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Determinants and characterization of exposure to phthalates, DEHTP and DINCH among pregnant women in the PROTECT birth cohort in Puerto Rico

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Abstract

Background: As a result of evidence suggesting phthalate toxicity, their use has decreased in recent years. However, new phthalates and non-phthalate replacements have emerged in their place, with unknown potential impacts on health.

Methods: We measured 15 phthalate, two di(2-ethylhexyl)terephthalate (DEHTP), and two di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH) urinary metabolites, collected up to three times during pregnancy from 994 women in Northern Puerto Rico (2011-2017). We used tests of linear trend to asses changes in concentrations over time and linear mixed models to identify predictors of exposure (sociodemographic characteristics, drinking water sources, diet, product use).

Results: Several phthalate metabolites decreased over the study period indicating decreased exposure, while the geometric mean of DEHTP metabolites (molecular sum) increased 3-fold between 2014-2017. Intraclass correlations revealed low to moderate reproducibility of these

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biomarkers across pregnancy. Several metabolites were associated with maternal age, income, education, pre-pregnancy BMI, drinking public water, use of cleaning and personal care products and ice cream consumption. DINCH metabolite concentrations remained low throughout the study period.

Conclusion: Although exposure to some phthalates may be decreasing, exposure to replacements, such as DEHTP, is increasing. Additional studies are needed to further characterize sources of phthalate replacement chemicals and potential exposure-related health effects among vulnerable populations.

Keywords

phthalate; DEHPT; terephthalate; DINCH; pregnancy

Introduction

Phthalates are chemicals widely used in industrial and consumer applications, resulting in ubiquitous human exposure (1). High molecular weight phthalates such as di(2-ethylhexyl) phthalate (DEHP), di-isononyl phthalate (DINP) and dioctyl phthalate, are used as plasticizers in polyvinyl chloride (PVC) plastics, food packaging, medical devices and vinyl products, while low molecular weight phthalates such as diethyl phthalate (DEP) and dibutyl phthalate (DBP) are used as solvents in personal care products including perfumes, lotions and cosmetics (2). Epidemiological studies suggest that phthalate exposure during pregnancy is associated with increased risk of pregnancy loss, preeclampsia, preterm birth and gestational hypertension (3-9). In addition, gestational phthalate exposure has been associated with altered neurodevelopment (10-13), endocrine, reproductive (14-18), and cardiometabolic outcomes during infancy and childhood (19-22).

In response to concerns about the safety of exposure, several phthalates have been banned from use in children's toys and other child care articles in the United States. However, phthalate alternatives, including di-2-ethylhexyl terephthalate (DEHTP) and di(isononyl)cyclohexane-1,2-dicarboxylate (DINCH), are now being used in their place for a variety of consumer applications with limited information on potential impacts on health (23, 24). DEHTP is now used in flexible PVC products, children's toys, medical devices and food contact materials in place of DEHP (23). Current studies in human exposure provide evidence for this trend, as several studies demonstrate decreases in urinary DEHP metabolite concentrations in recent years (25-28), while urinary DEHTP metabolites have increased (25, 29). Similarly, DINCH is now used in the U.S. in a range of applications, including children's toys, food contact materials, vinyl flooring and medical devices (30). With increasing demand and use of phthalate replacement chemicals, studies show increasing detection of urinary DINCH metabolites both within the U.S. (24) and elsewhere (31-33). Although epidemiological studies of health effects related to DEHTP or DINCH exposure are extremely limited (34), recent animal studies suggest that gestational DINCH exposure can affect the function of Leydig cells, which produce testosterone and other androgens (35). In addition, DINCH metabolites can activate human estrogen receptor (ER) α, ERβ, androgen receptor, peroxisome proliferator-activated receptor (PPAR) α and PPARγ (36),

which play key roles in metabolism, inflammation, and many other disease processes (37, 38).

In a study of DEHTP exposure in rats, adverse effects on reproductive system, kidneys or liver were not observed (39), however the chronic oral intake of DEHTP in animal models have reported general toxicity related to changes in hematologic parameters and weight loss (40). Additionally, in a study of DEHP and DEHP replacements utilizing a murine cell line, DEHP was more cytotoxic that DINCH, but the decrease in cell viability was ≤50% for both compounds. Interestingly, mono-(2-ethylhexyl) phthalate (MEHP, a DEHP metabolite) and several DINCH and DEHTP metabolites presented more cytotoxic dose-response effects than their parent compounds at the same concentrations, with MEHP having the smallest effect of all metabolites (41). These findings highlight the need for characterizing and identifying sources of exposure to both phthalates and phthalate replacement chemicals, particularly among pregnant women and children.

In the present study, we measured urinary concentrations of metabolites of phthalates, DEHTP, and DINCH among women from the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) birth cohort at three time points during pregnancy as biomarkers of prenatal exposure. We characterized trends in plasticizer exposure over time and evaluated self-reported demographic, socioeconomic, product use, and diet information as predictors of urinary metabolite concentrations to help inform potential sources of exposure.

Methods

Study participants

Pregnant women were recruited from prenatal clinics and hospitals in northern Puerto Rico for participation in the PROTECT prospective birth cohort in 2010 through 2017. Women were recruited at approximately 14 ± 2 weeks of gestation (n=994) and were eligible if they were between 18 to 40 years old, lived in the Northern karst region, did not use oral contraceptives three months prior to pregnancy, did not use *in vitro* fertilization to become pregnant, and did not have known medical/obstetrics complications. The sample size required for this ongoing birth cohort was determined based on investigating relationships between environmental exposures with preterm birth, however, previous analyses have demonstrated that this sample size is more than adequate to assess predictors of exposure. Prenatal spot urine samples were collected at study visits at approximately 18, 22 and 26 weeks of gestation, and information on demographic and socioeconomic factors, as well as self-reported product use and food consumption in the previous 48 hours was collected using questionnaires at each study visit. Research protocols were reviewed and approved by the Ethics and Research Committees of the University of Puerto Rico, the University of Michigan School of Public Health, Northeastern University, and participating hospitals and clinics. All study participants provided informed consent prior to participation. Involvement of the CDC was determined not to constitute engagement in human subjects research.

