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Research Article

Impact of Pregnancy on the Levels of Parabens and Bisphenol A: Data from NHANES 2005–2010

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Using data from the National Health and Nutrition Examination Survey, regression models were fitted to assess the relationship between the levels of bisphenol A and selected parabens and pregnancy status among females 20–44 years old with adjustments made for factors that may affect the levels of these chemicals. Pregnancy did not affect the levels of bisphenol A, ethyl paraben, methyl paraben, and propyl paraben, but the pregnancy was found to be associated with increased levels of butyl paraben. Also, the levels of bisphenol A and butyl, ethyl, and methyl parabens increased as pregnancy progressed from the first trimester to the third trimester. The increasing levels of bisphenol A and parabens during pregnancy are of concern and need further clinical explanation.

1. Introduction

Parabens are a class of chemicals widely used as preservatives because of their antibacterial and fungicidal properties. For a long time, they have been used in cosmetics, pharmaceuticals, and personal care products [1] like shampoos, moisture solutions, shaving gels, spray tanning solution, and even toothpaste and as food additives to inhibit microbial growth and extend product shelf life [2]. They are considered to be possible endocrine disruptors and are considered to exhibit estrogenic properties. In a study of 177 pregnant females from a fertility clinic in Boston, Massachusetts, Braun et al. [3] found a monotonic dose-response relationship between the total number of products used and the levels of urinary paraben and phthalate metabolites. In a study [4] that administered butyl paraben (BUP) to pregnant rats from gestation day 1 to lactation day 21, BUP was found to induce neurodevelopmental disorders similar to those observed in valproic acid model of autism in the offspring. In a study [1] of 47 pregnant females and their matching newborn infants, methyl (MPB), ethyl (EPB), butyl (BUP), and propyl (PPB) parabens were detected in urinary samples of both mothers and their newborns with significant correlations. Levels of MBP and PPB were found to be more than fourfold higher in males than females and more than threefold higher in African Americans than Caucasians [5]. In the same study [5], levels of MPB and PPB were found to be 25–45% lower during pregnancy than before pregnancy.

Bisphenol A (BPA) is used in large quantities in production of polycarbonate plastics and epoxy resins (http://www.niehs.nih.gov/health/topics/agents/sya-bpa/). Polycarbonate plastics are used in food and drinking packaging, medical devices, and compact disks. Epoxy resins are used to coat metal products such as food cans, bottle tops, and water supply pipes. The majority of human exposure to BPA is through the diet. At high temperatures, BPA can leach from polycarbonate bottles into the liquid. Air, dust, and water are other sources of exposure to BPA. BPA has been detected in maternal plasma, fetal plasma, and fetal tissue and male fetuses were found to have higher levels of BPA than female fetuses [6]. In another study [7], BPA was found to be present in serum and follicular fluids as well as in fetal serum and full-term amniotic fluid. BPA has also been found in breast milk of healthy lactating females [8]. Thus, exposure to BPA is a risk factor for the developing fetus. This should be of concern since BPA has the potential to disrupt thyroid homeostasis which can have adverse consequences for the development of the brain. In a study [9] that measured BPA levels in

476 pregnant females and neonates, reduced total thyroxine (TT4) levels were associated with exposure to BPA during pregnancy. Also, decreased thyroid stimulating hormone (TSH) levels were found in male neonates but not in female neonates. Meeker et al. [10] observed inverse relationships between urinary BPA concentrations and thyroid stimulating hormone. However, for the urine and blood samples collected on the same day, BPA levels were not associated with free thyroxine (FT3), total tri-iodothyronine (TT3), and TSH levels. Among 28 workers in two semiautomatic epoxy resin factories, BPA levels were positively associated with the levels of TT3 and FT3 [11]. Meeker and Ferguson [12] found a possible inverse relationship ($p = 0.08$) between BPA and TT4 levels among adults aged ≥ 20 years. However, in the opinion of this author, a p value of 0.08 indicates a null relationship. de Renzy-Martin et al. [13] measured the levels of 10 phenols, 7 parabens, and 16 phthalate metabolites in spot urine samples of 200 healthy pregnant females during 8–30 weeks of pregnancy and detected 13 of the 26 chemicals simultaneously in 174 of the 200 females, thus raising the concern about the adverse health effects of the simultaneous exposure to multiple endocrine distrusting chemicals and the possibility that the true effect of these chemicals on the developing fetus may be underestimated. In another study [14], geometric mean concentration of BPA decreased from 2.6 μg/g creatinine from the first trimester to 2.0 μg/g creatinine in the third trimester. BPA was detected in cord serum collected from elective second-trimester pregnancy terminations in northern and central California, thus suggesting fetuses were exposed to BPA [15]. Lee et al. [16] found association between prenatal exposure to BPA and birth weight particularly among male neonates. Exposure to BPA was found to be associated with reduced gestation by 1.1 weeks [11]. High consumption of canned fish during pregnancy was found to be associated with higher levels of urinary BPA. Prenatal exposure to BPA was found to impair fetal growth [17]. Parental exposure to BPA in the workplace during pregnancy was found to be associated with decreased birth weight [18].

