important determinants of phthalate exposure.

GM urinary concentrations of the analytes at third trimester were comparable to those in urine samples from adults 20 years of age and older in US NHANES 1999–2004, except for MBP (US: 17.0–21.6 ng/ml) and MEHP (2.2–4.2 ng/ml), which were higher in this study, and MBZP (US: 8.2–9.2 ng/ml), which was lower in this study (CDC, 2013). Similar GM urinary concentrations of the phthalate metabolites at third trimester evaluated here have also been reported in pregnant Israeli women, except for MBP (Israel: 24.6 ng/ml), which was higher in our study, and MEP (Israel: 202 ng/ml) and MIBP (Israel: 13.4 ng/ml), which were lower in our study (Berman et al., 2009). GM urinary concentrations of BPA at third trimester were comparable to those in Chinese adults (He et al., 2009) 21 years of age and older and pregnant Spanish women (Casas et al., 2013) as well (data not shown).

GM urinary concentrations of the analytes at 8–13 years of age were comparable to those in urine samples from 6–11 year-old boys and girls in US NHANES 2009–2010, except for MEP (US: 35.2 ng/ml), MBP (US: 21.7 ng/ml), MEHP (US: 1.6 ng/ml), MEHHP (US: 15.0 ng/ml), MEOHP (US: 9.8 ng/ml), and MECPP (US: 27.7 ng/ml), which were higher in this study, and MBZP (US: 11.6 ng/ml), which was lower in this study. Children in our study also had similar GM urinary concentrations of MEOHP as 8–9 year-old South Korean girls, but had higher GM concentrations of MBP (South Korea: 48.9 ng/ml) and lower GM concentrations of MEHP (South Korea: 21.3 ng/ml) (Cho et al., 2010). In addition, children in our study had GM urinary concentrations of BPA that were similar to urine samples in 10–13 year-old Egyptian girls (Nahar et al., 2012) and lower than urine samples in 4 year-old Spanish boys and girls (Spain: 3.1 ng/ml) (Casas et al., 2013) (data not shown).

Our results are consistent with the findings of other studies that have examined associations between recent personal care product use and urinary concentrations of phthalate

metabolites in US men (Duty et al., 2005) and US (Buckley et al., 2012; Just et al., 2010; Parlett et al., 2012), Israeli (Berman et al., 2009), and Mexican women (Romero-Franco et al., 2011). Similar positive trends with urinary MEP concentration and number of personal care products used in the past 24–48-hr have also been reported in adults (Berman et al., 2009; Duty et al., 2005; Parlett et al., 2012; Romero-Franco et al., 2011), as well as in infants (Sathyanarayana et al. 2008). Our findings are additionally supported by information on personal care product formulations (ATSDR, 1995, 1997, 2001, 2002; Anonymous, 1985; Sathyanarayana, 2008) and studies that measured the phthalate content of personal care products (Houlihan et al., 2002; Khoo and Lee, 2004; Koniecki et al., 2011). This is especially the case for MEP whose parent compound, DEP, can be found in a wide variety of personal care products, such as fragrances, deodorants, hair products, detergents, and lotions. Determinants of phthalate metabolite concentrations may have differed between the boys and girls in our study due to differences in the content, amount, and/or frequency of personal care products used.

