Dietary Phthalate Exposure in Pregnant Women

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Abstract

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Background

Phthalates are a family of synthetic chemicals with use in a variety of industrial and consumer products. Due to their ubiquity in the environment, exposures are widespread in the U.S. population. Animal studies have shown that phthalates exhibit anti-androgenic activity and disrupt normal male reproductive tract development during gestation. Similarly, human studies document associations between prenatal phthalate exposure and harmful health outcomes. Food is considered the largest source of the most toxic phthalates for the general population, however, few U.S. studies have investigated diet's contribution to overall body burden, and none have assessed exposures specifically in pregnant women.

Methods

We used multivariate regression analysis to examine the association between reported dietary intake of various food groups (beef, seafood, poultry, oils, butter, lard, shortening, spices, soy, dairy products, restaurant food/delivery/take-out and fast foods, and drinks in cans and plastic) and first trimester urinary phthalate metabolite concentrations in a multicenter cohort of 283 pregnant women from Minnesota, New York, Washington, and California participating in The Infant Development and Environment Study (TIDES). Additionally, we examined whether reported use of environmentally friendly products and consumption of chemical free diets was associated with urinary phthalate concentrations compared with not following these practices. We adjusted all analyses for maternal age, BMI, race, education, and study center.

Results

Soy intake was found to be associated with increased levels of log mono-n-butyl phthalate (MnBP), a metabolite of di-n-butyl phthalate (DnBP) (β=0.05; 0.01, 0.08). Consumption of dairy was associated with decreased levels of the sum of log di-2-ethylhexyl phthalate (DEHP) metabolites (β = -0.02; -0.03, -0.004). No statistically significant associations were found between beef, seafood, oils, butter, lard, shortening, spices, and restaurant, delivery and fast foods and urinary phthalate metabolites. Additionally, no statistically significant associations were found between environmentally-friendly consumption practices and urinary phthalate metabolite concentrations.

Conclusions

These results suggest that soy products may be a dietary source of di-n-butyl phthalate (DnBP). It is possible that dairy was associated with decreased levels of phthalate metabolites in this study population because we were unable to differentiate between women consuming dairy products containing low concentrations of DEHP phthalates (yogurt, skim milk) versus higher concentrations of DEHP phthalates (cream, cheese, whole milk). This study also suggests that consumption of environmentally-friendly diets may not be protective against phthalate exposures in food.

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BACKGROUND

Use and Production

Phthalates, a family of synthetic chemicals derived from phthalic acid, are found in a variety of products for applications ranging from the automotive to medical and consumer product industries (CDC, 2009; Rahman and Brazel, 2004). Phthalates are most well-known as plasticizers, imparting thermo-mechanical properties to plastics to make them flexible, pliable and more durable. In cosmetic and personal care products, phthalates can be used as solvents, fragrance ingredients and denaturants (CIR, 2002; CDC, 2009). Phthalate production was initiated in the United States in 1920 and reached an annual peak of 180, 000 metric tons (397 million pounds) in 1976. In 2005, total U.S. phthalate production was 88, 000 metric tons (194 million pounds) (NTP, 2011). Di-2-ethylhexyl phthalate (DEHP) has been produced in the greatest volumes, constituting approximately 50% of all phthalate compounds used (NTP, 2011; Rahman and Brazel, 2004). Because phthalates are not chemically bound to products, leaching, migration, evaporation and degradation during product manufacturing, use and disposal may occur (CDC, 2009; Rahman and Brazel, 2004).

Toxicokinetics

Phthalates, composed of paired ester groups on a benzene ring, can undergo phase I and phase II biotransformations in the body (Fig. 1). During phase I, ester linkages are quickly hydrolyzed by esterases in the intestine to produce monoester metabolites that are easily absorbed and distributed. The monoesters can further form hydrolytic and oxidative products, which, in turn undergo phase II glucuronidation before being excreted (Samander et al. 2009). The majority of phthalate metabolites are eliminated in urine within 24 hours of exposure to parent compounds (Anderson et al. 2001; Wittassek et al. 2011). According to various reports, phthalates do not bioaccumulate in the body since humans and other mammals rapidly metabolize parent compounds to monoesters; however, some research suggests that due to its lipophilicity and longer oxidative metabolite half-lives, some DEHP may be stored in adipose tissues (ATSDR, 2001; Hauser et al. 2004; Koch et al. 2006; Genius et al. 2012). In pregnant women, parent compounds and/or phthalate metabolites have been found to pass through the placenta and expose the fetus (Singh et al. 1975; Silva et al. 2004; Enke et al. 2013).

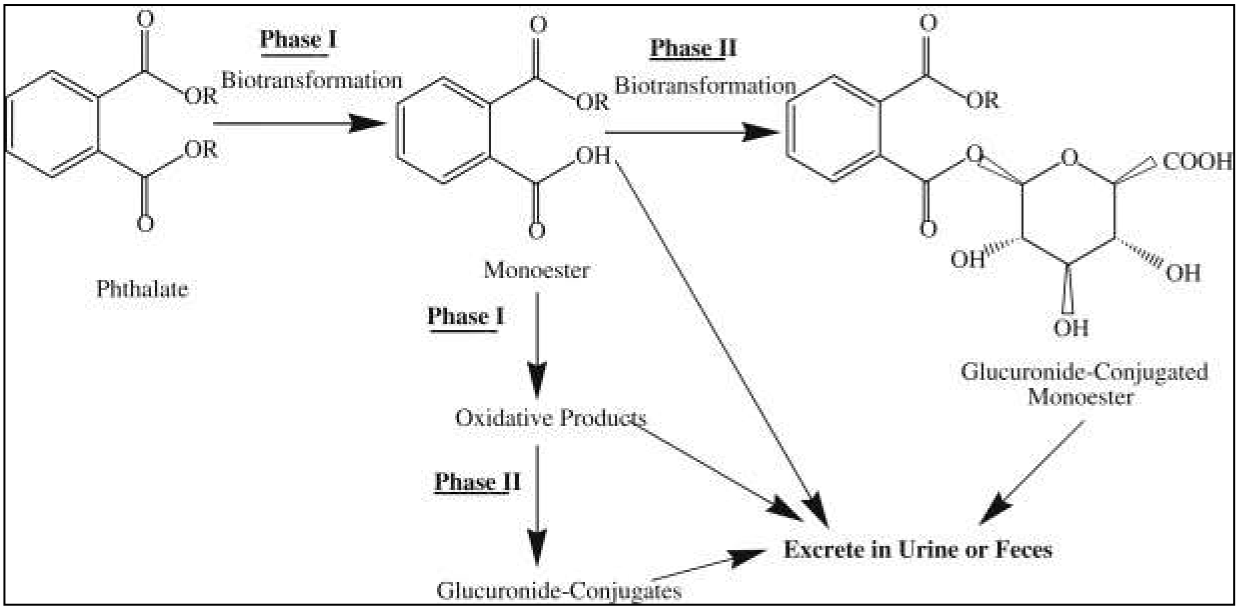

Figure 1: Metabolism of Phthalate Compound (Samander et al. 2009)

Toxicology

Phthalates are endocrine-disrupting chemicals that, during critical windows of development, disrupt proper differentiation and formation of male sex organs (Howdeshell et al. 2008). Animal studies have demonstrated that oral administration of di-n-butyl phthalate (DnBP), DEHP, and benzo-butyl phthalate (BzBP) induce a suite of genital tract disorders in male rodents exposed during gestation. This “phthalate syndrome” is characterized by shortened anogenital distance (AGD), a sensitive marker of feminization, hypospadias, cryptochidism, and malformations of the epididymis, vas deferens, seminal vesicles and prostrate. Retained nipples, testicular atrophy, and low spermatocyte count have also been observed in animal models (Mylchreest et al. 1998; Foster, 2006; Howdeshell et al. 2008; CDC, 2009; Gray et al. 2000). DEHP has been found to be the most potent phthalate species followed by DnBP and BzBP (Foster 2006).

These adverse effects on the male rat reproductive tract reflect suppression of androgens that are required for normal male development, therefore phthalates are classified as anti-androgenic chemicals. Some researchers have also shown that phthalates may be acting on genes responsible for Leydig and Sertoli cell development and cell to cell communication, but also indirectly and/or directly on genes involved in cholesterol transport, and hormone production, particularly insulin-like hormone 3 and testosterone (Howdeshell et al. 2008). Hence, the phthalate mechanism of action appears to be complex and multifactorial.

