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Gursharan K. Claire Date

Feminine hygiene products:
A potential source of phthalate exposure among pregnant African American women in Atlanta, GA

By

Gursharan K. Claire
Masters of Public Health

Environmental Health

Dana Boyd Barr, PhD
Committee Chair

Anne Dunlop MD, MPH
Committee Member

Paige Tolbert PhD
Committee Member

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By

Gursharan K. Claire

Bachelor of Science
University of California, Irvine
2014

Thesis Committee Chair: Dana Boyd Barr, Ph. D.

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Abstract

Feminine hygiene products:
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By Gursharan K. Claire

Background: Phthalate acid esters, more familiarly known as phthalates, are a family of industrial chemicals that are commonly used in a variety of consumer products. Phthalate exposure is considered an environmental public health concern, because of their well-documented developmental, endocrine, and reproductive system toxicity. Phthalate exposure in the United States has been reported higher among African Americans than any other racial/ethnic group. Little research has been conduct on feminine hygiene product use as possible source of phthalate exposure.
Objective: To evaluate feminine hygiene products, as a hypothesized source of phthalate exposure, among pregnant African American women in Atlanta, GA.
Methods: The study population consisted of pregnant African American women, approximately 8-14 weeks' gestation with singleton pregnancies, who were free of chronic medical conditions, living in Atlanta, GA. Via survey questionnaire, women self-reported the use of feminine hygiene products: vaginal douches, feminine sprays, and vaginal creams. Spot urine samples were taken at the time of the survey. Samples were analyzed for phthalate concentration using HPLC-MS/MS. Descriptive statistics and univariate analysis was conducted on natural log transformed metabolite concentrations to determine differences in exposure among feminine hygiene product users and non-users. Multivariate logistic regression models were constructed to further examine the association between feminine hygiene product use and urinary phthalate metabolite concentrations.
Results: Both unadjusted and adjusted multivariate linear models did not report significant association between phthalate metabolite concentrations and self-reported feminine product use. In an adjusted model, women who reported any type of feminine product use in the past month, had a 32.53 % (95% CI: -66.01, 133.95) lower concentration of ΣMBzP than non-users (P-trend= 0.0339), suggesting a negative association. There was evidence of a positive association between vaginal spray use and MEP metabolite concentration (152.43% change; CI: -18.16, 778.67), but it did not reach statistical significance.
Conclusion: This study is only one, of few, to assess self-reported feminine hygiene product use as a source of phthalate metabolite exposure. Although this pilot analysis presented null results, evaluation can be conducted as more data is collected on this cohort. Since this study did not make any direct connections to adverse health effects, there is potential for further analysis and follow up with the infants in this study population as well.

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INTRODUCTION

Phthalates

Phthalate acid esters, more familiarly known as phthalates, are a family of industrial chemicals used in an array of consumer products such as personal care products, cosmetics, toys, food containers, paints, medical devices, and industrial solvents, adhesives, and sealants. Phthalates are most commonly used as plasticizers, providing softness to otherwise ridged materials. They are also used in products to hold color or fragrance, applied on consumer goods as a final varnish, and provide a coating on pharmaceutical pills allowing for the timed release of medication (ATSDR, 1995, 1997, 2001, 2002). An examination of the 1999-2000 National Health and Nutrition Examination Survey (NHANES) found detectible levels of phthalates among over 75 percent of samples, suggesting widespread human exposure in the United States (Silva et al., 2004).

Because they are not chemically bound, phthalates can easily be absorbed dermally, inhaled, ingested, or directly administered through medical equipment treated with phthalate plasticizers (Yan et al., 2009). After human exposure compounds are quickly metabolized into their respective monomers, half-lives of less than 24 hours, and undergo further oxidation and/or glucuronidation, which makes them more hydrophilic (ATSDR, 1995, 1997, 2001, 2002). Once compounds are more water soluble, they can be easily excreted via urine or feces (ATSDR, 1995, 1997, 2001, 2002).

Phthalates are typically categorized into two groups (table 1): Low molecular weight phthalates (LMWPs) and high molecular weight phthalates (HMWPs).

LMWPs include diethyl phthalate (DEP), di-n- butyl phthalate (DBP), diisobutyl phthalate (DiBP), and benzyl butyl phthalate (BBzP), which produce the following monoester metabolites monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), monoisobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), and mono-n-butyl phthalate (MnBP). HMWPs include di-2-ethylhexyl phthalate (DEHP) which forms the following monoester metabolites mono(2-ethyl-5-carboxypentyl) phthalate (MECPP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono(2-ethyl-5-hydroxyhexyl) (MEHHP), and mono(2-ethylhexyl) phthalate (MEHP).

Health effects

Phthalate exposure is an environmental public health concern because of their ubiquitous presence in the environment and their well-documented developmental, endocrine, and reproductive system toxicity. In animal studies, phthalates and their metabolites have demonstrated antiandrogenic effects during prenatal stages (Lee et al., 2007; Moore et al., 2001; Mylchreest et al., 1998; Parks et al., 2000). Phthalates interfere with normal androgenic signaling leading to an array of reproductive abnormalities (Hotchkiss et al., 2004; Mylchreest et al., 1998; Parks et al., 2000). Some observed effects include reduced mass among androgenic reliant tissues, such as seminal vesicles, epididymis, and prostate (Agarwal et al., 1986; Ema et al., 2001; Foster et al., 2001; Mylchreest et al., 1998). Phthalates also increase the incidence of hypospadias, decrease anogenital distance, create testicular lesions, and delay the onset of puberty milestones in male rodents (Agarwal et al., 1986; Ema et al., 2001; Foster et al., 2001; Mylchreest et al., 1998). The phthalate DPB and its metabolite MnBP have been specifically linked to reduced

testosterone production in male rats (Mylchreest et al., 2002). Several animal studies indicate that testes are targeted by the phthalate DEPH as well, resulting in decreased testicular tissue weight (ATSDR, 2002).

The female reproductive system is believed to be less sensitive to phthalate exposure than the male reproductive system. Nevertheless, animal study data does suggest that chronic exposure to phthalates leads to estrogen deficiency, anovulatory menstruation cycles, and polycystic ovary syndrome (Davis et al., 1994). In a more recent study, DEHP and its specific metabolite MEHP was linked to the suppression of estradiol production, resulting in anovulation (Lovekamp-Swan et al., 2003). Underdeveloped or absent reproductive systems were observed among female rat offspring who were exposed to DBP, consistent with Mayer-Rokitansky-Küster-Hauser Syndrome (Hannas et al., 2013).