Urinary Biomarker Measurements

Urine was collected in polypropylene containers, divided into aliquots, and frozen at −80 °C until shipment overnight to the Division of Laboratory Sciences at the Centers for Disease Control and Prevention (CDC) for analysis. CDC personnel were blinded to all participant information. Urinary concentrations of 15 phthalate, two DEHTP, and two DINCH metabolites were measured using on-line solid phase extraction coupled with isotope dilution-high performance liquid chromatography-electrospray ionization-tandem mass spectrometry as previously described (24, 29, 42). Measured phthalate metabolites comprised 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), mono-benzyl phthalate (MBzP), monocarboxyoctyl phthalate (MCOP), mono-isononyl phthalate (MNP), mono-oxoisononyl phthalate (MONP), monocarboxynonyl phthalate (MCNP), mono (3-carboxypropyl) phthalate (MCPP), mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MBP), mono-3-hydroxybutyl phthalate (MHBP), mono-isobutyl phthalate (MiBP) and mono-2-hydroxy-iso-butyl phthalate (MHiBP). Measured DEHTP metabolites comprised mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP) and mono-2-ethyl-5-hydroxyhexyl terephthalate (MEHHTP) (23, 43). Measured DINCH metabolites were cyclohexane-1,2-dicarboxylic acid monohydroxy isononyl ester (MHiNCH) and cyclohexane-1,2-dicarboxylic acid monocarboxy isooctyl ester (MCOCH) (24). The sum of di-2-ethylhexyl phthalate metabolites (ΣDEHP) was calculated by adding the molar fractions of MEHP, MEHHP, MEOHP and MECPP; the sum of dibutyl phthalate (ΣDBP) was calculated by adding the molar fractions of MBP and MHBP; the sum of di-isobutyl phthalate (ΣDiBP) by adding the molar fractions of MiBP and MHiBP; and di(2-ethylhexyl)terephthalate (ΣDEHTP) by adding the molar fractions of MECPTP and MEHHTP. To achieve unit comparability, ΣDEHP (nmol/ml) was multiplied by the molecular weight (MW) of MEHP (278.348 g/mol), ΣDBP (nmol/ml) by the MW of MnBP (222.24 g/mol), ΣDiBP (nmol/ml) by the MW of MiBP (222.24 g/mol) and ΣDEHTP (nmol/ml) by the MW of MEHHTP (294.34 g/mol). The resulting units were ng/ml. The number of samples analyzed for each metabolite are presented in Supplemental Material Table S1, stratified separately by prenatal visit and by year of sample collection. Specific gravity (SG) was measured using a handheld digital refractometer (Atago Co., Ltd., Tokyo, Japan) at the University of Puerto Rico Medical Sciences Campus at the time of sample collection. Values below the limit of detection (LOD) were imputed with the metabolite-specific LOD/√2 (44).

Statistical Analysis

First, geometric means, geometric standard deviations, and percentiles were calculated to describe distributions of urinary biomarker concentrations. We compared geometric means of urinary biomarker concentrations among PROTECT women to concentrations reported in NHANES 2011-2016 (45) among women aged 16 to 49 years using a two-sample t-test. For the following analyses, biomarker concentrations were natural log-transformed for normalization, and corrected for SG to account for urinary dilution. The SG correction was made according to the following formula (46): Pc=P (1.019-1)/(SG-1); where Pc = corrected metabolite concentration, P = measured metabolite concentration, SG = SG of the sample, and 1.019 = median SG of all samples collected. Spearman rank correlations were calculated

to assess relationships between phthalate and phthalate replacement metabolites. Differences in biomarker concentrations by study visit were tested using linear mixed models to account for within participant correlation, and intraclass correlation coefficients (ICCs) were calculated to assess the reproducibility and variability of biomarker concentrations across pregnancy. Changes in biomarker concentrations by year were also assessed to determine trends in individual metabolites over time using tests of linear trend. Population geometric mean concentrations of SG-corrected biomarker concentrations were calculated across demographic and socioeconomic factors, such as maternal age, education, employment, marital status, and income, as well as pre-pregnancy body mass index (BMI). We used linear mixed effects models with compound symmetry covariance structure (47) to examine relationships of urinary biomarker concentrations with demographic and socioeconomic factors, reported water use, water sources and storage, and 48-hour recall of product use and food consumption. Linear mixed models include both fixed and random effects to account for intra-individual correlation between repeated measures. For metabolites detected in less than 80% of samples, generalized linear mixed effects models with the logistic link function were used to determine predictors of metabolite detection versus non-detection. In response to potential time trends in phthalate use in manufacturing, we assessed changes in associations between personal care product use and biomarker concentrations over time by evaluating interactions between predictors and year of sample collection. Our analyses met the appropriate statistical assumptions and were conducted using R version 3.2.2 and SAS 9.4 (SAS Institute Inc., Cary, NC), with code available upon request.

Results

The mean age of study participants was 26.8 years, 92% had a high school education or higher, and the majority of women reported a household income below $40 000 per year. Less than 1% of participants reported ever smoking cigarettes, 56% were underweight (BMI $\leq$25 kg/m^2), on average they had one child previous to study participation, and 78% were either married or living with their partner (48).

Distributions and time trends

With the exception of MNP, MHiNCH, and MCOCH, all phthalate and DEHTP metabolites were detected in at least 82% of the 2027 urine samples analyzed, representing widespread prenatal exposure among 994 PROTECT participants (Table 1). MNP and the DINCH metabolites MCOCH and MHiNCH were detected in 29, 18 and 35 percent of PROTECT samples, respectively. However, detection rates of DINCH metabolites increased over time, with MHiNCH detected in 26% of samples in 2013-2014 and 45% of samples in 2015-2017. A similar trend was seen for MCOCH, with detection rates increasing from 8% to 24% in the same time frame, although geometric mean concentrations of both metabolites remained just above the LOD (Supplemental Material Table S1). In comparison to female NHANES participants of child-bearing age, PROTECT women had significantly higher concentrations of MEHP, MEOHP, MECPP, MBP, MHBP, MiBP, MHiBP, and MECPTP, but significantly lower concentrations of MBzP, MCOP, MONP, MCNP, MCPP, and MEHHTP (Table 1).