Epidemiology

In humans, Swan et al. (2005) found that higher maternal urinary concentrations of metabolites of diethyl phthalate (DEP), diisobutyl phthalate (DiBP) and DnBP were associated with shorter anogenital distance (AGD) in male infants. In an update to this study, DEP, DnBP and three DEHP metabolites were significantly and inversely related to AGD. Furthermore, decreased penile width and a greater probability of incomplete testicular descent were found to be significantly associated with higher DEHP metabolite concentrations (Swan et al. 2008). All study participants were healthy, part of the general population and exposed to phthalate levels that are normally encountered in the environment. Endocrine disrupting chemicals, like phthalates, are suspected to be linked to an increased trend of conditions related to abnormal sexual organ development that have been observed in the United States and in other industrial nations (EWG, 2005). These disorders have their roots in fetal development and can be influenced by genetic and environmental factors (Fisher 2006).

Exposure Assessment

Due to the ubiquity of phthalates in industrial and consumer products, exposure is widespread in the United States. In fact, greater than 97% of a representative sample from the National Health and Nutrition Examination Survey (NHANES 1999–2000) has measurable concentrations (Silva et al. 2004). Phthalates have been found to readily enter the bloodstream via ingestion, inhalation, dermal absorption, and parenteral pathways from medical devices (ATSDR, 2001). Although regarded as non-persistent chemicals because of their fast elimination, nearly daily exposures can result in consistent detection of biomarkers in the body (Koch et al. 2012).

Two general methods for assessing human exposures include 1) calculating internal doses by combining data on concentrations in different exposure media with exposure scenario assumptions and 2) measuring internal doses through biomarkers (Wittassek et al. 2011). Standard protocols developed by the Center for Disease Control and Prevention (CDC) indicate that phthalate biomarkers of exposure can be measured by their monoester and oxidative metabolite products in urine (CDC, 2010). Advantages of evaluating phthalate metabolites are that these biomarkers reflect exposures from all sources and routes and provide actual internal doses (Wittassek, 2011).

The simple monoesters are the major urinary metabolites of the short-chain phthalates such as DnBP, DiBP and BBzP with their urinary excretion representing between 70 and 84% of an oral dose (Anderson et al. 2001; Koch et al. 2012). In the case of the long-chain phthalate, DEHP, 93.6% of the dose is excreted as its simple monoester and a number of oxidative metabolites (MEHP, MEHHP, MEOHP, MECPP, MCMHP) (Silva et al. 2006). For the most accurate exposure assessment of DEHP, measurement of its multiple metabolites is therefore recommended.

Spot urine samples, taken at one point in time, are typically used to measure phthalate exposures within the last approximately 24 hours. However, on the individual level, such a sample may not be representative of a mean daily concentration but instead a peak or a minimum value depending on the time of day sample collection took place. To obtain a complete profile of phthalate metabolite concentrations, a 24-hour urine sample is the ideal measurement.

Unfortunately, 24-hour specimens are more logistically difficult to obtain, requiring greater cost, time and effort from the participant and study team, therefore they are not normally utilized. Having a large sample population size helps to balance out extreme values observed on the individual level while taking spot urine samples (Wittasek et al. 2011).

Dietary Exposures

Food can be contaminated with parent phthalate compounds by contact with phthalate-containing materials (Heudorf et al. 2007; Colacino et al. 2010). In a review of international studies by Cao (2010), phthalates were found to migrate into food from plasticized PVC tubing typically used in the milking process, food-packaging films, PVC gaskets of lids for glass jars, printing inks and adhesives used on the outside of food wrappers, PVC gloves used in the preparation of foods, and coatings on cookware contaminated from packaging; food conveyor belts have also been identified as a source for these compounds (NTP, 2003; Cao, 2010). In the United States, phthalates have been approved by the Food and Drug Administration (FDA) as plasticizers in food packaging materials and as food contact substances used in producing, manufacturing, packaging, processing, preparing, treating, transporting or holding food (21CFR 181.27, 178.3740) (Table 1). It is worth mentioning that foods high in fat are more readily contaminated by higher weight phthalates that are more lipophilic (DEHP) (Cao, 2010). Thus, there is substantial variability in phthalate concentrations within food groups based on processing practices, packaging and lipid content (Wittasek et al. 2011; Schecter et al. 2013).

According to an assessment in Europe, Asia, and North America, diet is the greatest source of exposures to DiBP, DnBP, BzBP and DEHP (Wormuth et al. 2006). In the United States, Schecter et al. (2013) analyzed 72 individual samples in 13 food groups from Albany, New York and found that DEHP was detected most frequently at 74%, followed by DEP (57%), DiBP (55%), BBzP (54%), dimethyl phthalate (DMP) (37%) and DnBP (31%). Of all the phthalates, DEHP concentrations were highest for beverages, milk, other dairy, fish, fruits/vegetables, grain, pork, poultry, meat and meat products, condiments and infant food but not beef and vegetable oils. Pork had the highest estimated mean DEHP concentration of any food group (mean= 300 ng/g; range=8.16-1158 ng/g), followed by other dairy products (mean=144 ng/g; range=3.71-285 ng/g), vegetable oils (mean=117; range=1.735-300 ng/g) and the sum of all meat and meat products (mean=101.8; range=1.735-1158 ng/g). Twenty assessments of phthalate concentrations in U.S. and international foods were reviewed and compared to these results. Dairy products, cooking oils and meat products were consistently found to have DEHP levels at 100 µg/kg or greater.

A cross-sectional study by Colacino et al. (2010) aimed to analyze the association between various foods and total and individual phthalate body burden in the general U.S. population utilizing diet and exposure biomarker data from NHANES 2003-2004. Information about foods consumed, portion and meal times for each participant was collected using 24-hr diet recall during face to face interviews. Using multiple regression analysis, researchers found statistically significant positive associations between intake of poultry and eggs and DEHP metabolites, vegetables and meat and the metabolite of DEP, fish and the metabolite of DiBP, dairy and the metabolite of di-n-octyl phthalate (DnOP) and fruit and the metabolite of DMP.

Purpose and Specific Aims

Because some of the phthalate species detected in food have also been linked to reproductive toxicity in both rats and humans exposed prenatally, research that aims to understand the dietary exposure of pregnant women is important for informing exposure reducing practices and helping to protect a vulnerable population. To date, only two U.S. studies have investigated dietary contributions to overall phthalate body burden and none have specifically examined exposures in pregnant women whose dietary decisions may differ from the general population. Thus, this study aims to determine the dietary contribution to urinary phthalate metabolite concentrations in U.S. women in the first trimester of pregnancy. Subsequent analysis to determine if reported practices of using environmentally friendly products and consuming chemical free diets are associated with reduced urinary phthalate concentrations compared with not following these practices is also investigated.

MATERIALS AND METHODS

Study Participants

The population for the present analysis was drawn from participants of The Infant Development and Environment Study (TIDES), designed primarily to examine the association between maternal phthalate exposures and adverse reproductive outcomes in infants measured by genital landmarks. The study population consisted of pregnant women at least 18 years of age receiving prenatal care and delivering at hospitals in Minneapolis, MN, (University of Minnesota), Rochester, NY (University of Rochester School of Medicine and Dentistry), Seattle, WA (Seattle Children's Hospital and University of Washington School of Medicine) and San Francisco, CA (University of California at San Francisco). Participating women completed questionnaires and provided urine samples during each trimester. Additionally, healthy newborns were examined using specific anthropometric measurements at each study center. Human subject committees at all participating institutions approved TIDES and related research, and all participants signed informed consents.

For this study, the analytical population was derived from the cohort of participants who enrolled in TIDES between August 2010 and April 2012. Subjects were included if 1) they were mothers of girl infants 2) provided one first trimester questionnaire and urine sample and 3) completed a TIDES birth exam. A total of 298 women met these eligibility criteria. Fifteen women (5%) with incomplete data on covariates including BMI, urine specific gravity, race, and consumption practices were excluded. A population of 283 women remained for analysis.

Dietary Intake

Questionnaires were completed online, by mail, over the phone or in person. Information about maternal demographics, anthropometrics, lifestyle/occupation, medical history, health status, risk perceptions and potential environmental exposures was collected. First trimester questionnaire data were utilized for this analysis.