Data on human phthalate exposure and related health effects is limited. An epidemiological study provided recent evidence that prenatal phthalate exposure was associated with reduced anogenital distance in male infants (Swan et al., 2005). A study that examined the relationship between environmental DEP exposure among humans found that phthalate exposure is associated with increased DNA sperm damage (Duty et al., 2003). Recent studies have found phthalate exposure is associated with increased risk for diabetes (James-Todd et al., 2012) and endometriosis (Reddy et al.) among adult women. DEP exposure among postmenopausal women has been linked to elevated breast density and increased risk for breast cancer (Sprague et al., 2013). A study that examined DEHP exposure during pregnancy found that detectable metabolite concentration in cord blood was

associated with shorter pregnancies and newborns with significantly lower gestational age (Latini et al., 2003). A longitudinal investigation found increased biomarkers of oxidative stress among couples who were highly exposed to phthalates, and researchers suggest phthalate exposure as a mechanism for observed diminished fertility (Guo et al., 2014).

Phthalate Exposure

Phthalate exposure in the United States varies among gender, racial/ethnic groups, and socioeconomic status (SES). Analysis of survey data from the National Health and Nutrition Examination (NHANES) 1999- 2000 found higher concentrations of MEP, MBP, and MBzP among females than males (Silva et al., 2004). Several studies have found that both black females and males have higher levels of DEP metabolites compared to their Caucasian counterparts (Duty et al., 2003; Serrano et al., 2014; Silva et al., 2004; Wolff et al., 2010). Lower SES level has been associated with elevated levels of DBP and its metabolite (Koo et al., 2004; Serrano et al., 2014). At this time, little is known about the underlying reason for this observed difference in phthalate exposure among socioeconomic groups.

Personal care products

Personal care products, such as cosmetics, perfumes, hair spray, hair gel, nail polish, body lotion, deodorant, etc. have been assessed and many have levels of detectable phthalates (Koniecki et al., 2011; Koo et al., 2004). Phthalates, used as industrial plasticizers and solvents, are used in personal care products to hold color and fragrance (ATSDR, 1995, 1997, 2001, 2002). Several studies have found associations between fragranced personal care products and higher urinary

phthalate concentrations among product users and non-users (Braun et al., 2014; Duty et al., 2005; Just et al., 2010; Parlett et al., 2013). Researchers found that for women of reproductive age, personal care products are an important exposure pathway to examine, because they use several products several times throughout the day (Parlett et al., 2013).

Feminine care product used vaginally, which include douches, deodorizing sprays, vaginal creams, and tampons, may be a potential source of phthalate exposure among women of reproductive age. These products are often times overlooked exposure sources for phthalates. Because these products contain added fragrances (Brotman et al., 2008; Houlihan, 2002), and a possible source of phthalate exposure, feminine hygiene products in particularly should warrant further investigation. A recent study conducted by Branch et al., aimed to investigate the association between feminine product use and phthalate concentrations, among women or reproductive age, using National Health and Nutrition Examination Survey(NHANES) 2001-2004 data. Researchers found significant association between phthalate concentrations and vaginal douching, the practice of cleansing the vagina with a premade solution, to rid body of vaginal "odors" (Brotman et al., 2008). Specifically, they found that self-reported vaginal douche users had higher concentrations of urinary DEP metabolite than non-users (Branch et al., 2015). They also observed a greater proportion of vaginal douche user, feminine spray users, feminine powder users, and wipe/towelette users, among African American Women than Caucasian or Mexican American women (Branch et al., 2015), which was consistent with prior literature (Duty et al., 2005; Wolff et al., 2010). These

findings allow for us to better understand a possible source of racial/ethnic disparity in phthalate exposure among women of reproductive age.

Analysis at this time will aim to evaluate feminine hygiene products, as a hypothesized source of phthalate exposure, among pregnant African American women in Atlanta, GA. The particular feminine products of exposure in this analysis include: vaginal douches, feminine sprays, and vaginal creams. Urinary metabolite concentrations will be compared between product users and non-users, for each respective product type. With my findings, I aim to recommend further examination of chemicals in feminine hygiene products and their effects on infant development.

METHODS

Research Context

Researchers at the Center for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM^2) at Emory University have started a longitudinal cohort study which aims to investigate the dynamic interaction of prenatal and postnatal environmental exposures, and their effect on infant health. The cohort includes pregnant African American women in the metropolitan Atlanta area and examines how environmental exposures - toxicant exposures, the microbiome, and the metabolome - affect birth outcomes, and infant microbiome and neurological development.

The study examines prenatal exposure at three time points: maternal visit #1 (18-14 weeks' gestation), home visit #1 (20-24 weeks' gestation), and then again at

maternal visit #2 (24-30 weeks' gestation). The study then gathers medical record data post-delivery, and then follows the infant and mother for an additional 18 months. Data collected at maternal visit #1 (18-14 weeks' gestation), was used the purposes of this study.

Study Population

Participants were enrolled in the study on a rolling basis, beginning January 2016. Pregnant 18-40 year-old African American women living in the metro Atlanta area were asked to participate in the study at the time of their first prenatal appointments, approximately 8-14 weeks' gestation. Eligible participants included women with singleton pregnancies, who were free of chronic medical conditions. All participants selected were either clinic patients at Grady Memorial Hospital or Emory Midtown Hospital. Preliminary data collected at this time, survey questionnaires and urine samples, were used to conduct the analysis for this study.

Data Collection

Participant enrollment and preliminary data collection both occurred during the participant's prenatal appointments, at 8-14 weeks' gestation. Data collection at this stage of the study took place in clinical settings, at either Grady Memorial Hospital or Emory Midtown Hospital. Written consent was obtained from study participants using an IRB-approved consent form. Subject IDs were assigned to de-identify participant information, and confidentiality was maintained throughout the duration of the study. Feminine hygiene product use is low among the general population, therefore women who self-reported product use were purposely

included for analysis in this study. The frequency of feminine product use is higher in this study than the true population.

Survey Data

Surveys were conducted face-to-face by interviewers to evaluate participant stress, diet, and health behaviors. Baseline information including participant sociodemographic information was also evaluated at this time. Data was initially recorded on questionnaire forms and then entered into Research Electronic Data Capture (RedCap), a browser-based database.

Feminine hygiene product use was evaluated by a series of questions: "Have you douched?", "Have you used feminine sprays or wipes?", and "Have you used any creams or other home remedies in your vagina?" Participants responded with either a "yes" or "no", and binary variables were created for each of the questions.

Urine Sample

Spot urine samples were taken at the same time of survey administration. All samples were labeled and with corresponding sample IDs. The specimen was then transported to Rollins School of Public Health for analysis in the Barr-Ryan (LEADER) laboratory, and corresponding chain of custody was documented. Samples were stored in a freezer until further analysis was conducted.

