Prenatal Phenol and Phthalate Exposures and Birth Outcomes

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BACKGROUND: Many phthalates and phenols are hormonally active and are suspected to alter the course of development.

OBJECTIVE: We investigated prenatal exposures to phthalate and phenol metabolites and their associations with body size measures of the infants at birth.

METHODS: We measured 5 phenol and 10 phthalate urinary metabolites in a multiethnic cohort of 404 women in New York City during their third trimester of pregnancy and recorded size of infants at birth.

RESULTS: Median urinary concentrations were > 10 µg/L for 2 of 5 phenols and 6 of 10 phthalate monoester metabolites. Concentrations of low-molecular-weight phthalate monoesters (low-MWP) were approximately 5-fold greater than those of high-molecular-weight metabolites. Low-MWP metabolites had a positive association with gestational age (0.97 day gestational age per ln-biomarker; 95% confidence interval (CI), 0.07–1.9 days, multivariate adjusted) and with head circumference. Higher prenatal exposures to 2,5-dichlorophenol (2,5-DCP) predicted lower birth weight in boys (—210 g average birth weight difference between the third tertile and first tertile of 2,5-DCP; 95% CI, 71–348 g). Higher maternal benzophenone-3 (BP3) concentrations were associated with a similar decrease in birth weight among girls but with greater birth weight in boys.

CONCLUSIONS: We observed a range of phthalate and phenol exposures during pregnancy in our population, but few were associated with birth size. The association of 2,5-DCP and BP3 with reduced or increased birth weight could be important in very early or small-size births. In addition, positive associations of urinary metabolites with some outcomes may be attributable partly to unresolved confounding with maternal anthropometric factors.

We analyzed maternal urine samples for 5 phenol and 10 phthalate metabolites using laboratory and quality control methods that have been reported previously (Kato et al. 2005; Ye et al. 2005). From the 401 urine samples collected, sufficient specimen amounts remained after other earlier analyses to determine phthalate metabolites in 382 and phenols in 367 specimens. Limits of detection were calculated as three times the standard deviation of near-zero or blank quality control specimens. Urinary concentrations of the biomarkers were examined both as micrograms per liter and as corrected for creatinine (micrograms per gram creatinine; µg/gC) to normalize for urine dilution. In addition to the 10 individual phthalate analytes, three micromolar sums (µmol/L) were studied: four metabolites originating from di(2-ethylhexyl) phthalate (DEHP), monooester metabolites of high-molecular-weight (> 250 Da) monoester metabolites (high-MWP), and low molecular-weight (< 250 Da) monoester metabolites (low-MWP). These groupings were chosen because they each represent similar structures and biologic activity and are derived from similar sources.

Statistical analyses were performed using SAS-PC, version 9.1 (SAS Institute Inc., Cary, NC). Continuous biomarker values and creatinine were natural log transformed (ln) to produce more normal distributions. Tertiles of biomarkers were created using the creatinine-corrected values. Predictors of birth weight, length, head circumference, and gestational age at delivery were analyzed using geometric median models predicting gestational age at delivery individually into the multivariate-adjusted models; none altered the coefficients, so we did not include them in the final models. Weight gain during pregnancy was also available in a subset of the population; when included in the multivariate-adjusted models, it did not alter the coefficients of the exposure variables, and therefore we did not include it in the final models.

Very dilute urine samples (< 20 mg/dL creatinine, n = 28) we excluded because they altered the β-values for almost all analytes by more than 10%. We also used this restriction in our earlier study of pesticides for the same reason (Wolff et al. 2007a), and it follows common practice (Carrieri et al. 2001; Eskenazi et al. 2004). The rationale is that urine samples with very low creatinine may provide inaccurate biomarker measurements and, further, that dividing the biomarker value by a small creatinine value may create an inaccurately elevated analyte value. If the models with statistically significant coefficients that we report here had included these low-creatinine observations, the estimates would have changed by 2–40%.