Questionnaires provided information about the frequency of consumption, measured in servings per week, for various food groups. The following individual food groups were examined in this analysis: beef, seafood, poultry (such as chicken, turkey, etc.), spices (including salt/pepper, dried herbs, other seasonings), oils, butter, lard, or shortening, soy products (such as soy milk, tofu, soy nuts, edamame, soy protein, etc.) and dairy products (such as milk, cheese, yogurt, cottage cheese, ice cream, etc). Three new variables were created to test the hypothesis that foods high in fat and foods with reportedly high DEHP and DnBP concentrations contribute to greater urinary metabolite levels. These variables were created based on the current literature documenting phthalate concentrations in foods (Tomita et al. 1977; Wormuth et al. 2006; Cao 2010; Fierens et al. 2012a, b; FSA, 2012; Guo et al. 2012; Martine et al. 2012; Bradley et al. 2013; Sathyanarayana et al. 2013; Schecter et al. 2013). Food groups in the high fat category included peanut butter, beef, poultry, other meats, oils, butter, lard, or shortening, and dairy products. Food groups high in DEHP included peanut butter, other meats, spices and oil, butter, lard and shortening while food groups high in DnBP included peanut butter, poultry, spices and oil, butter lard, and shortening. Furthermore, daily servings of drinks in plastic bottles or cans and meals per week at restaurants, fast-food chains, for delivery or take-out were reported. One outlier representing 60 meals per week of restaurant food/take-out/delivery was identified and removed from analysis. No information in regard to portion size was collected. Each continuous variable was divided into three categories and analyzed both continuously and categorically. Categorical analysis was performed to compare effect size with continuous analysis and to allow for better translation of results into exposure reduction messaging.

Consumption Practices

The relationship between lifestyle and a variety of consumer practices with urinary phthalate concentrations was also examined. The following information measured as always/often, sometimes and rarely/never was assessed in relation to urinary phthalate concentrations: 1) how often individual tries to eat food that is organic, ecofriendly or chemical-free 2) how often food that is consumed is grown, raised or caught by individual/family/friends 3) how often food that is consumed is unprocessed 4) how often canned fruits and vegetables are consumed.

Phthalate Metabolite Analysis

Utilizing phthalate-free equipment, spot urine samples were collected in sterile specimen cups during 1st trimester recruitment visits, transferred to cryovials, and stored and frozen at <-80ºC until analysis.

Samples were shipped in two batches, approximately one month apart, to the Environmental Health Laboratory at the University of Washington (UW) for phthalate metabolite analysis. Per a modified version of the CDC method 6306.03, glucoronidated phthalate monoesters underwent enzymatic deconjugation, followed by online-solid phase extraction (SPE) coupled with reversed high performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS) to quantify the simple monoesters in urine (CDC, 2010). The ten phthalate metabolites that were studied are shown in Table 2. Process, laboratory and instrument blanks as well as field blanks were run with each batch of samples for quality assurance of analytical and sampling procedures. Two of 15 field blanks found to have levels of MnBP above the limit of detection (13 and 15 ng/mL) were identified as outliers and dropped. Specific gravity was measured using a handheld refractometer at the time of urine collection, which was calibrated with deionized water before each measurement. Urinary phthalate metabolite levels were normalized for dilution by specific gravity adjustment (Hauser et al. 2004). Because the majority of MMP and MCPP data were below the limit of detection (96.8% and 48.8%, respectively), these metabolites were not reported.

Statistical Analysis

The analytical limits of detection (LODs) were between 0.2 and 2.0 ng/mL for all phthalate metabolites tested. For concentrations below the LOD, a value equal to the LOD divided by the square root of 2 was used (Hornung 1990). All phthalate metabolite concentrations were logarithmically transformed to normalize distributions. As recommended by Silva et al. 2006, MEHP, MEHHP, MEOHP and MECPP concentrations, divided by their molecular weights, were combined to reflect total DEHP exposure (∑DEHP metabolites = (Conc. MEHP/278) + (Conc. MEHHP/294) + (Conc. MEOHP/292) + (Conc. MECPP/308)).

Bivariate linear regression models were used to estimate the relationships between demographic characteristics, other non-dietary phthalate exposures, and log-transformed urinary phthalate metabolite levels. Sources of non-dietary phthalate exposures included household/personal care products, medical devices, and medicine use and were categorized as use/no use. It was determined a priori that maternal age, BMI, and race would be included in multiple regression analysis. For the other demographic variables, those that were found to have statistically significant ($p < 0.05$) associations with at least one of the biologically relevant phthalate species (MnBP, MBzP, ∑DEHP metabolites) in bivariate models were included in all multiple regression models. Of the statistically significant non-dietary phthalate exposure variables, inclusion was determined through a step-wise forward procedure.

Each multiple regression model examined an individual dietary exposure or consumption practice variable and included covariates maternal age, BMI, race, study center, and education. MEP regression models also included use of fragrance, and MiBP and sum DEHP metabolite regression models also included use of air freshener as precision variables.

Final models to determine the best dietary predictors of each phthalate metabolite concentration were created utilizing a base model (maternal age, BMI, race, study center, education) and stepwise forward regression for the inclusion of food groups, consumption practices and other non-dietary phthalate exposures. In contrast to the individual models discussed above, this model took into account the influence of multiple food groups on phthalate metabolite concentrations.

All analyses were performed using urine-specific gravity adjusted log phthalate metabolite concentrations as well as log phthalate metabolite concentrations with urine specific gravity as a covariate.

RESULTS

Population Characteristics

Overall, participants included in this analysis were primarily white (71%) and had some college/graduate education or a college/graduate degree (87.3%). Women were distributed almost evenly among the four study centers. Age ranged from 18 to 44 years old with a mean of 31 years (median = 31 years), and BMI ranged from 14.12 to 61.10 with a mean of 26.18 kg/m^2 (median=24.36 kg/m^2). Mean urine specific gravity was 1.01 with a standard deviation of 0.01 (Table 3).

Dietary Intake and Consumption Practices

Of the single food groups, dairy was found to have the highest consumption rate with an average of 11.5 servings per week (range= 0-30) and seafood had the lowest with an average of 1.03 servings per week (range=0-6) (Table 4a). Almost half (49%) of the participants reported often or always consuming food that was organic, ecofriendly, and chemical free and 78% reported rarely or never eating canned fruits and vegetables. Often or always eating food grown, raised, or caught was only reported by 12 people (Table 5).

Urinary Phthalate Metabolite Concentrations

Of the single monoesters, MEP was detected at the highest concentration in the population (adjusted geometric mean = 53.40 ng/mL; range 45.60-62.52) while MEHP was detected at the lowest concentration (adjusted geometric mean = 4.80 ng/L; range 4.35-5.30) (Table 7). To compare to NHANES 2007-2008 data of the general U.S. female population of reproductive age (20-40 years), unadjusted geometric means were also reported. Table 6 demonstrates that the current study population had lower urinary concentrations for MEP, MnBP, MEHHP and MECPP from samples collected from 2010-2012 compared to the female population in the country from samples collected in 2007-2008.

Bivariate Regression Analysis

Bivariate regression analysis revealed a negative association between maternal age and all phthalate metabolite concentrations. Further, increasing BMI was found to be associated with higher levels of all metabolites. Participants within the Rochester study center had greater concentrations of all phthalate metabolites as compared to participants in San Francisco. In Seattle, participants had statistically significant lower levels for log MiBP (β=-0.33; -0.61, -0.05) and log

MnBP (β=-0.29; -0.57, -0.01) as compared to participants in San Francisco. Black/African American women were found to have greater urinary concentrations than Whites for log MEP (β= 0.82; 0.33, 1.32), log MiBP (β= 0.87; 0.55, 1.18), log MnBP(β= 0.86; 0.55, 1.17), log MBzP(β= 0.79; 0.43, 1.15), and the sum of log DEHP metabolites (β= 0.43; 0.16, 0.70). Finally, having a high school education or less was associated with increased concentrations of log MEP (β= 0.89; 0.40, 1.38), log MiBP (β= 0.87; 0.55, 1.18), log MnBP (β= 0.91; 0.61, 1.22), and log MBzP (β= 1.16; 0.82, 1.51) (Table 8).

Multivariate Regression Analysis

Analysis with continuous data demonstrated that one additional serving of soy per week was associated with an increase in log MnBP levels of 0.05 ng/mL (0.01, 0.08). Unexpectedly, consumption of one additional serving of dairy per week was found to be associated with a decrease in the sum of log DEHP metabolite levels of 0.02 ng/mL (-0.03, -0.004). Drinking one additional canned beverage per day was associated with a decrease in log MEP concentrations of 0.13 ng/mL (-0.25, -0.01). In contrast, drinking one additional canned beverage per day was associated with an increase in the sum of log DEHP metabolite levels of 0.07 ng/mL (0.01, 0.14).