Within the PROTECT samples, metabolites from the same parent compound tended to be highly correlated with one another, including the DEHP metabolites (MEHP, MEHHP, MEOHP, and MECPP; r >0.7), DBP metabolites (MBP, MHBP; r=0.88), di-isobutyl phthalate (DiBP) metabolites (MiBP, MHiBP; r=0.67), and DEHTP metabolites (r=0.84).

Geometric mean concentrations of MBzP and ΣDBP metabolites differed significantly across the three prenatal study visits, with higher concentrations at the first and second visits compared to the third (Supplemental Material Figure S1). ICCs for SG-corrected metabolite concentrations ranged from 0.16 to 0.57 (Supplemental Material, Table S2). MEP, MBzP and ΣDiBP metabolites had the highest reproducibility across pregnancy with ICCs of 0.46, 0.49, and 0.56, respectively, while MCNP and MONP had the lowest ICCs (0.16 and 0.18).

With the exception of MONP, geometric mean concentrations of all phthalate metabolites significantly decreased over the study period of 2011 to 2017, while concentrations of DEHTP metabolites increased (Figure 1 and Supplemental Material Table S1). For example, ΣDEHP concentrations decreased by almost 50%, from 43 ng/ml in 2011 to 23 ng/ml in 2017. In contrast, although DEHTP metabolites were only measured from 2014 onward, they increased 192% during this time frame.

Predictors of urinary phthalate and phthalate replacement metabolite concentrations

Higher maternal age and education were both associated with higher MCOP, MCNP, and ΣDEHTP metabolites and lower concentrations of MBzP, ΣDEHP and ΣDBP (Table 2). For example, women who were over 30 years of age had on average 10% lower ΣDEHP and 63% higher ΣDEHTP metabolite concentrations compared to women who were less than 25 years of age. Higher education level was also associated with higher odds of detectable MNP concentrations when compared to women with the lowest level of education (Table S3). Similarly, higher income was associated with higher MCOP, MCNP and ΣDEHTP, but lower MBzP and ΣDBP concentrations, with similar patterns observed with employment status (Table 2). Single women had significantly higher MBzP, and MEP, while women who were married or in a domestic partnership had significantly higher MCOP and MCNP. With the exception of the ΣDEHTP metabolites, all phthalate metabolites were significantly higher among women who were obese (BMI ;30 kg/m^2) prior to pregnancy (Table 2). Obese women also had higher odds of detectable levels of both DINCH metabolites (MCOCH and MHiNCH) (Table S3).

The use of perfume, cosmetics and “other hair products” within the 48 hours prior to urine sample collection was associated with 33.8, 12.2 and 22.6 ng/mL higher MEP concentrations, respectively, while hairspray use was negatively associated with MCOP (Table 3). In addition, shampoo and conditioner use was associated with higher odds of detectable MCOCH, while shaving cream use was associated with lower odds of detectable MNP (Table S4). There was a general trend of reported use of detergents, cleaners, or liquid soap associated with lower phthalate metabolite concentrations (Table 3). For example, liquid soap use was associated with lower MCOP and MCPP (Table 3). With the exception of ΣDBP and use of bar soap, there were no significant interactions between personal care product use and year of sample collection. In stratified analyses, the use of bar soap was

marginally associated with higher ΣDBP concentrations in 2011-2013 (p=0.06), but not in later years (2014-2017).

Eating ice cream in the 48 hours prior to sample collection was the only food item associated with higher phthalate metabolite concentrations, specifically MCOP, MCNP, and MCPP. In contrast, women who reported eating chicken or cheese in the previous 48 hours had lower MBzP concentrations compared to women who did not eat these foods, and eating meat was associated with lower concentrations of MONP (Table 4). Additionally, recently drinking milk was associated with decreased odds of detectable MHiNCH (Table S5).

Women who reported their primary drinking water source as public water supplied by the Autoridad de Acueductos y Alcantarillados de Puerto Rico (AAA) had higher concentrations of MBzP (23%), MCPP (11%), ΣDBP (19%) and ΣDiBP (14%) compared to women who reported drinking primarily bottled water (Table 4). Conversely, the primary use of bottled water for cooking and drinking was associated with higher odds of detectable MCOCH and MHiNCH (DINCH metabolites) when compared to AAA water (Table S5). In addition, storing water in a cistern made of plastic, metal, or other materials was associated with higher MONP concentrations and decreased MHiNCH detection. Finally, among women who reported drinking primarily AAA water, those who filtered their drinking water at home had lower MBzP and ΣDBP, but higher MCOP and MCNP concentrations (Table 4).

Discussion

In the present study, we characterize biomarkers of exposure to several phthalates and phthalate replacements among pregnant women participating in the PROTECT birth cohort study. This analysis builds on preliminary work (49) by providing new information on trends in phthalate exposure over time in this cohort, new data on exposure to phthalate replacements such as DEHTP and DINCH, and examining predictors of exposure biomarkers in a much larger sample size, including urinary phthalate and phthalate replacement metabolite measurements from repeated samples collected from 994 pregnant PROTECT participants from 2011 to 2017.

We observed a decreasing trend of almost all urinary phthalate metabolite concentrations, with the exception of MONP, over the course of 7 years in the PROTECT population. The reduction in DEHP, DBP, DEP and benzyl butyl phthalate (BBzP) exposure in the last 16 years has been reported previously in the U.S. general population. This trend might be derived from health concerns regarding these chemicals and subsequent changes in legislation and consumer practices (50), leading to the increasing use of phthalate replacements. Indeed, metabolites of DEHTP – a DEHP structural isomer and phthalate replacement – increased between 2014 and 2017 among PROTECT women. This is consistent with previous reports utilizing spot urine samples from U.S. adults collected from 2000 to 2016, in which an increasing percentage of detection and concentrations were observed for MEHHTP (range: 7 to 91%; <LOD to 3.1 ng/ml_) and MECPTP (range: 18–100%; <LOD to 13.1 ng/ml), while the DEHP metabolites, MEHHP and MECPP decreased 53% and 44.6%, respectively, in the 16 year period (25). Additionally, NHANES results

from 2015-2016 confirm that DEHTP exposure is now widespread within the U.S. population (29).

