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Phthalates and the diets of US children and adolescents

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ABSTRACT

Background: Di-2-ethylhexylphthalate (DEHP) is an ester of phthalic acid commonly found in processed foods. DEHP may contribute to obesity and insulin resistance in children and adolescents, yet dietary exposures have been not been studied in this vulnerable subpopulation.
Objective: To assess diet and its relation to urinary phthalates in a nationally representative sample of US children and adolescents.
Design: Cross-sectional analysis of 24-h dietary recall and urinary phthalate metabolites from 2743 6–19 year olds participating in the 2003–8 National Health and Nutrition Examination Surveys. Regression analyses examined relationships of food consumption with log-transformed metabolite concentrations, examined as low-molecular weight, high molecular weight and di-2-ethylhexylphthalate categories, controlling for urinary creatinine, age group, body mass index category, race/ethnicity, caloric intake and gender.
Results: We identified a −0.04% (95% CI: −0.08, −0.01) increment in di-2-ethylhexylphthalate metabolite concentration/additional gram fruit consumption, a +0.01% increment/additional calorie dietary intake (95% CI: +0.003, +0.02), and a +0.09% (95% CI: +0.02, +0.17) increment/additional gram meat/poultry/fish consumption. Soy consumption (−0.40% increment/additional gram consumed, 95% CI: −0.66, −0.14) was inversely associated with di-2-ethylhexylphthalate, while poultry (+0.23% increment/additional gram consumed, 95% CI: +0.12, +0.35) was positively associated. Findings were robust to examination of metabolite concentrations per unit body mass index and weight, and inclusion of fasting time.
Conclusions: Diet contributes to urinary phthalate concentrations in children and adolescents. Further study is needed to examine the implications of di-2-ethylhexylphthalate exposure, especially earlier in life, when more permanent metabolic changes may occur.

1. Introduction

Esters of phthalic acid (phthalates) are environmental chemicals widely used in consumer products. Low-molecular weight phthalates (diethylphthalate, di-n-butylphthalate, di-n-octylphthalate and di-n-isobutylphthalate) are predominantly used in shampoos, cosmetics, lotions and other personal care products to preserve scent (Hauser and Calafat, 2005; Sathyanarayana, 2008; Sathyanarayana et al., 2008), whereas high-molecular weight phthalates (di-2-ethylhexylphthalate, di-n-octylphthalate and butylbenzylphthalate) are used to produce vinyl plastic used in diverse settings ranging from flooring, clear food wrap and intravenous tubing (Schettler, 2006). Di-2-ethylhexylphthalate is a high-molecular weight phthalate that is thought to be introduced into food through industrial processes (Fromme et al., 2007). Though medical devices (US Food and Drug Administration, 2012) and toys (Bouma and Schakel, 2002) can contain di-2-ethylhexylphthalate, dietary intake from contaminated food is the largest contributor to exposure in children (Schettler, 2006; US Agency for Toxic Substances & Disease Registry, 2012). Migration from di-2-ethylhexylphthalate-lined food packaging films appears to be the major route of contamination, though polyvinyl chloride tubing (Petersen and Breindahl, 2000), gaskets in metallic

Abbreviations: MEP, mono-ethyl phthalate; MBP, mono-n-butyl-phthalate; MiBP, mono-isobutyl phthalate; MCPP, mono-(3-carboxypropyl) phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxy-hexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MBzP, monobenzylphthalate; SD, standard deviation

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caps for glass jars (Tsumura et al., 2002), and printing inks on labels (Cao, 2010) may also contribute.

Dietary exposure to di-2-ethylhexylphthalate is a major concern for children because increasing laboratory animal and human research suggests that exposures to endocrine active compounds early in life may disrupt developmental endocrine processes, permanently changing how calories are processed into fat and producing chronic excessive weight gain and obesity (Newbold et al., 2007). Mono-(2-ethylhexyl) phthalate, a di-2-ethylhexylphthalate metabolite, increases expression of three peroxisome proliferator-activated receptors which play key roles in lipid and carbohydrate metabolism, providing biological plausibility for di-2-ethylhexylphthalate metabolites in childhood obesity and insulin resistance (Desvergne et al., 2009; Trasande et al., 2013a). Indeed, strong correlations of di-2-ethylhexylphthalate metabolites with homeostatic model assessment of insulin resistance and categorical insulin resistance in adolescents (Trasande et al., 2013b) and adults (Stahlhut et al., 2007) have been identified.

Indeed, a previous cross-sectional analysis of 6–85 year olds using data from the 2003–4 National Health and Nutrition Examination Surveys suggested the possibility that diet could strongly influence urinary phthalates. Controlled for age, ethnicity, sex and Body Mass Index, it identified a 5.7% increase in di-2-ethylhexylphthalate metabolites for each ounce increase in poultry consumption as reported in a 24-h diet diary (Colacino et al., 2010). Eliminating processed and canned foods and minimizing use of food packaging among primarily white older children and adults reduced di-2-ethylhexylphthalate metabolites by 53–56% in a small crossover trial (Rudel et al., 2011). Together, this evidence raises the possibility that metabolic derangements in children and adolescents may be prevented through dietary modification that reduces chemical exposures independent of caloric intake.