Recognizing that the metabolites or their parent compounds are hormonally active, we examined the possibility that associations differed by infant sex by adding an interaction term (infant sex*ln-biomarker). We also present deviations from additivity (evidenced by a p-value for the interaction term < 0.1). In addition, to further elucidate relationships between the phthalate metabolites and body size, we ran logistic regression models predicting small- or large-for-gestational age (defined as the race- and infant sex-specific lower and upper 10th percentile of weight for gestational age) (Oken et al. 2003).
In bivariate analyses, we examined the relationship between phthalate and phenol biomarkers and maternal characteristics. Several biomarkers were significantly inversely correlated with marital status, BMI, education, and smoking history (data not shown). Inverse relationships of biomarkers with maternal age were not statistically significant. Most of the phthalate biomarkers and three phenols were higher among nonwhites, but TCS and benzophenone-3 (BP3) were higher among whites. BPA, 2,5-DCP, and 2,4-DCP were positively correlated with maternal prepregnancy BMI if the biomarker was expressed as micrograms per liter, but not if expressed as micrograms per gram creatinine. BP3 was inversely correlated with BMI, regardless of creatinine correction. When expressed as micrograms per liter or micromoles per liter all phthalate metabolites except monomethyl phthalate (MMP) had significant positive correlations with BMI. With creatinine-corrected concentrations (micrograms per gram creatinine or µmol/gC), the only significant correlations with BMI among phthalate biomarkers were MBzP (positive) and MMP (negative).

No phenols were significantly associated with any birth outcomes in models adjusted for covariates (Table 3). However, interaction terms between infant sex and three maternal urinary phthalates (2,5-DCP, TCS, and BP3) revealed possible sex-specific effects in four models for birth weight or length (Table 4). Boys were 210 g smaller (95% confidence interval (CI), 71–348 g) in the third tertile of maternal 2,5-DCP (highest exposure) compared with the first tertile (adjusted predicted means: third tertile, 3,370 g; 95% CI, 3,250–3,490 g; first tertile, 3,160 g; 95% CI, 3,020–3,300 g; Figure 1). Similar effects on birth weight were seen for TCS in boys (non-significant) and for BP3 in girls (Figure 1). However, in boys, BP3 predicted higher birth weight for prenatal exposure to this sunscreen agent (Figure 1). Because racial/ethnic exposures to BP3 differed, we examined the models separately for nonwhites (n = 269) and for Hispanics (n = 168); in both groups, the trends were similar to those among all women, with the third tertile of maternal BP3 associated with heavier boys and lighter girls. The number of white mothers (n = 66) was too small to examine separately. Effects of both 2,5-DCP and TCS on birth length were similar to findings on birth weight, such that boys were approximately 0.3 cm shorter (95% CI, –0.6 to –0.4 cm) per ln-2,5-DCP (Table 4).

**Table 2.** Third-trimester urinary phenol and phthalate biomarkers among mothers enrolled in the Children’s Environmental Health Study, 1998–2002.