The observed differences in the biomarker concentrations of the PROTECT women (2010-2017) when compared to the NHANES 2011-2016, could be attributed in part to the time period evaluated and the fact that the NHANES sample included non-pregnant women, who may possibly have different exposure sources and consumer habits than pregnant women in Puerto Rico. The measured urinary phthalate and phthalate replacement metabolites had low to moderate reproducibility during pregnancy. Compared to two cohorts of pregnant women in the mainland U.S. (51, 52), the reproducibility of MiBP among PROTECT women was similar, while the reproducibility of DEHP metabolites, MBzP, MCPP, MEP and MBP showed more variability across studies. These variances could be attributed to differences in consumer habits and product usage related to product access or cultural habits, as well as timing (53) or frequency of the measurements.

We observed associations between higher MBzP and ΣDBP concentrations with demographic and socioeconomic characteristics such as being single, unemployed, and with lower age, education, and income. On the other hand, we observed that being married, employed, or higher age, education and income was associated with higher MCOP, MCNP and ΣDEHTP metabolite concentrations. Associations between markers of phthalate exposures and socioeconomic factors have been reported previously among pregnant women (54-56). Together, these findings suggest different sources of phthalate and phthalate replacement exposure according to demographic and socioeconomic characteristics, and potential differences in phthalate usage in various consumer products. For example, diet (49, 57-59), household products, and personal care products are important known sources of phthalate exposures (60). However, while diet is influenced by diverse factors, such as race, socioeconomic status and education (61-63), the factors that affect the access or decision to buy certain consumer products are unclear. For instance, the higher price of phthalate-free alternatives (64) and the awareness of the effects of chemical exposures might play a role in purchasing decisions. Women with higher education might consider environmental exposures as “dangerous” and consequently try to consume organic food, avoid fast food, and buy eco-friendly products (65), whereas women with lower income may not be able to do so. For these reasons, it is possible that the observed differences in phthalate and phthalate replacement exposures by socioeconomic variables might be explained by the amount and quality of purchased dietary and personal care products.

Urinary concentrations of MBzP and MONP, as well as detection of MNP and DINCH metabolites, were negatively associated with the consumption of dairy and meat products. This is somewhat consistent with findings from The Infant Development and Environment Study (TIDES) in which the frequency of consumption of dairy products was negatively associated in a dose-response manner to MiBP and ΣDEHP urine concentrations (57). However, in the present study, ice cream consumption was associated with increased concentrations of several phthalate metabolites (MCOP, MCNP and MCPP). This may possibly be due to the high fat content of ice cream, as previous studies suggest that fatty foods may increase migration of phthalates from plastic food packaging into food products (66).

Phthalate exposure through the use of personal care products has been reported extensively in the literature (60, 67-69), and our findings in the present study are generally consistent with previous reports. For example, perfume, cosmetics, and hair product use were all positively associated with urinary MEP. Personal care product use was not associated with ΣDEHTP and its metabolites and inconsistently associated with detection of DINCH metabolites, which is somewhat expected, as these phthalate replacements may be typically used for other applications (e.g. plastics) (70). We also observed negative associations between cleaning products, such as liquid soap or detergent, and a number of phthalate metabolites. This may be consistent with previous research in which hand-washing was associated with a 35-75% reduction of phthalates on hands (71), suggesting a reduction in exposure by the removal of phthalates from the skin.

Interestingly, urinary phthalate concentrations (MBzP, MCPP, ΣDBP, and ΣDiBP), and detection of DINCH metabolites were higher among women whose primary drinking water source was public water compared to bottled water. These findings are in the context of extensive contamination of water resources in Northern Puerto Rico (72, 73) by phthalates derived from rainwater runoff and industrial (mining, pharmaceutical) and domestic activities (74). Moreover, wastewater treatment plants do not remove 100% of phthalates from discharged water, which may further contaminate additional water sources (75). Additionally, DEHTP could leach from polyethylene terephthalate water bottles, which could potentially explain higher, although not statistically significant, ΣDEHTP metabolite concentrations among women who reported using bottled water for drinking and cooking compared to women using public water.

The relation between patterns of consumer product use and environmental exposures is complex and influenced by several factors, such as the time period, socioeconomic characteristics, location, housing, diet and physiology (76), some of which may also differ between Puerto Rico and the mainland U.S. This makes it complicated to fully characterize sources of phthalate and phthalate replacement exposure, especially considering the diversity of consumer products on the market (77), regional differences in products available in Puerto Rico and mainland U.S., temporal changes in product composition, and the frequent appearance of new replacement chemicals (78). One limitation of the present study is the lack of information on potentially important sources of phthalate and phthalate replacement exposure, such as medical devices, other housing products and characteristics, childcare products, toys, and textiles (78). Due to the relatively low detection frequency of MNP and DINCH metabolites, we also were not able to assess associations between urinary concentrations and product use or evaluate temporal changes of these chemicals during pregnancy and during the study period. In addition, we were unable to assess metabolite concentrations in relation to use of fragrance-free products due to a very small number of women who reported using these products. Finally, due to the multiple comparisons evaluated in this analysis, the role of chance in our findings should not be ruled out. Despite these limitations, one strength of the study is repeated measurements of phthalate and phthalate replacement metabolites across three separate visits in pregnancy. Phthalates are quickly metabolized and excreted, thus have short biological half-lives (hours), so repeated measurements allow us to more accurately characterize exposure during pregnancy. In addition, urinary phthalate levels reflect only recent exposure, so concurrent collection of

product use information in the 48 hours prior to sample collection is a strength that allowed us to identify several predictors of urinary phthalate and phthalate replacement metabolite levels. Additionally, we were able to assess important temporal trends in exposure biomarker levels across 7 years among PROTECT women.