Metabolite Measurements

Urine aliquots (0.5 mL) were spiked with stable isotopically labeled ^{13}C analogues of the target phthalate metabolites (Table 1) then mixed. 2000 units of β-glucuronidase in 1 mM ammonium acetate (pH 5) buffer were added. Samples were incubated at 37° C overnight to liberate glucuronide-bound phthalate metabolites.

Following incubation, 0.15 M sodium phosphate buffer was added to terminate enzyme activity. The hydrolysates were loaded onto preconditioned ABS Elut-NEXUS mixed mode polymeric solid phase extraction (SPE) cartridges (Agilent, Santa Clara, CA) and the hydrolysate was pulled through to waste. The SPE cartridges were washed with 0.1 M formic acid followed by purified water. All SPE cartridges were then dried thoroughly by vacuum. The SPE cartridges were then eluted with acetonitrile, followed by ethyl acetate. The eluates were collected, concentrated to dryness, re-suspended in 0.1% acetic acid, and then transferred to vials.

The extracts were separated using high performance liquid chromatography on a Betasil Phenyl (3µ 150 x 2.1 mm, Thermo Scientific, San Jose, CA) column and analyzed by tandem mass spectrometry on an Agilent 6460 triple quadrupole mass spectrometer (Agilent, Santa Clara, CA). The ions monitored and their respective limits of quantification are listed in Table 2. Concentrations were derived from a linear regression analysis of the area of the analyte ion divided by the area of the internal standard ion and the calibrant concentrations.

Quality assurance and control parameters were incorporated into the analyses. In each analytic run of 23 unknown samples, two blank samples (1 urine blank, one reagent blank), 2 quality control materials and a full calibration set (0.1 ng/mL to 400 ng/mL) were analyzed. To be considered a valid run, quality control material concentrations had to fall within two standard deviations of the mean expected concentration. Target analytes that possessed the correct retention times,

coeluted with their labeled analogue, and had both quantification and confirmation ion transitions to be considered valid measurements.

Statistical Analysis

All statistical procedures were conducted using SAS 9.4(SAS Institute, Cary, NC). An alpha level of 0.05 was considered statistically significant.

Urinary phthalate metabolite levels were natural log transformed due to their non-normal distributions. All subsequent statistical analysis was conducted with these metabolite values. Individual phthalate metabolites that represent the same parent compound and had similar biologic activity were combined using a molar sum procedure (Figure 1). These values were also log transformed due to their non-normal distributions.

Any phthalate metabolite concentrations that were below the limit of detection were imputed with the following formula: metabolite LOQ/ $\sqrt{2}$. The functional sensitivity (LOQ) for each respective phthalate metabolites is (in ng/mL): MCPP: 0.2, MEP: 0.2, MECPP: 2.5, MEHHP: 0.2, MBP 0.2, MiBP 0.1, MEOHP: 0.2, MBzP: 0.1, MEHP: 0.1 (Table 2).

Descriptive Statistics & Univariate Analysis

Descriptive statistics for continuous demographic variables were calculated and reported as means and standard deviations. Maximum and minimums values were provided for each variable as well. Descriptive statistics for continuous log transformed metabolite data was calculated and reported as geometric means and geometric standard error. 95th percentile concentrations were also reported for the

log transformed metabolite data. Descriptive statistics for categorical variables were calculated and reported as numbers and proportions.

Data were first analyzed for the entire study population and then analyzed based upon stratified exposures: any feminine hygiene product use, vaginal douche use, feminine spray use, and vaginal cream use. For each type of feminine hygiene product and use of any feminine product, T-tests were conducted to compare users and non-users, for continuous variables. For each type of feminine hygiene product and use of any feminine hygiene product, Fisher's Exact Test was conducted to compare users and non-users, for each categorical variable. Fisher's Exact Tests were performed in place of Chi- square analyses due to the low frequency of feminine hygiene product users. Fisher's Exact Test is significantly more accurate in estimating difference between groups, with small numbers of observations.

Multivariate Analysis & Model Construction

Multivariate maximum likelihood logistic regression models were constructed to further examine the association between feminine hygiene product use and urinary phthalate metabolite concentrations. Interaction and confounding was evaluated prior to model creation. Exposure was stratified by feminine product type, and non-users were assigned as the reference group. An additional exposure variable "any feminine product use" was evaluated which combined exposure among all feminine hygiene products. Study participants who did not use any type of feminine hygiene products were assigned to the reference group.

First an unadjusted model was evaluated where outcome was individual phthalate metabolites and the main exposure was individual hygiene product use. A

second unadjusted model was evaluated where the outcome was individual phthalate metabolite, while the main exposure was "any feminine hygiene product use". Next, association between feminine hygiene product use and urinary phthalate metabolite concentrations were assess accounting for the following covariates: age (continuous), BMI (continuous), and educational attainment (8^{th} grade or less; some high school, graduated high school or GED; Graduated college; Some graduate work of degree). Household income was not evaluated because the study population's SES status was quite diverse and education was thought to be a batter indicator of social disparity. The same association, with corresponding covariates was assessed for any feminine hygiene product use. All model selection was conducted by backward elimination.

Percent change in phthalate metabolite concentration was estimated from the regression models using the following equation: $(e^{(\beta)} -1) * 100$, where β is the estimated regression coefficient. 95 % confidence intervals (Cl) were estimated from the regression models using the following equation: $(e^{(\beta \pm 1.99 * SE)} - 1) * 100$, where β is the estimated regression coefficient and SE is the standard error.

RESULTS

Demographic Characteristics and Feminine Hygiene Product Use

Demographic characteristics of the study population are presented in table 3. The study population consisted of 60 pregnant African American women, at 8-14 weeks' gestation. The average age of the study population was 26 years, with a standard deviation of 4 years. The maximum study population age was 40; the

minimum study population age was 19. Fifty-three of the study participants (88.3%) had at least graduated from high school or had obtained their GDE, indicating a high level of educational attainment. Additionally, annual household income (in USD) was fairly distributed among study participants. Over 60 percent of enrolled women lived in a household with an average household income of $100,000 USD. Every study participant had health insurance. A majority of women (83.33 %) had Medicaid insurance coverage during their pregnancy.

Two participants (3.33%) self-reported the use of vaginal douches in the past month (30 days). Eleven women (18.33 %) reported the use of feminine sprays in the past month (30 days). Six women (10.00%) reported the use of vaginal cream in the past month (30 days). Seventeen study participants (28.33 %) reported the use of any of the three feminine hygiene products in the past month (30 days).

Univariate Analysis

Study population demographic information and feminine product univariate analysis is presented in table 4. Age was statistically significant among vaginal cream users (Fisher's Exact Test, p-value= 0.0414), indicating older women, greater than 30 years old, were more likely to use the product. Of the remaining demographic characteristics, none were statistically significant between feminine hygiene product users and non-users, among stratified products. The same was true when comparing users and non-users for any feminine product use.