<table>
<thead>
<tr>
<th>Analyte (ln)</th>
<th>Birth weight (gm)</th>
<th>Birth length (cm)</th>
<th>Head circumference (cm)</th>
<th>Gestational age (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenols (n = 367)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2,5-DCP</td>
<td>–10 (–41 to 20)</td>
<td>0.13 (–0.20 to 0.14)</td>
<td>–0.02 (–0.14 to 0.10)</td>
<td>0.01 (–0.12 to 0.14)</td>
</tr>
<tr>
<td>2,4-DCP</td>
<td>–0.2 (–43 to 24)</td>
<td>0.01 (–0.20 to 0.18)</td>
<td>0.01 (–0.12 to 0.14)</td>
<td>0.01 (–0.14 to 0.15)</td>
</tr>
<tr>
<td>TCS</td>
<td>–11 (–34 to 11)</td>
<td>0.04 (–0.17 to 0.08)</td>
<td>–0.04 (–0.13 to 0.04)</td>
<td>0.00 (–0.10 to 0.09)</td>
</tr>
<tr>
<td>BP3</td>
<td>1.7 (–18 to 22)</td>
<td>0.3 (–0.14 to 0.08)</td>
<td>0.01 (–0.07 to 0.08)</td>
<td>0.04 (–0.04 to 0.12)</td>
</tr>
<tr>
<td>BPA</td>
<td>0.8 (–6.0 to 82)*</td>
<td>0.11 (–0.14 to 0.36)</td>
<td>0.08 (–0.09 to 0.25)</td>
<td>0.03 (–0.16 to 0.21)</td>
</tr>
<tr>
<td>Phthalates (n = 382)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCPP</td>
<td>6.0 (–30 to 42)</td>
<td>0.08 (–0.10 to 0.25)</td>
<td>0.13 (0.01 to 0.24)**</td>
<td>0.14 (0.01 to 0.27)**</td>
</tr>
<tr>
<td>MEHHP</td>
<td>10 (–29 to 49)</td>
<td>0.07 (–0.13 to 0.27)</td>
<td>0.00 (–0.14 to 0.14)</td>
<td>0.10 (–0.05 to 0.24)*</td>
</tr>
<tr>
<td>MEHHP</td>
<td>10 (–21 to 42)</td>
<td>0.14 (–0.08 to 0.35)</td>
<td>0.04 (–0.11 to 0.19)</td>
<td>0.13 (–0.03 to 0.28)*</td>
</tr>
<tr>
<td>Individual phthalate monoesters (n = 352)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCPP</td>
<td>4.2 (–31 to 40)</td>
<td>0.04 (–0.16 to 0.24)</td>
<td>0.01 (–0.13 to 0.14)</td>
<td>0.07 (–0.08 to 0.21)</td>
</tr>
<tr>
<td>MEHHP</td>
<td>6.6 (–27 to 40)</td>
<td>0.08 (–0.10 to 0.27)</td>
<td>0.00 (–0.13 to 0.13)</td>
<td>0.05 (–0.07 to 0.20)</td>
</tr>
<tr>
<td>MEHHP</td>
<td>5.1 (–29 to 40)</td>
<td>0.07 (–0.12 to 0.27)</td>
<td>0.01 (–0.12 to 0.14)</td>
<td>0.05 (–0.09 to 0.20)</td>
</tr>
<tr>
<td>MBzP</td>
<td>4.9 (–26 to 38)</td>
<td>0.01 (–0.18 to 0.19)</td>
<td>0.01 (–0.11 to 0.14)</td>
<td>0.15 (0.02 to 0.29)**</td>
</tr>
<tr>
<td>MEHHP</td>
<td>1.4 (–34 to 37)</td>
<td>0.20 (0.00 to 0.40)**</td>
<td>0.11 (–0.02 to 0.25)</td>
<td>0.07 (–0.07 to 0.22)</td>
</tr>
<tr>
<td>MCP</td>
<td>–4.2 (–50 to 41)</td>
<td>0.18 (–0.07 to 0.44)*</td>
<td>0.06 (–0.12 to 0.23)</td>
<td>0.02 (–0.17 to 0.21)</td>
</tr>
<tr>
<td>MBzP</td>
<td>–4.2 (–57 to 28)</td>
<td>0.04 (–0.19 to 0.28)</td>
<td>0.03 (–0.20 to 0.14)</td>
<td>0.05 (–0.06 to 0.35)</td>
</tr>
<tr>
<td>MEHP</td>
<td>–5.5 (–45 to 34)</td>
<td>0.15 (–0.07 to 0.37)*</td>
<td>0.05 (–0.09 to 0.20)</td>
<td>0.10 (–0.06 to 0.35)</td>
</tr>
<tr>
<td>MEP</td>
<td>9.0 (–20 to 38)</td>
<td>0.05 (–0.11 to 0.21)</td>
<td>0.12 (0.01 to 0.23)**</td>
<td>0.11 (–0.01 to 0.22)*</td>
</tr>
<tr>
<td>MCPP</td>
<td>–6.6 (–44 to 30)</td>
<td>0.11 (–0.10 to 0.31)</td>
<td>0.07 (–0.07 to 0.21)</td>
<td>0.09 (–0.06 to 0.24)</td>
</tr>
</tbody>
</table>

Abbreviations: LOD, limit of detection; MCPP, mono-3-carboxypropyl phthalate; MEHHP, mono-2-ethyl-5-hydroxyhexylphthalate; MEHHP, mono-2-ethyl-5-oxoethylphthalate; MBzP, monoisobutyl phthalate.