Conclusion

The current study characterized temporal changes in and predictors of urinary phthalate and phthalate replacement metabolites among pregnant women in Puerto Rico in the context of changing trends in the global use of phthalates and their replacements. Our results suggest the increasing replacement of traditionally used phthalates for alternative plasticizers, such as DEHTP. Future epidemiological studies should evaluate sources of, and health effects related to exposure to phthalate replacements, such as DINCH and DEHTP, as these exposures may be increasing, with unknown effects on health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Disclaimer:

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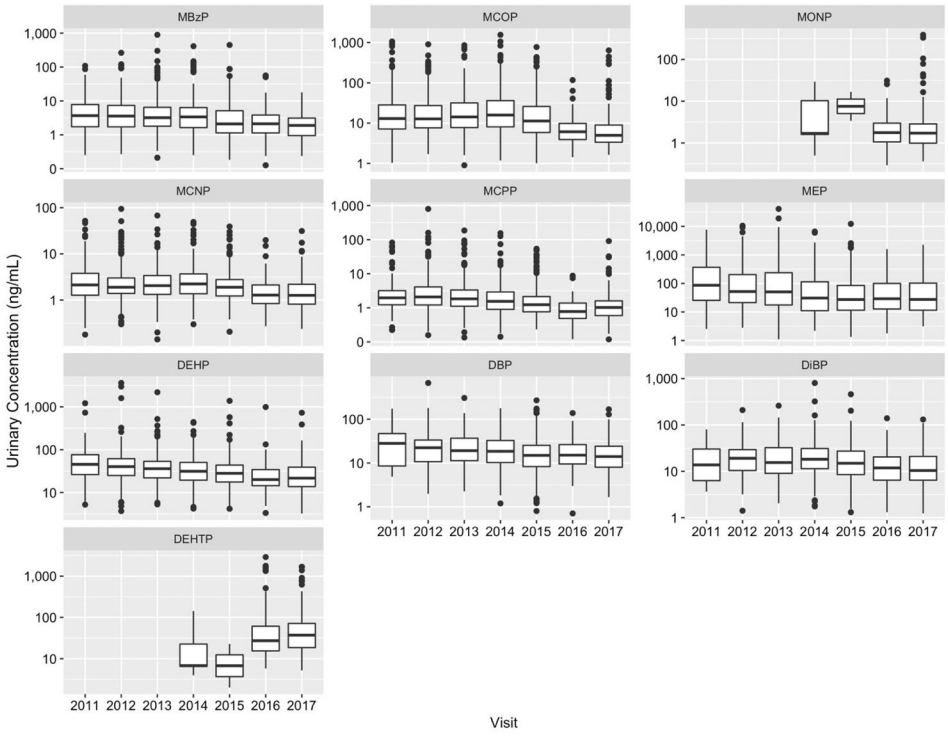

Figure 1.

Comparison of SG-corrected urinary phthalate and phthalate replacement metabolite concentrations by year (2011-2017).

Note: Temporal trends for all metabolites were statistically significant ($p<0.05$), with the exception of MONP. The y-axis is presented on the logarithmic scale.

Table 1.

Comparison of uncorrected urinary phthalate and phthalate replacement metabolite concentrations (ng/mL) in 994 pregnant women from Puerto Rico in 2011–2017 and NHANES female participants aged 16-49 years from 2009-2016.

Parent	Metabolite	Cohort	N (samples)	N(women)	% >LOD	GM	GSD	10th	25th	50th	75th	90th	Max.	*p* value[1]
DEHP	MEHP	PROTECT	2024	933	84.8	2.5	2.9	< LOD	1.1	2.6	5.1	9.2	620	<0.01
		NHANES	1517	1 517	72.4	1.7	3.0	< LOD	0.6	1.6	3.3	7.1	160	
	MEHHP	PROTECT	2022	932	99.6	7.8	2.9	1.9	4.2	8.4	16	26.9	1040	0.52
		NHANES	1517	1517	99.7	8.0	3.3	1.7	3.9	8.2	16.9	32.7	1030	
	MEOHP	PROTECT	2023	930	99.7	6.7	2.9	1.7	3.6	7.3	13.8	22.6	690	<0.01
		NHANES	1517	1517	99.5	5.5	3.2	1.2	2.6	5.8	11.4	21.6	585	
	MECPP	PROTECT	2026	934	100	14.5	2.6	4.4	8.1	14.7	27.1	44.2	1200	0.02
		NHANES	1517	1517	99.9	13.3	3.0	3.2	6.3	13.7	26.6	50.6	1422	
BBzP	MBzP	PROTECT	2025	935	95.5	2.8	3.7	0.5	1.2	2.8	6.4	13.8	1410	<0.01
		NHANES	1517	1517	98.5	5.7	3.8	0.9	2.3	5.9	15.4	29.4	340	
DNP	MCOP	PROTECT	2014	929	100	12.6	3.5	2.9	5.5	11.3	25.6	65.3	2460	<0.01
		NHANES	1517	1517	99.7	15.3	4.4	2.7	5.5	12.9	40.4	122	1363	
	MNP	PROTECT	1201	576	29.4	0.9	2.7	< LOD	< LOD	< LOD	1.1	3.5	299	NT
		NHANES	1517	1517	45.2	1.2	3.4	0.5	0.5	0.6	2.0	8.2	436	
	MONP	PROTECT	314	148	89.8	1.7	3.4	< LOD	0.8	1.6	3.4	6.2	512	<0.01
		NHANES	348	348	92.8	2.3	3.4	0.5	1.0	2.1	3.8	12.7	111	
DDP	MCNP	PROTECT	2010	925	98.7	1.9	2.5	0.6	1.1	1.9	3.2	6.0	79.1	<0.01
		NHANES	1517	1517	98.2	2.5	3.1	0.6	1.2	2.3	4.9	10.0	876	
DiNP	MONP	PROTECT	314	148	89.8	1.7	3.4	< LOD	0.8	1.6	3.4	6.2	512	<0.01
		NHANES	348	348	92.8	2.3	3.4	0.5	1.0	2.1	3.8	12.7	111	
DOP, DBP, others	MCPP	PROTECT	2017	930	91.1	1.6	3.2	< LOD	0.8	1.5	3.0	6.4	885	<0.01
		NHANES	1517	1517	90.4	2.1	3.9	< LOD	0.8	2.0	5.1	13.2	810	
DEP	MEP	PROTECT	2017	932	99.9	49.3	5.6	6.6	12.8	36.3	168	554	64500	0.27
		NHANES	1517	1517	99.9	52.4	4.7	8.4	17.5	46.4	140	405	30321	
DBP	MPB	PROTECT	2027	935	99.4	15.4	3.2	3.4	7.6	16.7	33.5	63.5	544	<0.01
		NHANES	1517	1517	97.3	11.5	3.6	2.4	6.0	13.5	26.1	47.7	1079	
	MHBP	PROTECT	1199	574	83.8	1.3	2.9	< LOD	0.6	1.4	2.9	5.3	60.1	<0.01