While these studies are informative, the unique, biologically age-based vulnerability of children to environmental toxicants raises the need to examine children and adolescents separately (National Research Council, 1993). Phthalate metabolites are not linearly related to age (Silva et al., 2004) and dietary consumption per unit body mass is highest among children (Committee on Nutrition Standards for Foods in Schools, 2007). Associations found for the overall sample might therefore not be applicable to children and adolescents. Exposures to certain phthalates in the US population have also decreased since 2004, suggesting a need to examine more recent data (Centers for Disease Control and Prevention, 2012). We therefore chose to examine associations of dietary intake and urinary phthalate metabolites among children and adolescents in the 2003–8 National Health and Nutrition Examination Surveys.

2. Material and methods

2.1. Data source and sample

The National Health and Nutrition Examination Survey is a continuous, multicomponent, nationally representative survey of the noninstitutionalized US population administered by the National Centers for Health Statistics of the Centers for Disease Control and Prevention. Data from the 2003–2008 questionnaire, laboratory, diet and physical examination components were used in the present analysis, for which data are available in biennial groupings. Written consent, and child assent as appropriate, was obtained after approval by the National Center for Health Statistics Research Ethics Review Board. The New York University School of Medicine Institutional Review Board exempted this study from review since it is based on previously collected and de-identified data.

2.2. Measurement of urinary phthalates

Phthalates were measured in one spot urine sample collected within 10 days of the dietary recall, and analyzed using high-performance liquid chromatography and tandem mass spectroscopy. More extensive methodological description is provided elsewhere (Silva et al., 2004). For phthalate concentrations below the level of detection (5.1% for MEHP, $<1\%$ for all other metabolites studied), we substituted the limit of detection divided by the square root of 2, as routinely assigned by the National Centers for Health Statistics. To adjust for variability in urinary dilution, we included urinary creatinine as a covariate in all analyses.

We grouped urinary biomarkers according to their use in product categories. We expressed the low-molecular weight concentration as the sum of molar concentrations of mono-ethyl phthalate (MEP), mono-n-butyl-phthalate (MBP), and mono-isobutyl phthalate (MiBP). The high-molecular weight concentration was calculated as the sum of mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono-(3-carboxypropyl) phthalate (MCPP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-(2-ethylhexyl) phthalate (MEHP) and monobenzylphthalate (MBzP) was expressed as a function of MEHP. Finally, we calculated the di-2-ethylhexylphthalate concentration by adding molarities of MEHP, MECPP, MEHHP and MEOHP.

All phthalate concentrations were (natural) log-transformed to account for skewed distribution. Our primary exposure variables were the log-transformed total molar concentrations of low-molecular weight, high-molecular weight and di-2-ethylhexylphthalate metabolites, though secondary analyses also analyzed individual metabolites.

2.3. Dietary measures

Trained interviewers fluent in Spanish and English elicited total 24-h calorie intake in person, using standard measuring guides to assist reporting of volumes and dimensions of food items (US Centers for Disease Control and Prevention). The primary independent variables for this analysis were volumes (typically in grams) of foods as categorized by the US Department of Agriculture (USDA) (US Department of Agriculture Agricultural Research Service, 2010). We used the first of two 24-h recalls collected, because the first is collected closer to the urine specimen collection and represents more closely exposure as detected in the phthalate metabolite measurements. We examined total consumption within eight major categories as defined by the USDA: grain, vegetable, dairy, fruit, meat/poultry/fish, discretionary oils, discretionary solid fats, and sugars added to foods when they are processed and prepared. Consumption was also analyzed by dietary subcategories as assigned by USDA. Within the grains category, we were able to examine whole and non-whole grains, while subcategories within the vegetable category we were able to examine included dark green vegetables, orange vegetables, potatoes, starchy vegetables, tomatoes, and all other vegetables. Within the fruit category, we separately examined citrus, melons and berries separately from other fruits. Within the dairy category, we separately examined milk, yogurt and cheese. Within the meat/poultry/fish category, we separately examined consumption of beef, pork, veal, lamb and game; organ meats; franks, sausages and luncheon meats; poultry; fish high in omega-3 fatty acids; fish low in omega-3 fatty acids; eggs; and soy.

2.4. Potential confounders

Because differences in phthalate metabolites by race/ethnicity and age group (6–11 versus 12–19 years of age) have been documented (Silva et al., 2004), we examined these factors as covariates. Race/ethnicity was categorized into Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black and Other, based on self-report by 17–19 year olds and caregiver report in 12–16 year olds. We also examined total caloric intake from the diet diary and body mass index category as covariates, given that these could plausibly be associated both with intake of specific foods and increase phthalate metabolites. Information on height and weight was based on measures taken by trained health technicians, who used data recorders and used standardized procedures. Total caloric intake was measured in kilocalories, as obtained through the 24-h diet diary used to measure food intake by category. Because Body Mass Index is not linearly related to age in children and adolescents, with rapid acceleration in height and weight gain in puberty, we used age- and gender-standardized measures of body mass (Body Mass Index Z-scores). We derived Body Mass Index Z-scores from 2000 Centers for Disease Control and Prevention (CDC) norms, incorporating height, weight and gender; overweight and obese were categorized as BMI Z-score ≥ 1.036 and ≥ 1.64 (Ogden et al., 2002). To maximize sample size in multivariable analysis, "missing" categories were created for all potential confounders, except BMI category ($n=8$) and calorie intake ($n=141$), given the plausible association of caloric intake with phthalate metabolites, and known association of phthalate metabolites with obesity (Teitelbaum et al., 2012; Trasande et al., 2012).

2.5. Statistical analysis

We conducted bivariate and multivariable regression analyses using environmental subsample weights and statistical techniques that reflect the complex survey sampling design, using Stata 12.0 (College Station, TX), and following NCHS guidelines (US Centers for Disease Control and Prevention 2012a, 2012b). Initial