*Adjusted for race, infant sex, gestational age (except for models predicting gestational age), ln-creatinine, smoking during pregnancy, maternal education, marital status, prepregnancy BMI, and restricted to observations with creatinine ≥ 20 mg/dL.

**Low-MWP comprises MMP, MEP, MBzP, and MCPP. DEHP-MWP comprises MCPP, MEHHP, MEHHP, and MEHHP. High-MWP comprises MBzP, MEHHP, MCPP, MEHHP, MEHHP, and MCPP. *p < 0.20. **p < 0.05.

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In the multivariate-adjusted models for phthalate biomarker sums, neither DEHP-MWP nor high-MWP metabolites were significantly associated with any birth outcome. Low-MWP metabolites were positively associated with head circumference (β = 0.13 cm; 95% CI, 0.01–0.24 cm) and gestational age (β = 0.14 week; 95% CI, 0.01–0.27 week, per ln-unit increase biomarker level, adjusting for race, infant sex, ln-creatinine, maternal education, marital status, and prepregnancy BMI; Table 3). However, the tertiles of low-MWP metabolites were not significantly associated with head circumference (data not shown). For gestational age, the second and third tertiles of low-MWP metabolites predicted 0.4 week longer gestation compared with the first tertile (adjusted predicted means: third tertile, 39.6 weeks; 95% CI, 39.1–40.1 weeks; second tertile, 39.7 weeks; 95% CI, 39.2–40.2 weeks; first tertile, 39.2 weeks; 95% CI, 38.7–39.6 weeks), suggesting a threshold effect. These associations were not modified by infant sex, although we may have had insufficient power to detect a sex–phthalate metabolic interaction.

The positive association we report between low-MWP metabolites and gestational age at delivery and birth length, although biologically plausible based on the animal literature, may also reflect unresolved confounding by the following mechanism. The correlation may also reflect unresolved confounding by education, marital status, and prepregnancy BMI (National Toxicology Program 2005). TCS is metabolized to 2,5-DCP and DCM (Centers for Disease Control and Prevention 2005). This difference is also similar to that between males and females at birth, where females are 135 g (median) lighter than males at 39 weeks of gestation (Oken et al. 2003). Like 2,5-DCP, TCS had sex-specific inverse but nonsignificant associations with birth weight and length among boy infants in this cohort. TCS is 5-chloro-2-(2,4-dichlorophenoxy) phthalate, and thus it is structurally similar to 2,5-DCP. Our finding of increased male birth weight with higher maternal BP3 concentrations than those reported in other studies (Stahlhut et al. 2007) support a positive relationship between phthalate exposure and adiposity. Prepregnancy BMI, in turn, is positively, but weakly, associated with gestational age (r = 0.18, p < 0.01) and strongly associated with urinary creatinine levels (r = 0.18, p < 0.01). And finally, low-MWP metabolites were also strongly correlated with creatinine (r = 0.40, p < 0.01). Therefore, it appears that, in our data, maternal anthropometric features may affect the measurement of the exposure level (low-MWP), the measurement of the metabolite-level correction factor (creatinine), and the measurement of the outcome (gestational age/head circumference). Because our estimates of anthropometry in this study population were relatively crude (self-reported prepregnancy weight and height, and self-reported weight gain), residual confounding of the low-MWP–gestational age/birth length relationship by maternal anthropometry is possible.