Parent	Metabolite	Cohort	N (samples)	N(women)	% >LOD	GM	GSD	10th	25th	50th	75th	90th	Max.	*p* value[1]
DiBP	MiBP	NHANES	392	392	72.7	0.9	2.6	0.3	0.3	1.0	1.8	3.1	94.3	<0.01
		PROTECT	2026	935	98.8	10.0	3.1	2.3	4.9	10.5	20.5	39.1	964	
	MHiBP	NHANES	1517	1517	98.7	8.8	3.1	2.0	4.3	9.6	19.3	33.7	627	<0.01
		PROTECT	1203	579	97.9	4.2	3.0	1.0	2.1	4.2	8.7	17.6	133	
DINCH	MHiNCH	NHANES	392	392	94.6	3.2	3.1	0.7	1.5	3.5	7.0	13.2	52.7	NT
		PROTECT	1698	819	34.8	0.4	2.1	< LOD	< LOD	< LOD	0.6	1.2	208	
	MCOCH	NHANES	1102	1102	40.1	0.5	2.5	< LOD	< LOD	< LOD	0.7	1.6	168	NT
		PROTECT	1204	579	17.5	0.4	1.8	< LOD	< LOD	< LOD	< LOD	0.7	106	
DEHTP	MECPTP	NHANES	348	348	60.1	0.7	2.4	< LOD	< LOD	0.6	1.0	2.5	37.4	<0.01
		PROTECT	314	148	100	29.8	3.9	6.4	12.1	24.9	58.3	160	2120	
	MEHHTP	NHANES	348	348	100	24.3	5.0	3.7	7.5	19.4	68.5	245	4312	<0.01
		PROTECT	314	148	96.5	4.7	4.1	0.8	1.7	4.4	11.1	26.3	217	
		NHANES	348	348	97.4	5.9	4.6	1.0	1.9	5.1	13.6	54.1	651	<0.01

Abbreviations: NHANES, National Health and Nutrition Examination Survey; PROTECT, Puerto Rico Testsite for Environmental Contamination Threats; DDP, Di-isodecyl phthalate; DOP, di-n-octyl phthalate; GM, geometric mean; GSD, geometric standard deviation; NT, not tested.

[1] p-value of two-sample t-test.

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Table 2.

Geometric means[1] of SG-corrected urinary phthalate and phthalate replacement metabolite concentrations (ng/mL) according to maternal characteristics.

Variables	n	MBzP	MCOP	MONP	MCNP	MCPP	MEP	ΣDEHP	ΣDBP	ΣDiBP	ΣDEHTP
Maternal age (years)											
<25	353	**4.1**	**12.4**	2.0	**2.0**	1.7	**48.5**	**35.0**	**19.1**	16.9	**27.9**
25-30	336	**2.6**	**13.5**	1.8	**2.0**	1.7	**52.3**	**30.4**	**14.2**	14.4	**40.1**
>30	250	**2.5**	**15.2**	2.0	**2.2**	1.7	**60.6**	**31.4**	**14.5**	14.0	**45.6**
p value		**<0.001**	**0.01**	0.79	**0.05**	0.82	**0.05**	**0.03**	**<0.001**	0.07	**0.01**
Maternal education (years)											
<12	73	**4.0**	**10.8**	1.3	**1.8**	1.9	52.8	33.3	**21.1**	20.0	**16.4**
12	112	**4.5**	**10.4**	1.6	**1.9**	1.8	39.6	32.1	**20.5**	16.5	**21.6**
>12	719	**2.8**	**14.5**	2.0	**2.1**	1.7	54.9	32.2	**14.9**	14.7	**42.3**
p value		**<0.001**	**<0.001**	0.21	**0.02**	0.19	0.42	0.62	**<0.001**	0.06	**0.003**
Marital status											
Single	197	**3.8**	**11.6**	1.9	**1.9**	1.8	**64.3**	33.3	17.4	15.5	35.7
Married[2]	709	**2.8**	**14.2**	1.9	**2.1**	1.7	**50.2**	32.0	15.5	15.1	38.8
p value		**<0.001**	**0.01**	0.81	**0.04**	0.69	**0.02**	0.47	0.14	0.68	0.80
Employment status											
Unemployed	342	**3.8**	**11.9**	1.9	1.9	1.8	49.8	**34.5**	**19.9**	**17.8**	**27.9**
Employed	558	**2.6**	**14.8**	1.9	2.1	1.7	55.4	**30.8**	**14.0**	**14.0**	**43.9**
p value		**<0.001**	**<0.001**	0.71	0.07	0.43	0.38	**0.01**	**<0.001**	**<0.001**	**0.01**
Income Status (USD)											
<$20K	349	**3.6**	**11.6**	1.8	**1.9**	1.6	51.0	32.7	**18.4**	16.2	**32.2**
$20 - <$40K	236	**2.7**	**15.4**	1.9	**2.2**	1.7	52.0	32.4	**14.2**	15.0	**40.8**
≥$40K	186	**2.5**	**16.2**	1.9	**2.2**	1.8	58.2	31.3	**13.9**	14.4	**52.1**
p value		**<0.001**	**<0.001**	0.69	**0.01**	0.18	0.40	0.37	**<0.001**	0.23	**0.02**
Prepregnancy BMI (kg/m^2)											
≥25	491	**2.9**	**13.0**	**1.7**	**2.0**	**1.6**	**48.6**	**31.6**	**14.9**	**14.8**	39.0
>25 to ≤30	245	**3.1**	**14.0**	**1.9**	**2.1**	**1.8**	**57.1**	**31.5**	**16.1**	**14.9**	39.7
>30	145	**3.5**	**15.9**	**2.6**	**2.2**	**2.1**	**66.7**	**37.3**	**19.6**	**18.7**	40.4
p value		**0.01**	**0.02**	**0.01**	**0.03**	**<0.001**	**0.01**	**0.02**	**0.004**	**0.04**	0.82