We found no statistically significant differences in urinary concentrations of BPA or the phthalate metabolites by age or time of day, which have been reported in adults (Braun et al., 2011; Chevrier et al., 2012; Mahalingaiah et al., 2008; Meeker et al., 2012) and children (Li et al., 2013). There were also no associations with urinary BPA concentrations by bottled water, canned food, or canned beverage consumption. BPA is found in the lining of food cans and beverage storage containers (Braun and Hauser, 2011), and oral dietary exposure is believed to be the dominant exposure pathway (Vandenberg et al., 2007). Positive associations have been reported between urinary BPA concentrations and polycarbonate bottle use (Carwile et al., 2009) and canned vegetable consumption frequency (Braun et al., 2011) in US men and women, canned fish consumption frequency in Spanish women (Casas et al., 2013), canned beverage and canned fish consumption frequency in 4 year-old Spanish boys and girls (Casas et al., 2013), plastic bottle use in 3–24 year-old Chinese boys and girls (Li et al., 2013), and storage of food in plastic containers in 10–13 year-old Egyptian girls (Nahar et al., 2012). In addition, we found no statistically significant differences in the urinary phthalate metabolite concentrations by external environment, water use, or foods microwaved on or in plastic containers or wrappers. Some phthalates are used in flexible vinyl plastic, which in turn is used in the manufacture of a variety of consumer goods, such as flooring and wall coverings and food packaging (Hauser and Calafat, 2005). Ingestion of foods that are contaminated with phthalates is believed to be an important route of exposure (Swan, 2008). Others have reported that foods stored in plastic containers in 10–13 year-old Egyptian girls (Colacino et al., 2011) and bottle use in Mexican women (Romero-Franco et al., 2011) are positively associated with urinary phthalate metabolites concentrations. High correlations between air phthalate and corresponding urinary phthalate metabolite concentrations have been reported in US women, suggesting that inhalation is an important route of exposure as well (Adibi et al., 2003).

A unique strength of our study was that we analyzed urine samples that were collected from children at 8–13 years and archived urine samples from their respective mothers during third trimester. We were interested in investigating the potential relationship between these two time points because a strong association would suggest that childhood urinary measures at 8–13 years may serve as an exposure surrogate for the prenatal environment (i.e. studies that report childhood associations with health outcomes may reflect effects related to childhood or in utero exposures or both). We found that the correlations between these two time points were weak, which may reflect differences in the toxicokinetics of the children and their mothers, BPA and phthalate content of sources over time, and magnitude and frequency of BPA and phthalate exposures. On the other hand, urinary BPA and phthalate metabolite concentrations between these two time points may be correlated, but because we relied on single spot measurements, which exhibit moderate to large intra-individual variability in

children (Teitelbaum et al., 2008) and adults (Adibi et al., 2008; Braun et al., 2011; Meeker et al., 2012), a correlation may not have been observed.

One limitation of our study was the small sample size, which limited the statistical power of the analyses. However, our study considered a greater variety of sources than previous studies of BPA and phthalate exposure predictors in infants (Calafat et al., 2004, 2009; Green et al., 2005), toddlers (Sathyanarayana et al., 2008), preschoolers (Casas et al., 2013), and school-aged children (Colacino et al., 2011; Li et al., 2013; Nahar et al., 2012), and was larger than all but three of these studies (Casas et al., 2013; Li et al., 2013; Sathyanarayana et al., 2008). We also did not adjust for multiple comparisons, so it is possible that some of the associations reported here may be due to chance. Nevertheless, our results are consistent with those reported in other published studies. Urinary BPA and phthalate metabolite concentrations reflect total exposure and, as a result, differentiation of exposure routes was not possible. BPA (5–6-hr) and phthalates (<24-hr) have a short biological half-lives (Braun and Hauser, 2011; Swan, 2008), and repeated measures of urinary BPA and phthalate metabolites in children (Teitelbaum et al., 2008) and adults (Adibi et al., 2008; Bruan et al., 2011; Meeker et al., 2012) have poor to moderate reproducibility. Thus, the spot urine samples collected from the children in our study may not reflect long-term exposures. In addition, the questionnaire did not ask the children to quantify the amount and frequency of personal care product use in the past 48-hr and lumped together certain personal care products into broad groups (e.g. colored cosmetics), which limited the analyses in this study. The questionnaire also did not ask about the consumption of foods not typically packaged in plastic containers or cans (e.g. fresh fruits, vegetables, and meats), which have been examined, but not found to be associated with urinary BPA in other exposure predictor studies (Braun et al., 2011; Casas et al., 2013), as well as tobacco smoke exposure, which has been reported to be positively associated with urinary BPA in adults (Braun et al., 2011; Casas et al., 2013; He et al., 2009) and children (Casas et al., 2013). However, the inclusion of increased detail and added items on the questionnaire would result in an increase in participant burden, and may introduce additional recall errors. Lastly, the results may not be generalizable to other populations, especially young children (<3 months) because they have glucuronidation pathways that are not fully mature (Lyche et al., 2009) and their personal care product use may be quite different as well.