Study population log transformed phthalate concentrations (in ng/mL) and feminine product use is presented in table 5. Significant differences in metabolite

concentration for MBZP (t-test, p-value= 0.0183), MIBP (t-test, p-value= 0.0163), and ΣMzBP (t-test, p-value= 0.0319) were observed among feminine spray users and non-users. Each metabolite difference observed indicated significantly lower phthalate concentration among users when compared to non-users. Of the remaining phthalates, none were significantly different among product users and non-users, for each respective product when stratified. The same was true when comparing the phthalate metabolite difference among users and non-users for the any feminine product use category.

Multivariate Linear Regression

Multivariate linear regression was used to investigate the association between categorical feminine product exposure and continuous phthalate metabolite concentration; this model was selected because the dependent variable was continuous in nature. Exposure was stratified by feminine product type: vaginal douche use, feminine spray use, and vaginal cream use. Feminine hygiene product non-users were assigned as the reference group, for each respective product. A single exposure variable called "any feminine product use," which combined all of specific types of feminine hygiene products was created. Study participants who did not use any type of feminine hygiene products (vaginal douches, feminine sprays, or vaginal creams) were assigned to the reference group. Results for both unadjusted and adjusted models are presented in table 6.

Unadjusted models did not demonstrate a significant association between phthalate metabolite concentration and self-reported feminine product use in the

past month. Adjusted models did not demonstrate a significant association between phthalate metabolite concentration and self-reported feminine product use in the past month either. In an adjusted model, women who reported any type of feminine product use in the past month, had a 32.53 % (95% CI: -66.01, 133.95) lower concentration of ΣMBzP than non-users (P-trend= 0.0339). Any feminine product use reported by women who used such products in the last month illustrated a negative association, that closely approach statistical significance (p-trend= 0.0656), between product exposure and MBP metabolites (21.14% change; CI: -60.02, 155.53). A similar negative association was observed between any feminine product use and MIBP metabolites (29.12% change; CI: -61.75, 131.34), which closely approach statistical significance (p-trend= 0.0887). There was evidence of a positive association between vaginal spray use and MEP metabolite concentration (152.43% change; CI: -18.16, 778.67), but it did not reach statistical significance. There was also evidence of a positive association between each individual feminine product (vaginal douche, feminine spray, and vaginal cream) use and MEHP metabolite concentration, particularly among douche users (109.59% change; CI: -57.05,1022.69), but it did not reach statistical significance.

DISCUSSION

No significant association was found between self-reported feminine product use and phthalate metabolite concentration among our study population. There are several possible reasons for these findings.

Study Limitations

This study was a preliminary investigation of phthalate exposure among pregnant women who were enrolled in the Center for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM^2) longitudinal cohort study. The number of women enrolled in the study with corresponding urinary metabolite data was limited, so the total sample size consisted of 60 observations. Feminine hygiene products of interest for this study were used less frequently among the C-CHEM^2 study population, when compared to the national use frequency among African American women, according to NHANES (2001-2004) survey data. Analysis of the NHANES (2001-2004) survey found that that 37% of African American women reported vaginal douche use in the previous month (Branch et al., 2015), whereas only 3.33% of our study population reported vaginal douching in the past month. For this reason, some observations were purposely selected to be part of this analysis, blind of corresponding phthalate concentrations. This same study found a significant positive association between vaginal douche use and phthalate concentration among African American women, but observed no such association with other feminine hygiene products (Branch et al., 2015). Due to a low observed frequency of vaginal douche user, this study was unable to conduct a robust analysis to try to reproduce these findings. The study also reported that 16% of African American women used feminine sprays in the past month and found no strong association between feminine spray use and elevated phthalate concentration (Branch et al., 2015), which was constant with the frequency of product use and results, observed in our population (table 3 & table 6). As this

young cohort becomes more established the sample size will increase, thus creating stronger power, allowing for better analysis of association.

No information on specific feminine hygiene product brands or feminine hygiene product ingredients were collected in the C-CHEM[2] survey. The formulation of products and levels of added phthalates may have varied, leading to a mixture of phthalate exposure levels among users in each of the different product categories. For instance, many homemade feminine hygiene product solutions do not contain manufactured phthalates for scent, but rather are made up of vinegar and water solutions (Brotman et al., 2008; Grimley et al., 2006). This could be a source of the wide confidence intervals observed in table 6.

Unaccounted for phthalate exposure may have led to residual confounding in this study. DEP is used as a plasticizer and can be found in an array of items such as toothbrushes, tool handles, toys, and automotive equipment (ATSDR, 1995). DEP has also been used as a surface lubricant for food packaging and pharmaceutical packaging (EPA, 1989; Verschueren, 1983), which may be alternative sources of oral phthalate exposure in our study population. The phthalate DEHP is used primarily as a plasticizer in the production of flexible polyvinyl chloride (PVC) (ATSDR, 2002). Everyday household products containing PVC include furniture, automobile upholstery, shower curtains, garden hoses, toys, shoes, and baby clothing (ATSDR, 2002). In the healthcare setting medical equipment containing tubing, blood storage bags, and medical examination and surgical gloves contain PVC (ATSDR, 2002). Because phthalates are used in general consumer products and an array of medical equipment, chronic occupational phthalate exposure could have been a confounder

of interest in this study. Survey data did not include this information; therefore, analysis could not account for this residual source of phthalate exposure.

Personal care products have also been linked to DEP, as it is used as a fragrance fixative (ATSDR, 1995). DEP has been reported in 67 cosmetic products including eyeshadow, nail polish, bath salts, bath soap, hair spray, laundry detergents, deodorant, aftershave, and both body and hand lotion (Houlihan, 2002; Kamrin et al., 1991). DBP is also used as a solvent and fragrance fixative, and can be found in cosmetics, lubricants, floor carpets, tapestries, and adhesives (ATSDR, 2001; Fishbein, 1992). It is possible that lack of survey data on personal care products effected the analysis of this study, because such products could have been confounders that directly affected our outcome of interest. At the next stages of follow-up in the C-CHEM^2 cohort, the questionnaire survey expands upon environmental chemical exposures and gathers information on personal care product (i.e. lotion, cosmetic, deodorant, fragrance) use. This data can be used in the future to more accurately understand the true sources of phthalates among this study population.

Another limitation of this study was associated with biomonitoring and the analysis of the urinary phthalate metabolites. The urinary spot samples collected pose the issue of sample dilution, as samples could vary in volume of void and concentration of chemicals (Barr et al., 2005). Urinary creatinine measurement is a technique, which creates a ratio of water to urine density and associated measurement of soluble solids, that can be used to correct for such dilution (Muscat

et al., 2011). In the analysis conducted, urinary metabolite samples were not adjusted for creatinine which could be a technique used for future analysis.