[1] Estimated from linear mixed effects models;

[2] Married or living together.

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Table 3.

Geometric means[1] of SG-corrected urinary phthalate and phthalate replacement metabolite concentrations (ng/mL) according to self-reported use of personal care and household products in the 48 hours prior to sample collection.

Product	Use	n	MBzP	MCOP	MONP	MCNP	MCPP	MEP	ΣDEHP	ΣDBP	ΣDiBP	ΣDEHTP
Cleaning and laundry products												
	Yes	452	3.1	14.7	1.6	2.1	1.8	54.1	33.3	16.5	16.2	33.5
Detergent	No	310	3.2	15.2	2.1	2.1	1.8	57.7	33.9	15.8	15.5	30.8
	p value		0.38	0.5	0.07	0.95	0.52	0.34	0.28	0.62	0.82	0.63
	Yes	423	3.1	14.2	**1.6**	2.1	1.8	57.8	33.0	16.3	15.5	34.2
Cleaner	No	339	3.3	16.0	**2.1**	2.1	1.8	52.7	34.3	16.1	16.5	30.1
	p value		0.48	0.09	**0.04**	0.93	0.69	0.33	0.11	0.87	0.24	0.73
	Yes	641	3.1	**14.6**	1.8	2.1	**1.8**	54.8	33.4	16.1	15.7	33.0
Liquid Soap	No	120	3.8	**17.5**	2.3	2.2	**2.1**	61.3	34.5	17.3	17.4	24.2
	p value		0.11	**0.02**	0.38	0.38	**0.04**	0.39	0.78	0.32	0.06	0.45
	Yes	693	3.2	14.9	1.8	2.12	1.8	55.9	33.7	16.3	16.0	33.1
Bar Soap	No	68	3.0	15.7	1.7	2.07	1.9	51.6	31.1	15.3	14.8	28.1
	p value		0.8	0.34	0.76	0.64	0.31	0.2	0.37	0.83	0.74	0.72
	Yes	390	3.2	14.4	1.6	2.1	1.78	54.7	33.9	16.8	16.4	34.9
Fabric softener	No	372	3.2	15.6	2.0	2.1	1.83	56.4	33.2	15.6	15.4	30.0
	p value		0.89	0.12	0.13	0.43	0.59	0.39	0.81	0.34	0.36	0.50
Personal Care Products												
	Yes	581	3.20	15.0	1.7	2.1	1.8	58.4	33.6	16.2	15.8	32.1
Lotion	No	180	3.18	14.6	2.2	2.1	1.7	46.7	33.2	16.3	16.3	32.8
	p value		0.26	0.99	0.16	0.79	0.35	0.11	0.44	0.24	0.74	0.91
	Yes	62	2.9	12.3	1.8	2.1	1.7	50.8	32.7	17.8	16.5	41.3
Shaving cream	No	700	3.2	15.2	1.8	2.1	1.8	56.0	33.6	16.1	15.8	31.1
	p value		0.21	0.06	0.72	1.00	0.32	0.49	0.65	0.94	0.65	0.42
	Yes	627	3.1	14.8	1.9	2.1	1.8	**62.9**	33.1	16.1	15.6	31.9
Perfume	No	135	3.5	15.6	1.5	2.2	1.9	**30.1**	36.0	16.9	17.6	33.8
	p value		0.46	0.39	0.27	0.17	0.4	**<0.001**	0.23	0.69	0.32	0.86
Cosmetics	Yes	574	3.1	15.3	1.8	2.2	1.8	**58.9**	33.7	16.3	15.7	31.3