**Discussion**

Of the 19 phenol and phthalate metabolites measured in this study, two showed higher concentrations than those reported in other U.S. populations: 2,5-DCP [median, 54 µg/L in our study vs. 30 µg/L as reported by Hill et al. (1995)] and MEP [median, 380 µg/L vs. 178 µg/L among female participants of all ages in the 1999–2000 National Health and Nutrition Examination Survey (NHANES) (Centers for Disease Control and Prevention 2005)]. 2,5-DCP was also relatively high in a population of New York City minority children compared with those at two other sites in the United States (Wolff et al. 2007b). Total phthalate biomarker concentrations were also relatively high in this study, approaching 1 mg/L total (-3 µM). Our population has a large proportion of minority women, and therefore the levels are consistent with those seen in NHANES data where several phthalate biomarkers were elevated among blacks and Hispanics compared with whites (Centers for Disease Control and Prevention 2005). Concentrations of BPA were relatively low in this population as in other recent reports of nonoccupational exposures (Kuklenyik et al. 2003; Liu et al. 2005; Matsumoto et al. 2003; Ouchi and Watanabe 2002; Wolff et al. 2007b; Ye et al. 2005).

Environmental sources of phenols and their precursors include personal care and home cleaning products. 1,4-DCB is used in mothballs and in room deodorizers; it is metabolized to 2,5-DCP. The high correlation of 2,4-DCP with 2,5-DCP suggests that 2,4-DCP is a metabolite of 1,3-dichlorobenzene, a minor contaminant of 1,4-DCB (National Toxicology Program 2005). TCS is a microbicide, and BP3 exposure comes mainly from sunscreen. Environmental sources of phthalates are numerous. MEP and MBP are found in cosmetics, shampoo, perfume, and products with fragrance. The higher-molecular-weight phthalates, including DEHP and butylbenzylphthalate, are found in soft plastics, vinyl wrap, plastic tubing, and home construction components such as vinyl floor tile.

We observed sex-specific associations of phenols with birth weight and length. Third-trimester 2,5-DCP exposure was associated with lower birth weight among male infants, and BP3 was associated with lower birth weight among female infants. For both biomarkers, the third versus first tertile of prenatal phenols predicted about 200-g-lower difference; this deficit is comparable to the reduction in birth weight seen for active smoking during pregnancy (Bernstein et al. 2005). This difference is also similar to that between males and females at birth, where females are 135 g (median) lighter than males at 39 weeks of gestation (Oken et al. 2003).

Like 2,5-DCP, TCS had sex-specific inverse but nonsignificant associations with birth weight and length among boy infants in this study. TCS is 5-chloro-2-(2,4-dichlorophenoxy) phthalate, and thus it is structurally similar to 2,5-DCP. Our finding of increased male birth weight with higher maternal BP3

**Table 4. Interaction of male infant sex with maternal third-trimester urinary phenol metabolites in models predicting birth weight and length: Children’s Environmental Health Study, Mount Sinai Hospital, 1998–2002.**

<table>
<thead>
<tr>
<th>Urinary biomarker (ln-µg/L)</th>
<th>No.</th>
<th>Estimate</th>
<th>95% CI</th>
<th>Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,5-DCP</td>
<td>339</td>
<td>–88</td>
<td>–140 to –36**</td>
<td>–0.33</td>
<td>–0.63 to –0.35**</td>
</tr>
<tr>
<td>TCS</td>
<td>339</td>
<td>–23</td>
<td>–68 to 22</td>
<td>–0.26</td>
<td>–0.51 to 0.001*</td>
</tr>
<tr>
<td>BP3</td>
<td>339</td>
<td>4.4</td>
<td>5.4 to 84**</td>
<td>–0.02</td>
<td>–0.24 to 0.21</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,5-DCP</td>
<td>339</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCS</td>
<td>339</td>
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<td></td>
</tr>
<tr>
<td>BP3</td>
<td>339</td>
<td></td>
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</tr>
</tbody>
</table>

β-values represent the difference between boys and girls in outcome for 1 ln-unit biomarker. The β-values for boys (referent) were, for birth weight, 30 (2,5-DCP), 1.2 (TCS), and –21 g (BP3), and for length, 0.13, 0.07, –0.02 cm, respectively (all p < 0.1). Estimates are adjusted for race, infant sex, gestational age at delivery, ln-creatinine, smoking during pregnancy, maternal education, marital status, and prepregnancy BMI and were restricted to observations with creatinine ≥ 20 µg/dL. p * for the interaction term < 0.10 and ** < 0.05.