Categorically, eating three or more servings per week of soy was associated with increased log MiBP concentrations as compared to eating zero servings per week (β = 0.33; 0.08, 0.59). Eating 15 or more servings of dairy per week was associated with decreased sum of log DEHP metabolite concentrations as compared to eating zero to seven servings per week (β= -0.31; -0.53, -0.09). Categorical data analysis also found that drinking four or more beverages in plastic per day was associated with decreased log MnBP (β = -0.26; -0.52, -0.003) and the sum of log DEHP metabolite concentrations (β = -0.25; -0.49, -0.01) as compared to drinking zero to one drink per day. Further, drinking two or more canned beverages per day was associated with decreased log MEP concentrations as compared to drinking zero per day (β =-0.76; -1.26, -0.27). Eating 18 to 30 servings of fatty foods per week was associated with decreased log MiBP concentrations as compared to eating zero to 17 servings per week (β =-0.28; -0.53, -0.03). Lastly, eating one serving of fast food per week was associated with decreased levels of MiBP (β =-0.26; -0.50, -0.02) as compared to zero meals per week. No statistically significant associations were found between beef, seafood, poultry, oils, butter, lard, shortening, spices, and restaurant, take-out and delivery foods and urinary phthalate metabolites (Table 9).

In regard to consumption practices, often or always eating food that is grown, raised, or caught was associated with increased levels of log MiBP (β = 0.56; 0.08, 1.04) and log MnBP (β =0.62; 0.16, 1.08) as compared to rarely or never following this practice. No statistically significant associations were found between environmentally-friendly consumption practices and reduced urinary phthalate metabolite levels.

Except for the positive association between soy products and log MnBP, multivariate regression results were comparable between analysis using urine specific gravity-adjusted log phthalate metabolite concentrations and analysis using log phthalate metabolite concentrations with urine specific gravity as a covariate.

In line with the aforementioned results, the association between soy intake and increased phthalate metabolite concentrations was also true of the predictor model for log MnBP (β=0.04; 0.003, 0.07). In this same model, one additional drink in plastic per day was associated with a decrease of 0.03 ng/mL (-0.06, 0.001) and often or always consuming food grown, raised and caught was associated with increased log MnBP levels (β=0.53; 0.08, 0.99) in comparison to rarely or never following this practice. For the log DEHP metabolites model, one additional serving per week of dairy was associated with a decreased concentration of 0.02 ng/mL (-0.03, -0.004). For the log MEP model, consuming one additional canned drink per day was associated with a decreased level of 0.13 ng/mL (-0.30, -0.01). For the log MiBP model, one additional serving of poultry per week was associated with a decreased level of 0.04 ng/mL (-0.09, -0.0001) and often or always consuming food grown, raised or caught was associated with increased levels (β= 0.54; 0.06, 1.02) in comparison to rarely or never following this practice (Table 10). Stepwise forward regression did not include dietary variables in the log MBzP model.

DISCUSSION

Of the food variables, only soy intake was found to be associated with increased mono-n-butyl and mono-isobutyl phthalate exposure as measured by urinary metabolite concentrations. Across all phthalates, environmentally-friendly and chemical-free consumption practices were not found to be predictive for reductions in phthalate exposure.

These results suggest that soy products may be a dietary source of di-n-butyl phthalate or di-isobutyl phthalate, but associations may be due to chance alone based on multiple comparisons analysis. To date, only one study considered phthalate contamination in this food group, however, it was conducted in Japan and published in 1977 (Tomita et al. 1977). Laboratory contamination of samples is a possibility in this study since quality control methods were not described. The United States is the leading producer and exporter of soy beans (USDA, 2013). According to the National Soybean Research Laboratory (NSRL) based in Illinois, soy beans undergo a multistep process prior to use in soy products that consists of threshing (separating beans from pods), drying, cleaning, packaging, transporting and storage. The beans can then be further processed for soy meal and soy oil with solvent extraction (NSRL, 2013). It is possible that phthalate contamination can occur during any one of these stages. One potential source could be from paper and board food packaging or storage containers since the FDA has approved the use of DnBP in these materials (21 CFR 176.170). DnBP and DiBP are also associated with inks and printing activity within paper packages and may migrate into food via the “set off” effect, where the printed surface and its components contaminate the non-printed surface that ultimately comes into contact with food. In a study by Zhang et al. (2008), DnBP was found in more than 90% of U.S. imported foreign paper food packages and in less than 20% of domestic packages. Investigators also tested dry foods packaged in these materials and detected DnBP in two domestic and four imported samples (<10 to 810 µg/kg) (Zhang et al. 2008). Future research is needed to determine whether soy products truly contain DnBP or DiBP and if so, where contamination is taking place.

Unexpectedly, dairy was associated with decreased levels of DEHP metabolites. In a review of nine studies on phthalate content in food, DEHP contamination in dairy was consistently reported; however, concentrations varied depending on product type (Table 11). The majority of reports found lower concentrations of DEHP in yogurt (0-102 µg/kg) , skim milk (20-25 µg/kg) and low fat milk (20-50 µg/kg) in comparison to butter (200-11,900 µg/kg), cream (180-2,700 µg/kg), cheese (41-16,800 µg/kg) and whole milk (35-2,260 µg/kg) which were typically reported to have significantly higher concentrations (Wormuth 2006; Cao 2010 - Castle et al. 1990, Page and Lacroix 1992, 1995, Sharman et al. 1994, Sorensen 2006; FSA, 2012; Martine et al. 2012; Sathyanarayana et al. 2013; Schecter et al. 2013;). It is possible that dairy was associated with decreased levels of phthalate metabolites in this study population because it was not possible to differentiate between women consuming dairy products containing low versus high DEHP concentrations.

In contrast to these results, Colacino et al. (2010) found poultry and egg consumption to be significantly associated with DEHP metabolite levels and Schecter et al. (2013) found DEHP at the highest concentrations in pork, dairy, vegetable oils and total meats. The authors concluded that diet is a significant route of exposure to DEHP, most likely from meat consumption or consumption of solid fats. Other studies that found similar results confirmed that DEHP is pervasive in food systems in Europe, Canada, and Asia and especially in foods high in fat (Sorenson 2006; Wormuth et al. 2006; Fierens et al. 2012a, b; FSA, 2012; Martine et al. 2012).

Polyethylene terephthalate (PET) is the material most commonly used to make plastic bottles for water, soda beverages and sports drinks in the United States. Although phthalates are not used as substrates or precursors in the manufacture of these bottles, phthalate contamination has been reported (Cao, 2010; Sax, 2010). Contamination is believed to occur prior to bottling or through the use of recycled PET previously in contact with phthalate-containing materials (Sax, 2010). In this study, the negative association between drinks in plastic bottles and log metabolite phthalate levels may have been observed because of women’s consumption of beverages in containers made of virgin PET material. Schecter et al. (2013) also observed low levels of DiBP and DEHP in juice and soda in plastic bottles (DiBP: 0.23-0.95 µg/kg; DEHP: 18.2 µg/kg).

In regard to specific consumption practices, often or always eating food that is grown, raised, or caught was associated with increased concentrations of some phthalate metabolites. However, of the 12 people in this category, 50% were found to be part of the Rochester study center which tended to have higher phthalate metabolite levels than the reference study center. Since exposure was already elevated possibly due to other factors associated with residing near or in the Rochester area, the relationship between often or always practicing consumption of foods that were grown, raised, or caught and expected reductions in concentrations was not observed.

It was anticipated that reports of consuming an ecofriendly, chemical-free and unprocessed diet may be associated with reduced phthalate metabolite levels as compared to never following these practices because of the assumption that contact with phthalate-containing packaging and processing materials would be eliminated or minimized. However, this was not observed. One possibility for this result is that although women reported following these diets, they may not have actually known how to shop for foods to meet these criteria. In a study by Rudel et al. (2011) which evaluated the contribution of food packaging to phthalate exposure using an intervention of mostly organic fresh foods prepared without plastics, investigators found reduced geometric mean concentrations of DEHP metabolites by 53-56% and at the most by 93-96%. However, only the decrease of one DEHP metabolite was statistically significant after adjusting for creatinine (Rudel et al. 2011). It is important to highlight that distinct from the subjects who reported having eco-friendly diets in the current study, participants in Rudel et al. (2011) consumed a catered diet to lead to phthalate metabolite reductions. Sathyanarayana et al. 2013 conducted a randomized dietary trial with 40 adults and children within 10 families to test the efficacy of a 5-day fresh foods and mostly organic diet in comparison to written recommendations to reduce phthalate exposure measured in urine samples before, during and after the intervention. An unexpected increase of median DEHP metabolite levels of 283.7 nmol/g at baseline to 7027.5 nmol/g was observed in the intervention group while no change was observed in the controls. DEHP decreased to baseline levels after the dietary intervention ended. Analysis of catered food showed that some spices and dairy had very high levels of DEHP (spices = 21, 400 μg/kg; dairy = 673 μg/kg). The authors concluded that their findings may have been indicative of a rare contamination event or that the U.S. food supply is systematically contaminated with phthalate concentrations.