5. CONCLUSIONS

We demonstrated that personal care product use in children is associated with exposure to multiple phthalates. Since exposure to phthalates in children is possibly associated with endocrine-related effects, reduced or delayed use of certain personal care products (e.g. cologne/perfume, colored cosmetics, etc.) in children may be warranted.

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ABBREVIATIONS

BPA	bisphenol A
ELEMENT	Early Life Exposure in Mexico to ENvironmental Toxicants
CDC	Centers for Disease Control and Prevention

BBZP	butylbenzyl phthalate
DBP	di- <i>n</i> -butyl phthalate
DEHP	di(2-ethylhexyl) phthalate
DEP	diethyl phthalate
DIBP	di-isobutyl-phthalate
DOP	di- <i>n</i> -octyl phthalate
FDA	Food and Drug Administration
FSRA	forward stepwise regression analysis
GM	geometric mean
ID-LC-MS/MS	isotope dilution-liquid chromatography-tandem mass spectrometry
LOQ	limit of quantitation
MBP	mono- <i>n</i> -butyl phthalate
MBZP	monobenzyl phthalate
MCPP	mono(3-carboxypropyl) phthalate
MECPP	mono(2-ethyl-5-carboxypentyl) phthalate
MEHP	mono(2-ethylhexyl) phthalate
MEHHP	mono(2-ethyl-5-hydroxyhexyl) phthalate
MEOHP	mono(2-ethyl-5-ox-o-hexyl) phthalate
MEP	monoethyl phthalate
MIBP	mono-isobutyl phthalate
NHANES	National Health and Nutrition Examination Survey
SG	specific gravity

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HIGHLIGHTS

- We studied urinary BPA and phthalate metabolite concentrations in Mexican children
- Urinary concentrations at third trimester and 8–13 years were not correlated
- Personal care product use was associated with exposure to several phthalates
- Reduced or delayed use of certain personal care products in children may be warranted

Figure 1. Change in log-urinary concentration of total (free + glucuronidated) MEP in girls 8–13 years of age (ng/ml, specific gravity-corrected) associated with 5 personal care products used in the past 48-hr with increasing number of personal care products used in the past 48-hr

Table 1

Urinary concentrations of total (free + glucuronidated) BPA and phthalate metabolites measured in mothers of cohort at third trimester (ng/ml, uncorrected for dilution)

Analyte	LOQ	Subject ^a	N	N (%) > LOQ	GM	Percentiles						
						10th	25th	50 th	75th	90th	95th	Max
BPA	0.4	Boys	49	34 (69)	0.7	<LOQ	<LOQ	0.6	1.0	2.6	4.5	8.9
		Girls	50	38 (76)	0.8	<LOQ	0.4	0.7	1.6	2.3	4.2	18.7
MEP	1.0	Boys	49	49 (100)	130	26.2	48.9	136	393	905	1140	2170
		Girls	50	50 (100)	136	21.9	49.4	119	221	1004	1900	9810
MBP	0.5	Boys	49	49 (100)	65.4	14.1	36.8	80.9	127	304	318	377
		Girls	50	50 (100)	64.6	17.0	31.1	63.8	157	200	606	1190
MIBP	0.2	Boys	49	47 (96)	1.9	0.4	1.4	2.1	3.5	5.3	7.3	39.4
		Girls	50	49 (98)	2.0	0.6	0.9	2.2	3.5	8.3	12.1	33.9
MCPP	0.2	Boys	49	49 (100)	1.2	0.2	0.7	1.4	2.3	3.3	4.3	8.9
		Girls	50	50 (100)	1.2	0.4	0.6	1.3	2.1	3.5	6.5	11.1
MBZP	0.2	Boys	49	48 (98)	3.6	0.9	2.0	3.4	8.3	15.9	16.8	32.5
		Girls	50	50 (100)	3.5	1.2	2.0	2.9	6.4	13.0	29.6	48.4
MEHP	1.0	Boys	49	49 (100)	7.0	2.3	3.5	7.8	10.8	16.1	18.8	24.7
		Girls	50	48 (96)	6.7	2.2	4.0	7.3	10.0	20.4	30.1	38.0
MEHHP	0.1	Boys	49	49 (100)	20.9	4.3	12.5	25.5	43.6	76.4	88.5	111
		Girls	50	50 (100)	23.4	7.3	14.4	25.6	38.7	67.8	96.7	148
MEOHP	0.1	Boys	49	49 (100)	12.1	2.5	6.6	15.0	25.2	46.0	48.4	64.7
		Girls	50	50 (100)	13.8	4.3	8.5	14.5	25.0	43.9	56.1	76.7
MECPP	0.2	Boys	49	49 (100)	34.1	6.6	22.8	34.1	58.9	107	119	172
		Girls	50	50 (100)	38.8	13.3	24.8	39.3	65.9	113	138	237