**Figure 1. Adjusted mean birth weight ± SE predicted by prenatal maternal 2,5-DCP (A) and BP3 (B) tertiles of creatinine-corrected urine concentrations. The male sex biomarker interaction terms in models with tertiles of biomarkers had p < 0.01. Adjusted means differed significantly between the first and third tertiles of 2,5-DCP for boys (p = 0.0016), and of BP3 for boys (p = 0.026) and girls (p = 0.021). Birth-weight predicted means are adjusted for race/ethnicity, gestational age, ln-creatinine, smoking during pregnancy, maternal education, marital status, and prepregnancy BMI and are limited to samples with ≥ 20 mg/dL creatinine. The ranges of values in the third tertiles were 114–9,950 µg/gC, 27–13,300 µg/L for 2,5-DCP, and 26–104,000 µg/gC, 7–92,700 µg/L for BP3.**
concentrations is unexpected and has no clear biologic basis. Although BP3 levels were higher in whites, consistent with putative use of sunscreen, the associations of BP3 with birth weight did not differ by race/ethnicity in this study. We saw no effects with BPA in our study, but BPA urinary concentrations were much lower than those of 2,5-DCP, TCS, and BP3 and may not have reached a level of biologic significance.

Pregnant ewes treated with BPA had offspring with reduced birth weights, and their blood levels were greater than 35 µg/L on average, with adiopose concentrations of 200 mg/kg (Savabieasfahani et al. 2006). Experimental findings for other phensols are consistent with our results, supporting a possible mechanism for reduced birth weight in boys prenatally exposed to 1,4-DCB or girls to BP3. In rats, 1,4-DCB reduced body weight at high doses (30–270 mg/kg; Bornatowicz et al. 1994). In addition, 1,4-DCB is an animal carcinogen and “reasonably anticipated to be a human carcinogen” by the National Toxicology Program and “possibly carcinogenic” by the International Agency for Research on Cancer (National Toxicology Program 2005). 1,4-DCB is also a respiratory toxin (Elliot et al. 2006) and was banned in schools in New York State in 2004 because of potential to exacerbate childhood asthma and in California in 2006 for use as room deodorizers. Phenols and 1,4-DCB are hormonally active in vitro, where bioassays have shown weak to modest estrogenicity (Fang et al. 2000). At doses above 1 µM, environmental phenoic residues exhibited both estrogenic and antiandrogenic potential (Paris et al. 2002). 1,4-DCB is likely to be a tumor promoter (Holmes and Rainsford 2001), signifying its potential hormonal activity. TCS is antiandrogenic (Chen et al. 2007). BP3 and its analog, benzophenone-2, are estrogenic (Ogawa et al. 2006; Seidlova-Wuttke et al. 2005), and benzophenone-2 is thought to cause hypospadias in mice through this mechanism (Hsieh et al. 2007).

In contrast to our hypothesis of an inverse effect of phthalate exposure on birth size and gestation, we found a positive association of low-MWP biomarkers with duration of pregnancy and infant head circumference. Effect sizes were small: <1 day longer gestation per ln-biomarker and 2.8 days between the third and first tertiles of low-MWP biomarkers. Similar but nonsignificant effects on gestational age were found for the DEHP-MWP and high-MWP biomarkers. Our maternal exposures may be too low to elicit the inverse effects we hypothesized based on the birth weight reductions reported in rodents. The lower cut point of the third tertiles were 0.01 µmol/L for BPA, 0.5 µmol/L for 2,5-DCP, 0.4 µmol/L for DEHP-MWP biomarkers, and 3.9 µmol/L for low-MWP biomarkers. Moreover, the effect sizes we observed were modest enough that residual confounding resulting from poorly measured maternal anthropometric features may account for these findings.