The aim of this study was to solely evaluate the association between feminine hygiene product use and phthalate metabolite concentration; however, recent studies suggest that these products actually contain a mixture of chemicals, with possible endocrine-disrupting potential (Scranton, 2013). In future evaluation of feminine hygiene products, other harmful chemical exposure should be explored. Additionally, little is known about the vaginal route of exposure and its potential in metabolizing harmful chemicals. A study that investigated the route of medical treatment administration, found that vaginal administration was significantly more effective in increasing serum and endometrial levels of estradiol, than oral delivery (Tourgeman et al., 1999). This finding could be applied to other sources of chemical exposures as well, and ultimately warrants further investigation of this pathway.

Study Strengths

This study is only one, of few, to assess self-reported feminine hygiene product use as a source of phthalate metabolite exposure. Additionally, this study is the first of its kind to focus its evaluation on a study population comprising of all pregnant African American women, in the southeast. Our study population's level of educational attainment and socioeconomic status was diverse. Since this preliminary investigation did not make any direct connection to adverse health effects in maternal and infant health, there is potential for further analysis and follow up with this cohort.

CONCLUSION

All though this study presented null results, further data will be collected by the C-CHEM^2 cohort, creating a more robust sample population and the opportunity to evaluate this association once more. Future studies should also evaluate other potential endocrine-disrupting chemicals that may be associated with feminine hygiene products. Lastly, feminine hygiene product chemical exposure among pregnant women should be evaluated for its potential adverse reproductive health effects on offspring.

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TABLES & FIGURES

Table 1: Target Phthalates, their metabolites, and environmental sources.

Parent Phthalate [Abbreviation]	Phthalate Metabolite(s) [Abbreviation]	Environmental Source
Diethyl phthalate [DEP]	Monoethyl phthalate [MEP]	Personal care products, cosmetics, industrial solvent, medications
Di-*n* -butyl phthalate [DBP]	Mono-*n* -butyl phthalate [MnBP]	Adhesives, caulk, industrial solvents, cosmetics, medications
Diisobutyl phthalate [DiBP]	Monoisobutyl phthalate [MiBP]	Adhesives, caulk, industrial solvents, cosmetics
Butyl benzyl phthalate [BBP]	Monobenzyl phthalate [MBzP]; Mono-*n* -butyl phthalate [MnBP]	Vinyl flooring, adhesives, sealants, industrial solvents
Di(2-ethylhexyl) phthalate [DEHP]	Mono(2-ethly-5-carboxypentyl) phthalate [MECPP]; Mono(2-ethyl-5-oxohexyl) phthalate [MEOHP]; Mono(2-ethyl-5-hydroxyhexyl phthalate [MEHHP]; Mono(2-ethlyhexyl) phthalate [MEHP]	Toys, food containers and packaging, tubing

Table 2. Analyte MS/MS transitions and limits of quantification.

Analyte	Quantification transition (m/z)	Labeled Standard Transition (m/z)	Limit of Quantification (ng/mL)
MEP	193→77.1	197.2→79.1	0.2
MECPP	307 →159.1	311.3→159.1	2.5
MEHHP	293→121	297.3→124.0	0.2
MBP	221→77.1	225.2→79.1	0.2
MiBP	221→77.1	225.2→79.1	0.1
MEOHP	291→121	295.3→124.0	0.2
MBzP	255→183.1/77.1	259.0→77.1	0.1
MEHP	277→134	281.3→137.0	0.1

Figure 1: DEHP & MzBP Molar Sum Equivalent Formulas

DEHP Phthalate Molar Sum Equation:

$\sum$ DEHP = MEHP + MEHHP + MEOHP + MECPP

$$\frac{Sample\ concentration\left(\frac{ng}{mL}\right)}{Phthalate\ Molar\ Mass\left(\frac{g}{mol}\right)} = \left(\frac{nmole}{1\ mL}\right) x\ \left(\frac{1000\ mL}{1\ L}\right) = \frac{ng/mL}{ng/nmol} = \mu M$$

MEHP Molar Mass = 278 g/mol

$$\text{MEHP} = \frac{Sample\ concentration\left(\frac{ng}{mL}\right)}{278\left(\frac{g}{mol}\right)} x\ 1000 = \mu M$$

MEHHP Molar Mass = 293 g/mol

$$\text{MEHHP} = \frac{Sample\ concentration\left(\frac{ng}{mL}\right)}{293\left(\frac{g}{mol}\right)} x\ 1000 = \mu M$$

MEOHP Molar Mass = 292 g/mol

$$\text{MEOHP} = \frac{Sample\ concentration\left(\frac{ng}{mL}\right)}{292\left(\frac{g}{mol}\right)} x\ 1000 = \mu M$$

MEOHP Molar Mass = 308 g/mol

$$\text{MEOHP} = \frac{Sample\ concentration\left(\frac{ng}{mL}\right)}{308\left(\frac{g}{mol}\right)} x\ 1000 = \mu M$$

BzBP Phthalate Molar Sum Equation:

$\sum$ BzBP = MnBP + MBzP

$$\frac{Sample\ concentration\left(\frac{ng}{mL}\right)}{Phthalate\ Molar\ Mass\left(\frac{g}{mol}\right)} = \left(\frac{nmole}{1\ mL}\right) x\ \left(\frac{1000\ mL}{1\ L}\right) = \frac{ng/mL}{ng/nmol} = \mu M$$

MnBP Molar Mass = 222 g/mol

$$\text{MnBP} = \frac{Sample\ concentration\left(\frac{ng}{mL}\right)}{222\left(\frac{g}{mol}\right)} x\ 1000 = \mu M$$

MBzP Molar Mass = 256 g/mol

$$\text{MBzP} = \frac{Sample\ concentration\left(\frac{ng}{mL}\right)}{256\left(\frac{g}{mol}\right)} x\ 1000 = \mu M$$

Table 3: Study population demographic characteristics and feminine product use.