GM, geometric mean; LOQ, limit of quantitation; max, maximum.

^aNo significant differences ($p > 0.05$) in concentrations between mothers of boys and mothers of girls based on Wilcoxon rank-sum test.

Table 2

Urinary concentrations of total (free + glucuronidated) BPA and phthalate metabolites measured in cohort at 8–13 years of age (ng/ml, uncorrected for dilution)

Analyte	LOQ	Subjects ^a	N	N (%)	>LOQ	GM	Percentiles						
							10th	25th	50th	75th	90th	95th	Max
BPA	0.4	Boys	53	47 (89)		1.1	<LOQ	<LOQ	1.2	1.9	2.8	4.1	9.4
		Girls	55	48 (87)		1.2	<LOQ	0.6	1.1	2.2	3.8	6.8	20.1
MEP	1.0	Boys	53	53 (100)		69.5	16.5	28.0	62.7	136	305	1240	1580
		Girls	55	55 (100)		95.2	23.2	33.1	78.4	311	621	1070	4970
MBP	0.5	Boys	53	53 (100)		92.4	25.2	56.8	91.2	130	317	420	732
		Girls	55	55 (100)		101	27.9	56.1	98.0	226	343	714	1760
MIBP	0.2	Boys	53	53 (100)		10.7	3.4	7.1	11.0	16.7	26.2	37.8	100
		Girls	55	55 (100)		11.0	3.6	5.9	12.7	18.3	26.8	50.4	71.8
MCPD	0.2	Boys	53	53 (100)		2.0	0.9	1.3	2.0	2.5	5.7	8.0	9.8
		Girls	55	53 (96)		2.2	0.6	1.0	2.5	4.1	6.0	13.7	140
MBZD	0.2	Boys	53	53 (100)		5.6	1.9	3.2	5.6	9.3	13.6	17.6	28.6
		Girls	55	55 (100)		5.1	1.6	2.6	5.0	10.7	16.3	19.4	28.3
MEHP	1.0	Boys	53	53 (100)		7.6	3.2	4.0	7.5	11.9	16.7	24.2	203
		Girls	55	53 (98)		6.1	2.2	3.5	6.4	10.6	16.1	18.7	33.7
MEHHP	0.1	Boys	53	53 (100)		49.9	20.9	29.3	45.4	71.9	124	208	2100
		Girls	55	55 (100)		44.5	17.1	22.2	42.5	70.7	129	201	543
MEOHP	0.1	Boys	53	53 (100)		22.0	8.5	11.2	20.9	34.7	56.4	88.4	751
		Girls	55	55 (100)		19.2	7.0	10.2	18.7	33.8	56.4	86.1	186
MECPD	0.2	Boys	53	53 (100)		77.3	30.2	42.2	71.8	129	190	280	1620
		Girls	55	55 (100)		68.0	22.9	39.2	69.8	117	180	259	762

GM, geometric mean; LOQ, limit of quantitation; max, maximum.