In humans, associations have been reported between prenatal and early postnatal phthalate exposures and shorter anogenital distance as well as lower serum testosterone in newborns (Main et al. 2006; Swan et al. 2005). In addition, shorter gestational age was associated with cord serum concentrations of DEHP and its metabolite mono-2-ethylhexyl phthalate (MEHP) (Latini et al. 2003, 2006). It is possible that in these studies exposures were higher than in our population, because MEHP levels in serum were slightly greater than 1,000 µg/L on average, which would be comparable to higher urinary concentrations than we observed. Other prenatal exposure biomarkers have been associated with reduced gestational age (Fenster and Eskenazi 2006), and both positive and negative associations with head circumference have also been reported (Apelberg et al. 2007; Eskenazi et al. 2004; Wolff et al. 2007a). However, increased weight and lengthened gestation as a result of androgen antagonist exposures have not been reported in children. Limited support exists for a hormonal mechanism for both shorter and longer gestation following phthalate exposures in animals, depending on dose. DEHP in rats has been reported to cause both longer (Dalgaard et al. 2003) and shorter (Marsman 1995) gestational age. Low perinatal exposure can be androgenic in male rats (earlier puberty), but can have the opposite effect at high doses compared with controls (Ge et al. 2007). High doses, in these and other studies, exceeded 100–3,000 mg/kg/day. Dibutyl phthalate, the precursor of MBP, has estrogenic effects in vitro at levels typically found for environmental estrogens, including BPA (van Meeuwen et al. 2007).

Overall, for both phenols and phthalates, we found few significant associations in this study; for example, the findings in Table 3 could be attributable to multiple comparisons (five associations at p < 0.05 among 72 comparisons). An additional limitation is that we had biomarkers measured once in the third trimester for exposures that ordinarily have relatively short half-lives (days). Consistency in levels during pregnancy has been observed for some environmental exposure biomarkers (Longnecker et al. 1999; Muckle et al. 2001), whereas pesticide levels, with ambient exposures that are likely to be sporadic, show more variability (Bradman et al. 2005). However, research in other populations has suggested that phthalate biomarkers are relatively stable for a period of weeks to months (Hauser et al. 2004; Hoppin et al. 2002; Teitelbaum et al. 2007); less is known for phenol biomarkers, but they also appear to have adequate stability to predict exposure over 6–12 months in children (Teitelbaum et al. 2007). It is reasonable that the biomarkers we describe here have modest intraindividual variability, because use of common products that result in these exposures may be fairly constant over days or months. Nevertheless, to more fully understand relationships between exposures with short half-lives and health outcomes, it may be necessary to investigate additional methods of exposure assessment, especially ones that might offer a more comprehensive and integrated picture of the individual environment, perhaps by evaluating specific products used over a long period of time in conjunction with indoor air levels as well as biomarkers of exposure.

Creatinine correction is commonly used for urinary biomarkers of phthalates, pesticides, phenols, and phytoestrogens. There are limitations to the use of creatinine to normalize for urine dilution; other investigators have used specific gravity instead of creatinine to adjust phthalate urinary biomarkers for urine dilution, but we did not have specific gravity measurements. However, specific gravity is highly correlated with creatinine (Barr et al. 2005), and therefore it is not likely that we overcorrected for urine dilution, especially because we discarded results from very dilute urines. In addition, parameters in our models were little changed by creatinine-corrected values (micrograms per gram creatinine) versus uncorrected values (micrograms per liter) for the biomarkers or by adjustment for creatinine as a covariate in the multivariable models.

The exposures we studied are relatively prevalent, and some biomarker levels approach those with significant effects in experimental models. In a healthy cohort such as ours, effects of hormonally active environmental exposures on birth size may be small, yet more sensitive end points such as infant neurologic development may be affected. A further dimension to consider in future research is multiple exposures of hormonally active agents such as these. In terms of prevention, exposure to these chemicals can be avoided if the product contents are known; unfortunately, they often are not listed on the label because they are not “active” ingredients.

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