Characteristics	Study Population (N=60)	
Age (years)	mean ± SD	Min-Max
	26 ± 4	19-40
BMI (kg/m^2)	mean ± SD	Min-Max
	30.0 ± 9.0	18.0-51.0
Education	n (%)	
8th grade or less	1 (1.67)	
some high school	6 (10.00)	
Graduated high school or GED	26 (43.33)	
Some college or technical school	20 (33.33)	
Graduated College	5 (8.33)	
Some graduate work or degree	2 (3.33)	
Relationship Status	n (%)	
Not in a relationship	14 (23.33)	
In a relationship, not living together	20 (33.33)	
In a relationship, living together	26 (43.33)	
Total annual household income (USD)	n (%)	
< 100,000	23 (38.33)	
100,000-132,000	15 (25.00)	
133,000-149,000	7 (11.67)	
150,000-199,000	8 (13.33)	
200,000-299,000	2 (3.33)	
300,000-399,000	3 (5.00)	
400,000 <	2 (3.33)	
Insurance type, n (%)	n (%)	
Medicaid	50 (83.33)	
Private through employer (own, spouse, parent)	7 (11.67)	
Private through federal health insurance marketplace (ObamaCare, Healthcare.gov)	3 (5.00)	
Feminine hygiene product use in past month[a]	n(%)	
Any Feminine Product	17 (28.33)	
Vaginal Douche	2 (3.33)	
Feminine Spray	11 (18.33)	
Vaginal Cream	6 (10.00)	

[a] *Some participants used multiple products*

Table 4: Demographic characteristics, by feminine product use among pregnant African American women enrolled in the Center for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM [2]) Cohort (2016)

Characteristics	Study Population (N=60)		Any Feminine Heygiene Product Use[b] (N=17)		P Value[a]	Vaginal Douche Users[b] (N=2)		P Value[a]	Feminine Spray Users[b,c] (N=11)		P Value[a]	Vaginal Cream Users[b,c] (N=6)		P Value[a]
Age (years)	mean ± SD	Min-Max	mean ± SD	Min-Max		mean ± SD	Min-Max		mean ± SD	Min-Max		mean ± SD	Min-Max	
	26 ± 4	19-40	25 ± 7	19-40	0.9051	27 ± 8	27-33	0.6708	23 ± 6	19-40	0.1207	30 ± 8	19-40	0.0222
BMI (kg/m^2)	mean ± SD	Min-Max				mean ± SD	Min-Max		mean ± SD	Min-Max		mean ± SD	Min-Max	
	30.0 ± 9.0	18.0-51.0	30.6 ± 9.5	20.0-51.0	0.8266	29.0 ± 1.1	28.2-29.8	0.8266	30.8 ± 9.6	20.0-51.0	0.838	31.2 ± 12.1	21.0-50.4	0.7866
Age, n (%)														
< 25	33 (55.00)		9 (15.00)		0.7981	1 (1.67)		0.7017	7 (11.67)		0.5505	2 (4.76)		0.0414
25-29	13 (21.67)		3 (5.00)			0 (0.00)			3 (5.00)			0 (0.00)		
≥30	14 (23.33)		5 (8.33)			1 (1.67)			1 (1.67)			4 (6.67)		
BMI (kg/m^2), n (%)														
<18.5	3 (5.00)		0 (0.00)		0.5978	0 (0.00)		0.2254	0 (0.00)		0.7016	0 (0.00)		0.8193
18.5-24.9	15 (25.00)		5 (8.33)			0 (0.00)			4 (6.67)			2 (3.33)		
25-30	16 (26.67)		6 (10.00)			2 (3.33)			2 (3.33)			2 (3.33)		
>30	26 (43.33)		6 (10.00)			0 (0.00)			5 (8.33)			2 (3.33)		
Education, n (%)														
8th grade or less	1 (1.67)		0 (0.00)		0.8614	0 (0.00)		0.3271	0 (0.00)		0.9721	0 (0.00)		0.4158
some high school	6 (10.00)		1 (1.67)			0 (0.00)			1 (1.67)			0 (0.00)		
Graduated high school or GED	26 (43.33)		8 (13.33)			1 (1.67)			6 (10.00)			2 (3.33)		
Some college or technical school	20 (33.33)		5 (8.33)			0 (0.00)			3 (5.00)			3 (5.00)		
Graduated College	5 (8.33)		2 (3.33)			1 (1.67)			1 (1.67)			0 (0.00)		
Some graduate work or degree	2 (3.33)		1 (1.67)			0 (0.00)			0 (0.00)			1 (1.67)		
Relationship Status, n (%)														
Not in a relationship	14 (23.33)		6 (10.00)		0.4409	0 (0.00)		1.0000	5 (8.33)		0.2137	1 (1.67)		0.5515
In a relationship, not living together	20 (33.33)		5 (8.33)			1 (1.67)			3 (5.00)			1 (1.67)		
In a relationship, living together	26 (43.33)		6 (10.00)			1 (1.67)			3 (5.00)			4 (6.67)		
Total annual household income (USD), n (%)														
< 100,000	23 (38.33)		7 (11.67)		0.4566	1 (1.67)		0.2808	5 (8.33)		0.3698	1 (1.67)		0.4190
100,000-132,000	15 (25.00)		3 (5.00)			0 (0.00)			2 (3.33)			2 (3.33)		
133,000-149,000	7 (11.67)		3 (5.00)			0 (0.00)			3 (5.00)			1 (1.67)		
150,000-199,000	8 (13.33)		1 (1.67)			0 (0.00)			0 (0.00)			1 (1.67)		
200,000-299,000	2 (3.33)		0 (0.00)			0 (0.00)			0 (0.00)			0 (0.00)		
300,000-399,000	3 (5.00)		2 (3.33)			1 (1.67)			1 (1.67)			0 (0.00)		
400,000 <	2 (3.33)		1 (1.67)			0 (0.00)			0 (0.00)			1 (1.67)		
Insurance type, n (%)														
Medicaid	50 (83.33)		12 (20.00)		0.1865	2 (3.33)		1.0000	7 (11.67)		0.0978	4 (6.67)		0.2594
Private through employer (own, spouse, parent)	7 (11.67)		4 (6.67)			0 (0.00)			3 (5.00)			2 (3.33)		
Private through federal health insurance marketplace (ObamaCare, Healthcare.gov)	3 (5.00)		1 (1.67)			0 (0.00)			1 (1.67)			0 (0.00)		

[a] *Group differences evaluated by T-Test for continuous variables and Fisher's Exact Test for categorical variables*

[b] *Referance group is non-user*

[c] *Some participants used multiple products*

Table 5: Phthalate metabolite concentration, by feminine product use among pregnant African American women enrolled in the Center for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM2) Cohort (2016)