^aNo significant differences ($p > 0.05$) in concentrations between boys and girls based on Wilcoxon rank-sum test.

Table 3

Spearman's rank correlation coefficients (r_s) of urinary concentrations of total (free + glucuronidated) BPA and phthalate metabolites measured in mothers of cohort at third trimester and in cohort at 8–13 years of age (specific gravity-corrected)

Analyte	Subjects	N	r_s^a
BPA	Boys	49	−0.08
	Girls	50	−0.05
MEP	Boys	49	−0.07
	Girls	50	0.02
MBP	Boys	49	0.08
	Girls	50	−0.09
MIBP	Boys	49	0.21
	Girls	50	−0.05
MCPP	Boys	49	0.09
	Girls	50	0.07
MBZP	Boys	49	0.15
	Girls	50	0.05
MEHP	Boys	49	0.10
	Girls	50	0.18
MEHHP	Boys	49	0.11
	Girls	50	0.01
MEOHP	Boys	49	0.08
	Girls	50	0.02
MECPP	Boys	49	0.10
	Girls	50	−0.07

^a $p > 0.05$.

Table 4

Association of urinary concentrations of total (free + glucuronidated) BPA and phthalate metabolites in cohort at 8–13 years of age (ng/ml, specific gravity-corrected) with personal care product use in the past 48-hr (listed only for those with $n \geq 5$ per group)

Subjects/variable	N	Analyte									
		BPA	MEP	MBP	MIBP	MCP	MBZP	MEHP	MEHP	MEHP	MECP
Boys											
Cologne/perfume											
No	29	**	+	***	+	**	+	+	***	+	***
Yes	24										
Deodorant											
No	22	—	—	+	—	—	—	—	—	—	—
Yes	31										
Hair spray/gel											
No	6	—	—	*	+	—	—	+	+	+	+
Yes	47										
Liquid soap											
No	10	—	+	+	—	+	—	+	+	—	+
Yes	43										
Lotion											
No	26	+	+	+	+	+	+	***	+	**	*
Yes	27										
Mouthwash											
No	37	+	+	—	—	—	+	—	—	—	+
Yes	16										
Girls											
Cologne/perfume											
No	18	—	**	+	—	—	+	+	+	—	—
Yes	37										
Colored cosmetics											
No	48	—	**	—	***	+	*	***	+	***	***
Yes	7										
Conditioner											

Subjects/variable	N	Analyte									
		BPA	MEP	MBP	MIBP	MCPP	MBZP	MEHP	MEHHP	MEOHP	MECPP
Deodorant	No	36	+	***	+	—	+	—	+	+	—
	Yes	19	+	+	+	+	+	—	+	+	—
Finger nail polish	No	25	—	***	+	—	—	+	+	—	—
	Yes	30	+	+	—	—	+	+	—	+	+
Hair cream	No	30	+	+	—	—	+	+	—	+	+
	Yes	25	+	+	+	—	+	+	—	+	+
Hair spray/gel	No	41	—	+	+	+	—	—	+	—	—
	Yes	14	—	+	+	—	—	—	+	—	—
Liquid soap	No	22	+	—	—	—	—	+	+	—	+
	Yes	33	+	+	+	+	+	—	+	+	+
Mouthwash	No	10	+	+	+	+	+	—	+	+	+
	Yes	45	+	+	+	+	+	—	+	+	+
Other hair products	No	37	—	+	+	+	—	—	—	—	—
	Yes	18	+	+	+	+	—	—	—	—	—
	No	50	+	+	+	+	+	+	+	+	+
	Yes	5	+	+	+	+	+	+	+	+	+

+, positive association (higher median urinary concentration in the “yes” group compared to the “no” group); —, negative association (higher median urinary concentration in the “no” group compared to the “yes” group).

Wilcoxon rank-sum test:

*** $p < 0.05$,

** $0.05 < p < 0.10$,

* $0.10 < p < 0.15$.