A Swiss study by Dickson-Spillman et al. (2009) assessed risk perceptions of chemicals in food and interest in a natural (unprocessed, organic and chemical-free) and healthy diets (balanced diet with vitamins and minerals). Higher risk perceptions and higher natural and healthy diet interest were correlated with higher daily doses of DEHP, BBP, and DEP. The authors concluded that even those consumers who expressed strong interest in natural food and low acceptance of food chemicals and who tried to make respective food choices were still exposed to phthalates. Therefore, the food industry plays a major part in reducing consumer exposure to phthalates (Dickson-Spillman et al. 2009).

It is possible that these results were due to chance since multiple testing increases the probability of false positives (type I errors). To address this, the p-value of individual tests is typically adjusted to ensure that the family-wise error rate for all tests remains at 0.05. Bonferroni adjustment is the classical method but is thought to be overly conservative and can lead to an increase in false negatives (type II errors). Results were not adjusted for in this analysis.

Some multivariate regression models revealed associations of decreased phthalate metabolite concentrations with increased consumption of foods when the opposite was expected (i.e. fatty foods, fast food, dairy) or did not show statistical significance for positive associations. In terms of study design, expected associations may not have been observed because of issues with timing of exposure in relation to outcome assessment. Phthalates have a very short half-life with nearly complete elimination in 24 hours therefore biomarkers mainly provide information about exposures from the previous day. In this study, food frequency surveys, which are typically used to determine long-term patterns of consumption, may not have provided accurate measures of dietary exposure as estimated by a spot urine sample. A 24-hour recall would have been a more appropriate measure. On the other hand, one spot urine sample taken by convenience only captured phthalate metabolite concentrations at one specific point in time for each participant; a 24-hour urine sample would provide a complete profile of metabolite concentrations throughout an entire day. Therefore, a 24-dietary recall coupled with a 24-hour urine sample would be the ideal design for a study of this nature. However there are limitations in terms of cost and feasibility in utilizing a 24-hour urine sample.

This is the first study to evaluate dietary phthalate exposures specifically in a population of pregnant women. Biomonitoring in combination with questionnaire data provided measures of association between dietary intake of various food groups and urinary phthalate metabolite levels. Furthermore, the impact of consumption practices for reducing phthalate exposures was evaluated. A major strength of this study is the use of biomarkers which allowed for the accurate measurement of internal dose thereby reducing exposure misclassification. Also, questionnaire data about each study participant provided information on demographics and other significant covariates which were included as confounder and precision variables in models to provide more accurate regression estimates.

Some of the limitations of this study in terms of design include the use of a food frequency survey as opposed to a 24-hour dietary recall to relate food intake to urinary phthalate metabolite levels. Furthermore portion size, food preparation, food packaging and product type, factors that could potentially impact phthalate exposure, were not considered. Only one spot urine sample was collected at the convenience of the study participant as opposed to a 24-hour urine sample; however there are logistic limitations for the use of the latter sample type. The cohort is non-representative of the general population in terms of race, education and urinary phthalate metabolite concentrations. During multiple regression analysis, low variability of urinary phthalate metabolite concentrations may have impacted the ability to observe a signal. Furthermore, the problem of multiple comparisons is present in this study.

CONCLUSION

Multiple regression analysis was used to evaluate associations between food intake/consumption practices and urinary phthalate metabolite levels in a population of pregnant women. A positive association between consumption of soy products and MnBP was observed suggesting that soy could be a potential source for DnBP, a reproductive toxicant. Future research should aim to determine the presence of DnBP in soy products and causes for contamination. Further, studies should attempt to utilize a 24-hour dietary recall, detailed assessments of food consumption that take factors like product type, portion size, and packaging into account, and collect 24-hour urine samples to most accurately assess dietary exposures to phthalates.

TABLES

Table 1: Potential dietary sources for phthalate parent compounds

Phthalate parent compound	Sources
DEHP	PVC-containing tubing Plasticizer in food-packaging (for foods of high water content only)
BBzP	Conveyor belts In polymeric substances used in food-contact articles As component of uncoated or coated food-contact surface of paper/paperboard
DnBP	Printing inks As component of uncoated or coated food-contact surface of paper/paperboard
DiBP	Printing inks
DEP	Plasticizer in food-packaging

Source: Bradley et al. 2013; Robertson 2013; 21 CFR 174-176

Table 2: Phthalate parent compounds and their metabolites

Phthalate Name	Abbreviation	Urinary Metabolite	Abbreviation
Di-n-octyl phthalate	DnOP	mono(3-carboxypropyl) phthalate	MCPP
Dimethyl phthalate	DMP	mono-methyl phthalate	MMP
Diethyl phthalate	DEP	mono-ethyl phthalate	MEP
Di-isobutyl phthalate	DiBP	mono-isobutyl phthalate	MiBP
Di-n-butyl phthalate	DnBP	mono-n-butyl phthalate	MnBP
Benzylbutyl phthalate	BzBP	mono-benzyl phthalate	MBP
Di-2-ethylhexyl phthalate	DEHP	mono-2-ethylhexyl phthalate	MEHP
		mono-(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP
		mono-(2-ethyl-5-oxohexyl) phthalate	MEOHP
		mono-(2-ethyl-5-carboxypentyl) phthalate	MECPP

Table 3: Characteristics of pregnant women within TIDES cohort (n=283)

Characteristic		No.	%
Age (years)			
	<20	6	2.1
	21-30	114	40.3
	31-40	157	55.5
	>40	6	2.1
BMI (kg/m^2)			
	Underweight	4	1.4
	Normal	155	54.8
	Overweight	62	21.9
	Obese	62	21.9
Study Center			
	San Francisco, CA	68	24.0
	Minneapolis, MN	77	27.2
	Rochester, NY	76	26.9
	Seattle, WA	62	21.9
Race			
	White	201	71.0
	Asian	20	7.1
	Black/African American	32	11.3
	Other	18	6.4
	More than One Race	12	4.2
Education			
	High School or Less	36	12.7
	Some college/tech. school or college/tech. school graduate	123	43.5
	Some graduate school or graduate degree	124	43.8
Urine Specific Gravity			
	Mean	1.01 (1.00 - 1.11)	

Table 4a: Mean servings per week of various food groups as reported by pregnant women within TIDES cohort (n=283)

Food Item	Mean	Standard Deviation	Median	Min	Max
Beef	1.9	1.8	2	0	10
Seafood	1.0	1.2	1	0	6
Poultry	3.1	2.3	3	0	15
Spices	8.9	5.5	7	0	30
Oils, butter, lard, shortening	6.9	5.3	6	0	30
Soy products	1.7	2.7	1	0	21
Dairy products	11.5	6.5	10	0	30
Restaurant, fast food, take-out[a]	4.0	4.0	3	0	32
Fast food	0.9	1.5	0	0	10
Beverage in plastic bottle	2.6	3.6	2	0	32
Beverage in can	0.6	1.3	0	0	10
Fats	27.0	12.1	25	1	91
High DEHP foods	30.8	15.2	29	1	87
High DBP foods	21.3	10.8	19	1	63

[a] Outlier of 60 meals/week removed; n=282

Table 4b: Reported dietary intake of various foods of pregnant women within TIDES cohort (n=283)

Food Item	Frequency	n	Percent
Beef	0-1/week	137	48.4
	2/week	68	24.0
	≥3/week	78	27.6
Seafood	0/week	113	39.9
	1/week	96	33.9
	≥2/week	74	26.2
Poultry	0-2/week	120	42.4
	3/week	61	21.6
	≥4/week	102	36.0
Spices	0-5/week	87	30.7
	6-8/week	81	28.6
	≥9/week	115	40.6
Oils, butter, lard, shortening	0-3/week	81	28.6
	4-7/week	122	43.1
	≥8/week	80	28.3
Soy products	0/week	129	45.6
	1-2/week	82	29.0
	≥3/wk	72	25.4
Dairy products	0-7/week	112	39.6
	8-14/week	89	31.5
	≥15/week	82	29.0
Restaurant, fast food, take-out	0-2/week	132	46.6
	3-4/week	63	22.3
	≥5/week	87	30.7
Fast food	0/week	154	54.4
	1/week	73	25.8
	≥2/week	56	19.8
Beverage in plastic bottle	0-1/day	135	47.7
	2-3/day	83	29.3
	≥4/day	65	23.0
Beverage in can	0/day	187	66.1
	1/day	63	22.3
	≥2/day	33	11.7