Characteristics	Study Population (N=60)		Any Feminine Heygiene Product Use[b] (N=17)		P Value[a]	Vaginal Douche Users[b] (N=2)		P Value[a]	Feminine Spray Users[b,c] (N=11)		P Value[a]	Vaginal Cream Users[b,c] (N=6)		P Value[a]
Phthalate metabolite concentration	GM (GSE)[d]	95th Percentile	GM (GSE)[d]	95th Percentile		GM (GSE)[d]	95th Percentile		GM (GSE)[d]	95th Percentile		GM (GSE)[d]	95th Percentile	
MBP (ng/mL)	10.25 (1.61)	4.02	8.81 (3.44)	4.13	0.5479	21.07 (0.31)	3.06	0.3974	5.49 (3.01)	4.13	0.0579	20.46 (7.37)	4.13	0.1426
MBZP (ng/mL)	5.26 (1.06)	3.99	3.32 (1.46)	3.59	0.1530	18.00 (3.56)	3.09	0.2610	1.95 (1.15)	3.59	0.0183	6.31 (2.31)	3.38	0.7671
MECPP (ng/mL)	6.80 (1.00)	3.70	6.44 (2.25)	4.07	0.8193	3.17 (1.16)	1.52	0.3401	5.51 (2.47)	4.07	0.5018	7.98 (4.84)	4.02	0.7192
MEHHP (ng/mL)	5.62 (0.83)	3.70	5.52 (1.73)	3.73	0.9398	2.41 (0.31)	1.01	0.2894	5.19 (2.14)	3.73	0.7981	7.48 (3.40)	3.66	0.5224
MEHP (ng/mL)	1.69 (0.32)	2.95	1.95 (0.56)	3.28	0.6408	0.90 (0.38)	0.31	0.5385	1.87 (0.62)	3.02	0.7977	2.41 (1.39)	3.28	0.5348
MEOHP (ng/mL)	3.33 (0.54)	3.13	3.29 (1.24)	3.51	0.9703	1.60 (0.58)	0.83	0.4060	3.00 (1.50)	3.14	0.7546	4.73 (2.52)	3.51	0.4736
MEP (ng/mL)	105.93 (19.25)	7.27	81.05 (27.10)	7.22	0.3589	52.16 (41.43)	4.75	0.4738	79.06 (35.70)	7.22	0.4504	87.18 (41.36)	6.29	0.7242
MIBP (ng/mL)	8.11 (1.15)	3.83	6.47 (1.94)	4.48	0.3198	11.02 (1.57)	2.54	0.6921	4.00 (1.33)	2.97	0.0163	14.12 (6.08)	4.48	0.1950
Σ DEHP (nM)	62.08 (8.98)	5.98	62.07 (19.69)	6.26	0.9992	27.41 (8.22)	3.61	0.2978	57.56 (23.13)	6.02	0.8067	80.62 (41.70)	6.26	0.5518
ΣMzBP (nM)	73.41 (12.00)	5.90	56.84 (22.13)	5.90	0.3275	166.14 (12.55)	5.19	0.3561	35.29 (19.16)	5.90	0.0319	127.93 (39.24)	5.69	0.2591

[a] *Group differences of natural log transformed phthalate metablite concentrations evaluted by T-Test.*

[b] *Referance group is non-user*

[c] *Some participants used multiple products*

[d] *GM, Geometric mean; GSE, Geometric standard error*

Figure 2: Distribution of log transformed MEHP concentration among study population, by feminine product use

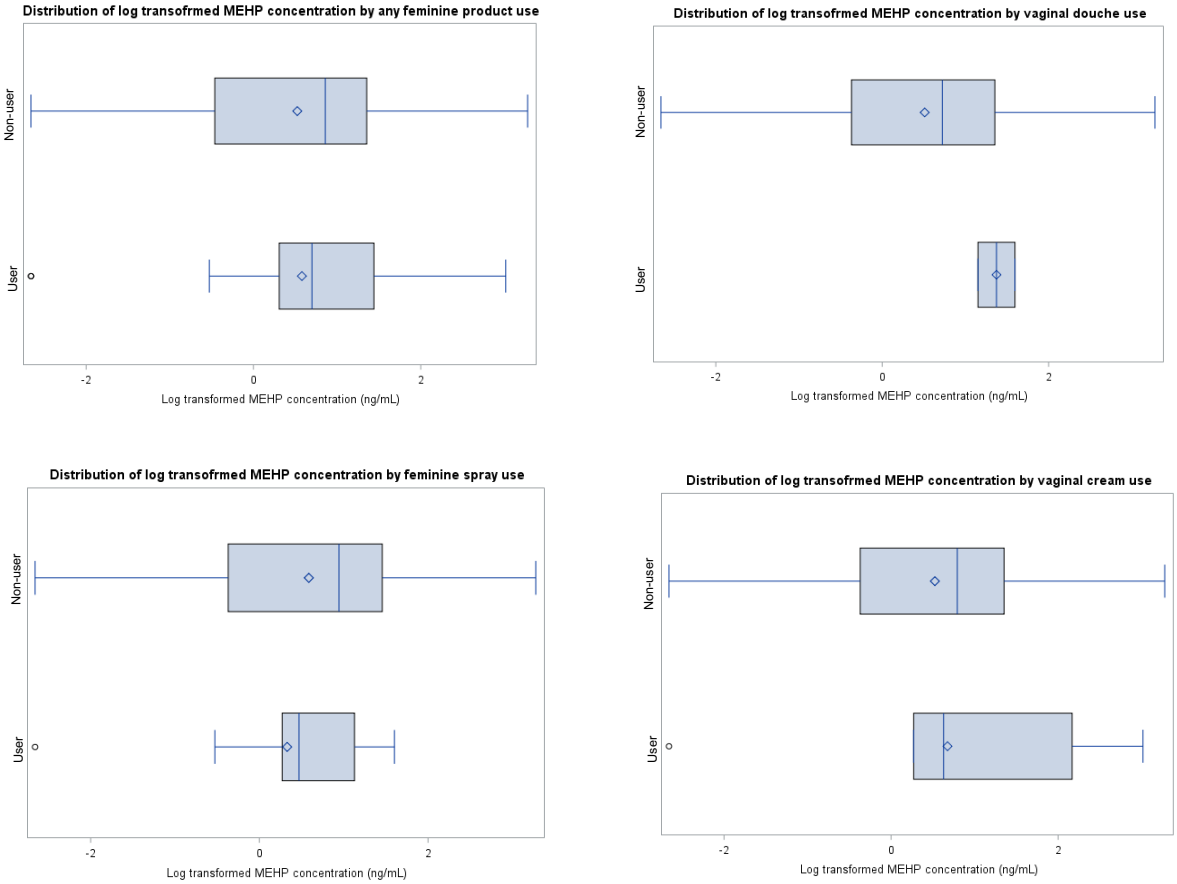

Table 6: Association of product use and phthalate metabolite concentrations (ng/mL) among pregnant African American women enrolled in the Center for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM2) Cohort (2016)[a]

	MBP					
	Unadjusted			Adjusted[b]		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	28.91	(-78.65, 778.26)	0.7797	22.77	(-78.39, 697.59)	0.8151
Feminine Sprays	-31.46	(-70.39, 158.70)	0.3745	-30.17	(-68.97, 157.16)	0.3822
Vaginal Cream	20.11	(-59.24, 353.92)	0.7371	24.59	(-56.16, 354.07)	0.6769
P-trend			0.8085			0.2113
Any Feminine product use	-22.36	(-61.56, 156.83)	0.4767	-21.14	(-60.02, 155.53)	0.4893
P-trend			0.4767			0.0656