Product	Use	n	MBzP	MCOP	MONP	MCNP	MCPP	MEP	ΣDEHP	ΣDBP	ΣDiBP	ΣDEHTP
	No	188	3.5	13.8	1.9	2.0	1.9	**46.7**	33.0	15.8	16.4	34.8
	p value		0.3	0.3	0.63	0.24	0.44	**0.04**	0.76	0.83	0.75	0.79
	Yes	248	3.3	**13.5**	2.2	2.0	1.8	64.4	33.5	15.9	16.4	40.0
Hairspray	No	514	3.1	**15.7**	1.6	2.2	1.8	51.6	33.4	16.3	15.7	29.1
	p value		0.93	**0.03**	0.11	0.19	0.55	0.08	0.96	0.53	0.55	0.17
	Yes	541	3.2	14.5	1.8	2.1	1.8	56.1	33.7	16.5	16.0	37.5
Shampoo	No	221	3.1	16.1	1.9	2.1	1.8	54.4	33.1	15.6	15.8	23.4
	p value		0.84	0.08	0.75	0.65	0.88	0.59	0.57	0.41	0.74	0.08
	Yes	526	3.3	14.4	1.80	2.1	1.8	55.6	33.8	16.6	16.0	37.4
Conditioner	No	235	3.1	16.2	1.82	2.1	1.8	55.8	32.9	15.4	15.6	24.4
	p value		0.41	0.06	0.9	0.87	0.93	0.8	0.42	0.24	0.61	0.10
	Yes	122	3.2	15.5	1.9	2.3	2.0	**71.3**	35.6	16.8	17.0	37.4
Other Hair products	No	483	3.2	14.8	1.4	2.2	1.8	**48.7**	32.2	17.3	16.3	25.9
	p value		0.93	0.83	0.41	0.63	0.36	**0.05**	0.32	0.76	0.80	0.76
	Yes	212	3.2	13.7	1.8	2.1	1.7	61.6	32.8	15.7	16.0	24.6
Nail Polish	No	550	3.2	15.4	1.8	2.1	1.8	53.6	33.8	16.4	15.9	35.3
	p value		0.65	0.07	0.74	0.85	0.13	0.12	0.48	0.44	0.97	0.21
Other household products												
	Yes	75	3.4	**18.4**	1.7	2.3	1.9	61.8	35.6	16.5	16.6	32.6
Vinyl gloves	No	687	3.2	**14.6**	1.8	2.1	1.8	55.0	33.3	16.2	15.8	32.2
	p value		0.72	**0.05**	0.87	0.18	0.65	0.21	0.38	0.63	0.81	0.96
	Yes	475	3.2	14.7	1.9	2.1	1.8	55.4	33.3	16.2	15.8	29.8
Vinyl curtain	No	287	3.1	15.3	1.7	2.1	1.8	55.9	33.8	16.1	16.0	35.6
	p value		0.86	0.33	0.60	0.54	0.56	0.57	0.68	0.88	0.40	0.45
	Yes	24	3.6	16.4	2.3	2.3	2.2	49.9	38.9	19.8	18.5	38.1
Paint	No	738	3.2	14.9	1.8	2.1	1.8	55.9	33.3	16.1	15.8	32.3
	p value		0.98	0.39	0.42	0.33	0.12	0.35	0.20	0.35	0.51	0.85

[1]Estimated from linear mixed effects models.

Table 4.

Geometric means[1] of SG-corrected urinary phthalate and phthalate replacement metabolite concentrations (ng/mL) according to self-reported food consumption and drinking water characteristics 48 hours prior to sample collection.

Food	Use	n	MBzP	MCOP	MONP	MCNP	MCPP	MEP	ΣDEHP	ΣDBP	ΣDiBP	ΣDEHTP
Dairy products												
	Yes	678	3.1	13.7	1.8	2.1	1.7	54.4	32.9	15.9	15.2	40.1
Milk	No	145	2.9	14.6	2.2	2.0	1.7	50.7	30.0	15.8	14.7	35.9
	p value		0.64	0.32	0.36	0.54	0.85	0.37	0.12	0.90	0.32	0.43
	Yes	694	**2.9**	13.9	1.9	2.0	1.7	53.8	32.4	16.0	15.0	40.5
Cheese	No	129	**4.0**	13.3	1.5	2.0	1.7	53.9	32.7	15.3	15.8	31.7
	p value		**0.002**	0.69	0.40	0.89	0.56	0.78	0.50	0.31	0.65	0.55
	Yes	288	3.0	**16.0**	1.7	**2.3**	**1.9**	53.3	33.6	16.2	15.1	39.5
Ice cream	No	535	3.0	**12.8**	1.9	**1.9**	**1.6**	54.1	31.8	15.7	15.2	39.1
	p value		0.80	**<0.001**	0.38	**<0.001**	**<0.001**	0.77	0.15	0.92	0.54	0.99
Meat												
	Yes	495	3.0	13.8	**1.7**	2.0	1.8	56.3	32.7	15.7	15.0	35.8
Meat[2]	No	328	3.2	13.8	**2.2**	2.0	1.6	49.9	32.0	16.1	15.3	45.4
	p value		0.76	0.80	**0.03**	0.92	0.29	0.26	0.44	0.85	0.75	0.25
	Yes	639	**2.9**	13.9	1.9	2.0	1.7	51.8	32.1	15.8	15.2	39.7
Chicken	No	184	**3.4**	13.5	1.6	2.0	1.8	61.6	33.5	16.0	14.8	37.1
	p value		**0.02**	0.99	0.56	0.95	0.26	0.34	0.59	0.95	0.72	0.77
	Yes	159	3.1	12.7	1.9	1.9	1.6	63.2	30.6	15.7	15.1	42.5
Fish	No	664	3.0	14.1	1.9	2.1	1.7	51.9	32.9	15.9	15.1	38.5
	p value		0.14	0.15	0.77	0.08	0.15	0.07	0.24	0.58	0.66	0.34
Drinking Water												
	AAA	501	**3.4**	14.2	2.1	2.1	**1.8**	53.0	33.1	**17.6**	**16.5**	31.1
Water source	Bottled	361	**2.6**	13.2	1.8	2.0	**1.6**	52.3	31.7	**14.3**	**14.2**	42.1
	p value		**<0.001**	0.26	0.27	0.68	**0.01**	0.83	0.20	**0.002**	**0.04**	0.10
	Yes	591	3.1	13.7	**2.1**	2.1	1.7	52.0	33.8	14.2	14.0	29.0
Store in Cistern[3]	No	290	2.9	13.8	**1.2**	2.1	1.8	56.1	31.6	16.6	15.9	40.0
	p value		0.28	0.92	**0.003**	0.94	0.2	0.41	0.15	0.06	0.15	0.11

Food	Use	n	MBzP	MCOP	MONP	MCNP	MCPP	MEP	ΣDEHP	ΣDBP	ΣDiBP	ΣDEHTP
Filter water[4]	Yes	362	**2.8**	**17.4**	1.6	**2.4**	2.0	54.5	33.4	**14.6**	16.0	39.4
	No	145	**3.7**	**13.1**	2.3	**1.9**	1.8	54.3	33.2	**19.0**	16.9	29.4
	p value		**0.003**	**0.001**	0.26	**<0.001**	0.25	0.88	1.0	**0.02**	0.79	0.51

[1] Estimated from linear mixed effects models;

[2] Meat=beef, veal, lamb, or pork;

[3] Cisterns made of plastic, metal, or other materials;

[4] Among women who reported AAA as primary drinking water source.