Fats	0-17/week	69	24.4
	18-30/week	114	40.3
	≥31/week	100	35.3
High DEHP Foods	0-20/week	88	31.1
	21-35/week	94	33.2
	≥36/week	101	35.7
High DBP Foods	0-13/week	69	24.4
	14-22/week	103	36.4
	≥23/week	111	39.2

Table 5: Distribution of the number of participants following four consumption practices (n=283) (count, %)

	Always/Usually	Sometimes	Rarely/Never
Individuals tries to make sure food consumed is organic, ecofriendly, chemical-free	139 (49.1)	87 (30.7)	57 (20.1)
Food consumed is grown, raised, caught by individual or family/friends	12 (4.2)	52 (18.4)	219 (77.4)
Food consumed is unprocessed	129 (45.6)	106 (37.5)	48 (17.0)
Fruit/vegetables consumed are canned	17 (6.0)	46 (16.3)	220 (77.7)

Table 6: Unadjusted geometric mean phthalate metabolite concentrations in pregnant women within TIDES cohort (ng/mL) (n=283)

Parent	Metabolite	% <LOD	Geometric Mean (95% CI)	NHANES 2007-2008[b]
DEP	MEP	1.4	24.30 (20.13, 29.33)	92.46 (76.43-111.85)
DiBP	MiBP	1.1	4.03 (3.44, 4.72)	8.09 (6.88-9.50)
DnBP	MnBP	11.7	6.32 (5.45, 7.33)	21.58 (18.34-25.39)
BzBP	MBzP	22.6	3.64 (3.11, 4.25)	9.01 (7.26-11.18)
DEHP	MEHP	33.9	2.18 (1.92, 2.48)	3.30 (2.65-4.10)
	MEHHP	2.5	6.53 (5.69, 7.48)	24.64 (19.97-30.39)
	MEOHP	5.3	5.38 (4.73, 6.11)	14.13 (11.47-17.41)
	MECPP	1.4	6.45 (5.61, 7.41)	37.31 (31.20-44.61)
	∑ DEHP Metabolites[a]		0.07 (0.06, 0.08)	

[a] Sum DEHP is the sum of each metabolite divided by its molecular weight (MEHP, MEHHP, MEOHP, MECPP)

[b] Female population of reproductive age (20-40 years) values obtained from the Centers for Disease Control, National Health and Nutrition Survey, Updated Tables, 2012 (http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Feb2012.pdf)

Table 7: Geometric mean urine specific gravity-adjusted phthalate metabolite concentrations in pregnant women within TIDES cohort (ng/mL) (n=283)

Parent	Metabolite	% <LOD	Geometric Mean (95% CI)
DEP	MEP	1.4	53.40 (45.60, 62.52)
DiBP	MiBP	1.1	8.86 (7.98, 9.83)
DnBP	MnBP	11.7	13.90 (12.55, 15.38)
BzBP	MBzP	22.6	8.00 (7.12, 8.98)
DEHP	MEHP	33.9	4.80 (4.35, 5.30)
	MEHHP	2.5	14.34 (13.08, 15.73)
	MEOHP	5.3	11.82 (10.89, 12.82)
	MECPP	1.4	14.17 (12.91, 15.55)
	∑ DEHP Metabolites[a]		0.16 (0.14, 0.17)

[a] Sum DEHP is the sum of each metabolite divided by its molecular weight (MEHP, MEHHP, MEOHP, MECPP)

Table 8: Bivariate relationships between participant characteristics and log USG-adjusted phthalate metabolite concentrations (point estimate, 95% CI)

	Log MEP	Log MiBP	Log MBP	Log MBzP	Log ∑DEHP Metabolites
Maternal Age	-0.04* (-0.07, -0.01)	-0.04* (-0.06, -0.02)	-0.05* (-0.07, -0.04)	-0.07* (-0.09, -0.05)	-0.02* (-0.03, -0.002)
BMI	0.03* (0.004, 0.05)	0.02* (0.01, 0.04)	0.03* (0.01, 0.04)	0.03* (0.01, 0.05)	0.01* (0.0001, 0.03)
Race					
White	ref	ref	ref	ref	ref
Asian	-0.06 (-0.67, 0.55)	0.10 (-0.29, 0.49)	0.23 (-0.15, 0.61)	-0.16 (-0.60, 0.29)	0.11 (-0.22, 0.44)
Black/African-American	0.82* (0.33, 1.32)	0.87* (0.55, 1.18)	0.86* (0.55, 1.17)	0.79* (0.43, 1.15)	0.43* (0.16, 0.70)
Other	0.77* (0.14, 1.41)	0.38 (-0.03, 0.79)	0.17 (-0.23, 0.57)	0.12 (-0.35, 0.58)	0.24 (-0.11, 0.58)
More than One Race	0.07 (-0.70, 0.84)	0.16 (-0.33, 0.66)	-0.06 (-0.54, 0.43)	-0.09 (-0.65, 0.47)	0.32 (-0.10, 0.74)
Center					
San Francisco	ref	ref	ref	ref	ref
Minneapolis	0.20 (-0.23, 0.63)	0.18 (-0.09, 0.45)	-0.02 (-0.28, 0.24)	0.20 (-0.11, 0.51)	0.16 (-0.08, 0.39)
Rochester	0.92* (0.49, 1.35)	0.64* (0.37, 0.91)	0.61* (0.34, 0.87)	0.83* (0.52, 1.13)	0.34* (0.10, 0.57)
Seattle	0.13 (-0.32, 0.58)	-0.33* (-0.61, -0.05)	-0.29* (-0.57, -0.01)	0.03 (-0.30, 0.35)	0.15 (-0.11, 0.40)
Education					
High School or less	0.89* (0.40, 1.38)	0.87* (0.55, 1.18)	0.91* (0.61, 1.22)	1.16* (0.82, 1.51)	0.25 (-0.02, 0.52)
Some College/Tech. School or College/Tech. School Graduate	0.34* (0.01, 0.67)	0.02 (-0.19, 0.23)	0.06 (-0.15, 0.26)	0.09 (-0.13, 0.32)	-0.07 (-0.25, 0.11)
Some Graduate Work or Graduate Degree	ref	ref	ref	ref	ref

* Indicates *p*<0.05

Table 9: Multiple regression analysis results for dietary intake/consumption practices and log USG-adjusted phthalate metabolite concentrations (point estimate, 95% CI)

	Log MEP	Log MiBP	Log MBP	Log MBzP	Log ∑DEHP Metabolites
Beef	-0.05 (-0.14, 0.04)	-0.01 (-0.07, 0.04)	-0.01 (-0.06, 0.05)	0.03 (-0.03, 0.09)	0.03 (-0.02, 0.08)
0-1 servings/week	ref	ref	ref	ref	ref
2 servings/week	0.01 (-0.38, 0.41)	-0.14 (-0.39, 0.10)	-0.12 (-0.36, 0.11)	-0.10 (-0.37, 0.17)	-0.21 (-0.42, 0.005)
≥ 3 servings/week	-0.17 (-0.55, 0.21)	-0.08 (-0.31, 0.16)	-0.08 (-0.30, 0.15)	0.16 (-0.10, 0.42)	0.11 (-0.10, 0.31)
Seafood	-0.002 (-0.15, 0.14)	0.03 (-0.06, 0.12)	0.03 (-0.06, 0.11)	0.01 (-0.09, 0.10)	0.02 (-0.05, 0.10)
0 servings/week	ref	ref	ref	ref	ref
1 servings/week	-0.06 (-0.43, 0.32)	0.12 (-0.12, 0.35)	-0.01 (-0.23, 0.21)	-0.13 (-0.38, 0.13)	0.10 (-0.11, 0.31)
≥ 2 servings/week	-0.14 (-0.57, 0.28)	0.04 (-0.22, 0.30)	0.03 (-0.21, 0.28)	-0.12 (-0.41, 0.17)	0.10 (-0.13, 0.33)
Poultry	-0.02 (-0.09, 0.05)	-0.04 (-0.09, 0.001)	-0.01 (-0.06, 0.03)	0.02 (-0.03, 0.07)	0.03 (-0.01, 0.07)
0-2 servings/week	ref	ref	ref	ref	ref
3 servings/week	-0.05 (-0.46, 0.36)	-0.09 (-0.34, 0.17)	-0.05 (-0.29, 0.19)	0.10 (-0.18, 0.39)	0.09 (-0.14, 0.31)
≥ 4 servings/week	-0.16 (-0.53, 0.20)	-0.17 (-0.39, 0.05)	-0.05 (-0.26, 0.17)	0.13 (-0.11, 0.38)	0.05 (-0.15, 0.25)
Spices	-0.02 (-0.05, 0.01)	0.002 (-0.02, 0.02)	-0.002 (-0.02, 0.02)	-0.01 (-0.03, 0.01)	-0.01 (-0.02, 0.01)
0-5 servings/week	ref	ref	ref	ref	ref
6-8 servings/week	0.23 (-0.18, 0.65)	-0.15 (-0.41, 0.11)	0.05 (-0.20, 0.30)	-0.09 (-0.38, 0.20)	-0.03 (-0.26, 0.20)
≥ 9 servings/week	-0.27 (-0.66, 0.12)	-0.07 (-0.32, 0.17)	-0.08 (-0.31, 0.15)	-0.19 (-0.46, 0.08)	-0.15 (-0.37, 0.06)
Oils, butter, lard, shortening	-0.0002 (-0.03, 0.03)	0.01 (-0.005, 0.03)	-0.003 (-0.02, 0.02)	-0.01 (-0.03, 0.02)	-0.001 (-0.02, 0.02)
0-3 servings/week	ref	ref	ref	ref	ref
4-7 servings/week	0.07 (-0.32, 0.45)	0.17 (-0.07, 0.41)	0.01 (-0.21, 0.24)	0.02 (-0.24, 0.29)	0.02 (-0.19, 0.23)
≥ 8 servings/week	0.01 (-0.43, 0.45)	0.12 (-0.15, 0.39)	-0.14 (-0.40, 0.12)	-0.02 (-0.32, 0.28)	-0.09 (-0.33, 0.16)
Soy products	0.06 (-0.001, 0.12)	0.02 (-0.02, 0.06)	0.05* (0.01, 0.08)	0.03 (-0.01, 0.07)	0.02 (-0.01, 0.06)