	MBZP					
	Unadjusted			Adjusted		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	36.39	(-86.24, 1351.72)	0.7887	36.39	(-86.24, 1351.72)	0.7887
Feminine Sprays	-26.72	(-74.89, 213.86)	0.5659	-26.72	(-74.89, 213.86)	0.5659
Vaginal Cream	-18.32	(-79.42, 324.21)	0.7713	-18.32	(-79.42, 324.21)	0.7713
P-trend			0.8996			0.8996
Any Feminine product use	-33.75	(-72.83, 161.55)	0.3618	-33.75	(-72.83, 161.55)	0.3618
P-trend			0.3618			0.3618

	MECPP					
	Unadjusted			Adjusted		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	193.25	(-42.38, 1492.46)	0.1936	193.25	(-42.38, 1492.46)	0.1936
Feminine Sprays	-26.41	(-65.58, 157.32)	0.4252	-26.41	(-65.58, 157.32)	0.4252
Vaginal Cream	39.54	(-47.53, 371.06)	0.5006	39.54	(-47.53, 371.06)	0.5006
P-trend			0.7951			0.7951
Any Feminine product use	19.10	(-37.68, 227.61)	0.5933	19.10	(-37.68, 227.61)	0.5933
P-trend			0.5933			0.5933

	MEHHP					
	Unadjusted			Adjusted		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	131.51	(-71.12, 1855.89)	0.4256	131.51	(-71.12, 1855.89)	0.4256
Feminine Sprays	-21.71	(-70.38, 206.91)	0.6182	-21.71	(-70.38, 206.91)	0.6182
Vaginal Cream	25.03	(-64.22, 436.90)	0.7237	25.03	(-64.22, 436.90)	0.7237
P-trend			0.7951			0.7951
Any Feminine product use	5.69	(-53.35, 239.44)	0.8934	5.69	(-53.35, 239.44)	0.8934
P-trend			0.8934			0.8934

Table 6 (*cont.*): Association of product use and phthalate metabolite concentrations (ng/mL) among pregnant African American women enrolled in the Center for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM2) Cohort (2016)[a]

	MEOHP					
	Unadjusted			Adjusted		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	193.42	(-49.57, 1707.24)	0.2289	193.42	(-49.57, 1707.24)	0.2289
Feminine Sprays	-4.22	(-57.91, 217.95)	0.9172	-4.22	(-57.91, 217.95)	0.9172
Vaginal Cream	20.84	(-58.07, 348.26)	0.7233	20.84	(-58.07, 348.26)	0.7233
P-trend			0.8085			0.2113
Any Feminine product use	25.70	(-37.13, 251.33)	0.5138	25.70	(-37.13, 251.33)	0.5138
P-trend			0.5138			0.5138

	MEHP					
	Unadjusted			Adjusted		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	109.59	(-57.05, 1022.69)	0.3569	109.59	(-57.05, 1022.69)	0.3569
Feminine Sprays	6.62	(-49.14, 223.50)	0.8638	6.62	(-49.14, 223.50)	0.8638
Vaginal Cream	8.23	(-58.26, 280.63)	0.8693	8.23	(-58.26, 280.63)	0.8693
P-trend			0.8085			0.2113
Any Feminine product use	28.17	(-30.96, 237.96)	0.4279	28.17	(-30.96, 237.96)	0.4279
P-trend			0.4279			0.4279

	MEP					
	Unadjusted			Adjusted		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	-11.62	(-86.43,575.74)	0.8961	-11.62	(-86.43,575.74)	0.8961
Feminine Sprays	-48.74	(-78.63, 122.98)	0.1342	-48.74	(-78.63, 122.98)	0.1342
Vaginal Cream	152.43	(-18.16, 778.67)	0.1075	152.43	(-18.16, 778.67)	0.1075
P-trend			0.8085			0.2113
Any Feminine product use	-5.21	(-55.58, 202.30)	0.8889	-5.21	(-55.58, 202.30)	0.8889
P-trend			0.4767			0.4767

	MIBP					
	Unadjusted			Adjusted[b]		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	-21.94	(-84.48, 392.75)	0.7615	-24.81	(-84.52, 365.17)	0.7209
Feminine Sprays	-7.11	(-56.31, 197.52)	0.8465	-5.77	(-54.94, 197.08)	0.8733
Vaginal Cream	-44.03	(-78.81, 147.81)	0.2393	-42.44	(-77.74, 148.86)	0.2524
P-trend			0.8085			0.2113
Any Feminine product use	-29.97	(-62.74, 131.64)	0.2660	-29.12	(-61.75, 131.34)	0.2715
P-trend			0.4767			0.0887

Table 6 (*cont.*): Association of product use and phthalate metabolite concentrations (ng/mL) among pregnant African American women enrolled in the Center for Children's Health, the Environment, the Microbiome, and Metabolomics (C-CHEM2) Cohort (2016)[a]

	Σ DEHP					
	Unadjusted			Adjusted		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	151.02	(-47.99, 1211.47)	0.7615	151.02	(-47.99, 1211.47)	0.7615
Feminine Sprays	-9.90	(-56.80, 187.90)	0.8465	-9.90	(-56.80, 187.90)	0.8465
Vaginal Cream	22.59	(-52.41, 315.75)	0.2393	22.59	(-52.41, 315.75)	0.2393
P-trend			0.6611			0.6611
Any Feminine product use	23.25	(-33.65, 228.93)	0.5044	23.25	(-33.65, 228.93)	0.5044
P-trend			0.5044			0.5044

	ΣMzBP					
	Unadjusted			Adjusted[c]		
	% Change	95 % CI	P-value	% Change	95 % CI	P-value
Feminine hygiene product use						
Vaginal Douche	18.63	(-81.71, 769.44)	0.8564	-10.50	(-85.58, 555.29)	0.9042
Feminine Sprays	-30.65	(-71.03, 166.04)	0.4077	-36.44	(-72.00, 144.26)	0.2764
Vaginal Cream	0.79	(-67.24, 310.08)	0.9890	15.96	(-60.00, 336.18)	0.7831
P-trend			0.8085			0.2113
Any Feminine product use	-28.43	(-65.43, 148.19)	0.3642	-32.53	(-66.01, 133.95)	0.2587
P-trend			0.3642			0.0339

[a] All phthalate concentrations were were natural log transformed. Referance group is non-users.

[b] Models were adjusted for BMI

[c] Models were adjusted for BMI and educational attainment