0 servings/week	ref	ref	ref	ref	ref
1-2 servings/week	-0.22 (-0.62, 0.17)	0.16 (-0.09, 0.40)	-0.14 (-0.37, 0.09)	-0.19 (-0.46, 0.08)	-0.06 (-0.28, 0.15)
≥ 3 servings/week	0.15 (-0.26, 0.57)	0.33* (0.08, 0.59)	0.08 (-0.16, 0.33)	0.02 (-0.26, 0.31)	0.07 (-0.16, 0.30)
Dairy products	0.02 (-0.003, 0.05)	-0.01 (-0.03, 0.002)	-0.001 (-0.02, 0.01)	0.01 (-0.01, 0.02)	-0.02* (-0.03, -0.004)
0-7 servings/week	ref	ref	ref	ref	ref
8-14 servings/week	0.24 (-0.15, 0.63)	-0.08 (-0.32, 0.16)	0.01 (-0.22, 0.24)	0.10 (-0.17, 0.36)	-0.08 (-0.29, 0.14)
≥ 15 servings/week	0.20 (-0.20, 0.61)	-0.24 (-0.49, 0.01)	-0.13 (-0.37, 0.11)	0.004 (-0.28, 0.28)	-0.31* (-0.53, -0.09)
Take-out, delivery, restaurant food	0.02 (-0.01, 0.06)	-0.02 (-0.04, 0.01)	-0.01 (-0.04, 0.01)	-0.001 (-0.03, 0.03)	-0.003 (-0.03, 0.02)
0-2 servings/week	ref	ref	ref	ref	ref
3-4 servings/week	0.32 (-0.09, 0.72)	-0.09 (-0.34, 0.16)	-0.003 (-0.24, 0.24)	0.10 (-0.17, 0.38)	0.02 (-0.20, 0.24)
≥ 5 servings/week	0.15 (-0.22, 0.52)	-0.02 (-0.25, 0.21)	-0.08 (-0.30, 0.15)	0.02 (-0.24, 0.27)	-0.09 (-0.30, 0.11)
Fast food	-0.05 (-0.16, 0.07)	-0.03 (-0.10, 0.04)	0.01 (-0.06, 0.08)	0.07 (-0.01, 0.15)	-0.02 (-0.09, 0.04)
0 servings/week	ref	ref	ref	ref	ref
1 serving/week	0.09 (-0.29, 0.48)	-0.26* (-0.50, -0.02)	-0.04 (-0.27, 0.18)	0.20 (-0.07, 0.46)	-0.13 (-0.34, 0.08)
≥ 2 servings/week	-0.12 (-0.58, 0.34)	-0.15 (-0.44, 0.13)	-0.04 (-0.31, 0.24)	0.21 (-0.11, 0.53)	-0.03 (-0.29, 0.22)
Fats	0.004 (-0.01, 0.02)	-0.004 (-0.01, 0.005)	0.001 (-0.01, 0.01)	0.002 (-0.01, 0.01)	-0.001 (-0.01, 0.01)
0-17 servings/week	ref	ref	ref	ref	ref
18-30 servings/week	0.11 (-0.30, 0.51)	-0.28* (-0.53, -0.03)	-0.05 (-0.29, 0.19)	0.20 (-0.08, 0.48)	-0.10 (-0.32, 0.13)
≥ 31 servings/week	0.12 (-0.31, 0.56)	-0.15 (-0.41, 0.12)	-0.08 (-0.34, 0.17)	0.17 (-0.13, 0.46)	-0.16 (-0.40, 0.08)
High DEHP foods	0.001 (-0.01, 0.01)	-0.001 (-0.01, 0.01)	0.001 (-0.01, 0.01)	-0.001 (-0.01, 0.01)	-0.003 (-0.01, 0.003)
0-20 servings/week	ref	ref	ref	ref	ref
21-34 servings/week	-0.18 (-0.60, 0.23)	-0.14 (-0.40, 0.12)	-0.01 (-0.25, 0.24)	0.13 (-0.15, 0.42)	-0.12 (-0.35, 0.11)
≥ 35 servings/week	-0.01 (-0.43, 0.40)	-0.12 (-0.38, 0.14)	-0.15 (0.40, 0.09)	0.0003 (-0.29, 0.29)	-0.20 (-0.43, 0.03)

High DnBP foods	-0.004 (-0.02, 0.01)	0.002 (-0.01, 0.01)	0.001 (-0.01, 0.01)	-0.003 (-0.01, 0.01)	0.002 (-0.01, 0.01)
0-13 servings/week	ref	ref	ref	ref	ref
14-21 servings/week	0.04 (-0.39, 0.47)	0.0001 (-0.26, 0.26)	0.21 (-0.04, 0.46)	0.20 (-0.09, 0.50)	-0.05 (-0.28, 0.18)
≥ 22 servings/week	-0.07 (-0.49, 0.36)	0.03 (-0.24, 0.29)	0.001 (-0.25, 0.25)	0.02 (-0.27, 0.31)	-0.09 (-0.33, 0.14)
Drinks in plastic bottles	-0.005 (-0.05, 0.04)	-0.02 (-0.05, 0.005)	-0.03* (-0.06, -0.005)	0.005 (-0.03, 0.04)	-0.03* (-0.06, -0.005)
0-1 drinks/day	ref	ref	ref	ref	ref
2-3 drinks/day	0.14 (-0.24, 0.52)	0.06 (-0.18, 0.29)	-0.19 (-0.41, 0.04)	0.03 (-0.23, 0.29)	-0.02 (-0.23, 0.19)
≥ 4 drinks/day	0.10 (-0.33, 0.54)	-0.02 (-0.29, 0.25)	-0.26* (-0.52, -0.003)	0.13 (-0.17, 0.43)	-0.25* (-0.49, -0.01)
Drinks in cans	-0.13* (-0.25, -0.01)	0.0001 (-0.08, 0.08)	0.02 (-0.05, 0.09)	0.02 (-0.07, 0.10)	0.07* (0.01, 0.14)
0 drinks/day	ref	ref	ref	ref	ref
1 drink/day	-0.15 (-0.53, 0.23)	-0.15 (-0.39, 0.09)	-0.03 (-0.26, 0.20)	-0.03 (-0.29, 0.24)	0.08 (-0.13, 0.29)
≥ 2 drinks/day	-0.76* (-1.26, -0.27)	-0.02 (-0.34, 0.29)	0.07 (-0.23, 0.37)	0.14 (-0.21, 0.48)	0.15 (-0.13, 0.42)
Food consumed is organic, ecofriendly, chemical-free					
Always/Often	ref	ref	ref	ref	ref
Sometimes	-0.18 (-0.55, 0.19)	-0.20 (-0.43, 0.03)	-0.08 (-0.30, 0.14)	-0.12 (-0.37, 0.14)	0.04 (-0.16, 0.25
Rarely/Never	0.16 (-0.31, 0.62)	-0.27 (-0.56, 0.01)	0.02 (-0.26, 0.29)	0.02 (-0.30, 0.34)	-0.08 (-0.35, 0.18)
Food consumed is grown, raised, caught					
Always/Often	0.38 (-0.41, 1.16)	0.56* (0.07, 1.04)	0.62* (0.16, 1.08)	0.30 (-0.24, 0.83)	0.09 (-0.34, 0.52)
Sometimes	-0.01 (-0.42, 0.40)	-0.04 (-0.29, 0.21)	-0.04 (-0.28, 0.20)	-0.06 (-0.34, 0.22)	0.23* (0.01, 0.45)
Rarely/Never	ref	ref	ref	ref	ref
Food consumed is unprocessed					
Always/Often	ref	ref	ref	ref	ref
Sometimes	0.01 (-0.34, 0.37)	0.11 (-0.10, 0.33)	0.14 (-0.06, 0.35)	-0.14 (-0.38, 0.10)	-0.03 (-0.22, 0.16)
Rarely/Never	0.08 (-0.42, 0.57)	-0.05 (-0.36, 0.26)	0.20 (-0.09, 0.49)	0.08 (-0.26, 0.42)	0.22 (-0.05, 0.50)
Fruits/vegetables consumed are canned					

Always/Often	0.06 (-0.66, 0.78)	0.19 (-0.26, 0.64)	0.11 (-0.32, 0.53)	0.26 (-0.23, 0.76)	0.02 (-0.38, 0.41)
Sometimes	-0.37 (-0.83, 0.09)	0.02 (-0.27, 0.31)	-0.12 (-0.40, 0.15)	-0.23 (-0.54, 0.09)	-0.06 (-0.32, 0.19)
Rarely/Never	ref	ref	ref	ref	ref

* Indicates $p < 0.05$

All models adjusted for maternal age, BMI, study center, race, and education

MEP models adjusted for use of fragrance

MiBP & ∑DEHP metabolites models adjusted for use of air freshener

Table 10: Stepwise forward multiple regression analysis results for dietary intake/consumption practices and log USG-adjusted phthalate metabolite concentrations (point estimate, 95% CI)

Model	Dietary intake/consumption practice variables included in model	Point Estimate (95% CI)
Log MEP	Drinks in Cans	-0.13* (-0.25, -0.01)
Log MiBP	Poultry	-0.04* (-0.09, -0.0001)
	Food consumed is grown, raised, caught	
	Always/Often	0.54* (0.06, 1.02)
	Rarely/Never	ref
Log MnBP	Soy Products	0.04* (0.002, 0.07)
	Drinks in Plastic	-0.03* (-0.06, -0.0005)
	Food consumed is grown, raised, caught	
	Always/Often	0.53* (0.08, 0.99)
	Rarely/Never	ref
Log ∑ DEHP Metabolites	Dairy Products	-0.02* (-0.03, -0.004)

* Indicates $p < 0.05$

All models adjusted for maternal age, BMI, study center, race, and education

MEP models adjusted for use of fragrance

Table 11: DEHP concentration in dairy products as reported by various studies (µg/kg)

Study (Location)	n	Product	DEHP Concentration (mean/median)
Bradley et al. 2013 (North England)	15	Dairy products (including milk)	(159/)
Casajuana and Lacorte 2004 (Spain)*	5	Milk	15.1-27.2
Castle et al. 1990 (Norway, UK)*	1	Milk, full, pasteurized	35
Castle et al. 1990 (Norway, UK)*	2	Milk, skimmed, pasteurized (Norwegian)	20, 25
Castle et al. 1990 (Norway, UK)*	2	Cream, pasteurized, homogenized	1200, 1400
Fierens et al. 2012a (Belgium)	56	Milk and dairy products	ND-743.0 (/27.5)
FSA, 2012 (UK)	1	Jersey milk	109
FSA, 2012 (UK)	1	British double cream	328
FSA, 2012 (UK)	1	Cornish clotted cream	690
FSA, 2012 (UK)	1	Extra thick real cream - UHT	222
FSA, 2012 (UK)	1	Greek style natural probiotic yoghurt	78
FSA, 2012 (UK)	1	Lemon curd yogurt	102
FSA, 2012 (UK)	1	Blue stilton	496
FSA, 2012 (UK)	1	Grated Emmental	366
FSA, 2012 (UK)	1	TDS Group Dairy	141
FSA, 2012 (UK)	1	Dairy butter	347
FSA, 2012 (UK)	1	Unsalted butter	2592
FSA, 2012 (UK)	1	Butter ghee	960
Guo et al. 2012 (China)	10	Milk or beverage w/milk	ND-88.3 (28.5/19.2)
MAFF 1996a (UK)*	2	Milk, total diet	(300/)
Martine et al. 2012 (Paris , France)	1	Plain yoghourt (wet weight)	3.4
Martine et al. 2012 (Paris , France)	1	Gruyere cheese (wet weight)	172.7
Martine et al. 2012 (Paris , France)	1	Camembert cheese (wet weight)	105.7
Page 1996 (Canada)*	11	Dairy, total diet	20-3200
Page and Lacroix 1992 (Canada)*	12	Butter	2300-11900
Page and Lacroix 1992 (Canada)*	8	Margarine	700-11300
Page and Lacroix 1995 (Canada)*	17	Cheese	300-5500
Page and Lacroix 1995 (Canada)*	11	Dairy, total diet	10-3400
Petersen 1991 (Denmark)*	8	Milk	50-140
Sathyanarayana et al. 2013 (United States)	1	Butter	595
Sathyanarayana et al. 2013 (United States)	1	Heavy cream	488
Sathyanarayana et al. 2013 (United States)	1	Milk	673
Sathyanarayana et al. 2013 (United States)	1	Cheese	396
Sathyanarayana et al. 2013 (United States)	1	Egg yolk	39
Schecter et al. 2013 (U.S.)	1	Milk	28
Schecter et al. 2013 (U.S.)	1	Milk	69.1
Schecter et al. 2013 (U.S.)	1	Ice cream	341
Schecter et al. 2013 (U.S.)	1	Ice cream	10.2
Schecter et al. 2013 (U.S.)	1	Pudding	92.8
Schecter et al. 2013 (U.S.)	1	Yogurt	3.71
Schecter et al. 2013 (U.S.)	1	Yogurt	16.6
Schecter et al. 2013 (U.S.)	1	Shredded cheese	285
Schecter et al. 2013 (U.S.)	1	Sliced cheese	69.7

Schecter et al. 2013 (U.S.)	1	Butter	275
Schecter et al. 2013 (U.S.)	1	Butter	200
Sharman et al. 1994 (UK, Norway, Spain)*	5	Milk <1% fat	20-40
Sharman et al. 1994 (UK, Norway, Spain)*	3	Milk, 1% fat	50-50
Sharman et al. 1994 (UK, Norway, Spain)*	9	Milk, 3% fat	200-2260
Sharman et al. 1994 (UK, Norway, Spain)*	16	Milk, doorstep (UK)	<10-90
Sharman et al. 1994 (UK, Norway, Spain)*	5	Milk, fresh (Spain)	<10-50
Sharman et al. 1994 (UK, Norway, Spain)*	1	Cream 31% (Spain)	480
Sharman et al. 1994 (UK, Norway, Spain)*	1	Cream, 33% fat (Spain)	550
Sharman et al. 1994 (UK, Norway, Spain)*	5	Cream, 35% fat	1060-1670
Sharman et al. 1994 (UK, Norway, Spain)*	10	Cream (UK)	200-2700
Sharman et al. 1994 (UK, Norway, Spain)*	25	Cheese	200-16800
Sharman et al. 1994 (UK, Norway, Spain)*	10	Butter (UK)	2500-7300
Sharman et al. 1994 (UK, Norway, Spain)*	1	Margarine, sunflower	1200
Sharman et al. 1994 (UK, Norway, Spain)*	1	Margarine, soft	2000
Sorensen 2006 (Denmark)*	4	Milk, pasteurized, homogenized	13-27
Sorensen 2006 (Denmark)*	18	Milk, raw	7-30
Sorensen 2006 (Denmark)*	3	Yogurt with fruit	15-37
Wormuth et al. 2006 (Europe, North America, Asia)		Milk, milk beverages	8.5-170 (40/)
Wormuth et al. 2006 (Europe, North America, Asia)		Cream	180-320 (224/)
Wormuth et al. 2006 (Europe, North America, Asia)		Ice Cream	165-390 (242/)
Wormuth et al. 2006 (Europe, North America, Asia)		Yogurt	0-90 (51/)
Wormuth et al. 2006 (Europe, North America, Asia)		Cheese	41-1230 (496/)

* Reported in Cao 2010

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