From the studies reviewed above, it is certain that prenatal exposure to parabens and BPA are risk factors for the developing fetus as well as children in their life later on. However, it is not quite clear if and to what degree metabolic changes during pregnancy affect the levels of these endocrine disrupting chemicals (EDC). While there have been some relatively large studies in special populations to measure the impact of parabens and BPA on the health of developing fetus and children, we do not know of a study done in the general population to delineate the differences in the levels of parabens and BPA in pregnant and nonpregnant females. Consequently, this study was undertaken to evaluate the impact of pregnancy on the levels of parabens and BPA among females 20–44 years old. The data from the National Health and Nutrition Examination Survey (http://www.cdc.gov/nchs/nhanes.htm) for the period 2005–2010 were used for this purpose. However, it should be noted that the author has previously used the same NHANES data for 2005–2010 to evaluate the impact of pregnancy on the urinary levels of triclosan [19]. As such, while the present paper evaluates the impact of pregnancy on the levels of selected parabens and PBA, the previous paper [19] evaluated the impact of pregnancy on the levels of triclosan.

2. Materials and Methods

Data were downloaded from demographic (http://wwwn.cdc.gov/nchs/nhanes/2005-2006/DEMO_D.htm), BPA and paraben data (http://wwwn.cdc.gov/nchs/nhanes/2005-2006/EPH_D.htm), serum cotinine, body measures, and pregnancy files (http://wwwn.cdc.gov/nchs/nhanes/2005-2006/UCPREG_D.htm) from NHANES for the survey years 2005–2010 and match merged. NHANES uses a complex, stratified, multistage, probability sampling designed as representative of the civilian, noninstitutionalized US population based on age, gender, and race/ethnicity (http://www.cdc.gov/nchs/nhanes.htm). Sampling weights are created in NHANES to account for the complex survey design, including oversampling, survey nonresponse, and poststratification. This study was limited to those females who were aged 20–44 years. Nonsmokers were defined as those who had serum cotinine levels below 10 ng/mL and smokers were defined as those who had serum cotinine levels ≥ 10 ng/mL. Laboratory methods to measure BPA and parabens are provided elsewhere (http://wwwn.cdc.gov/nchs/nhanes/2005-2006/EPH_D.htm#Description_of_Laboratory_Methodology). Laboratory methodology to test for pregnancy is also provided elsewhere (http://wwwn.cdc.gov/nchs/nhanes/2005-2006/UCPREG_D.htm#Description_of_Laboratory_Methodology). In addition to BPA, data were available for BUP, MPB, EPB, and PPB. Irrespective of the survey period, namely, 2005-2006, 2007-2008, or 2009-2010, and pregnancy status, BPA was detected (i.e., at or above the limit of detection) in at least 86.7% of the NHANES participants (Figure 1). BUP was detected in at least 60% of the participants for the overall study period of six years. PPB was detected in at least 92.6% of the participants. MPB was detected in at least 99.6% of the participants. EPB was detected in 60.8% of the participants (51.5% for pregnant and 61.3% for nonpregnant females) for the overall study period of six years. However, detection rate for the period 2005-2006 was 50.1% (Figure 1, 40.3% for pregnant and 51.2% for nonpregnant females).

All analyses were done using SAS version 9.2 (http://www.sas.com, SAS, Cary, North Carolina, USA) and SUDAAN version 11.0 (https://www.rti.org/SUDAAN, Research Triangle Institute International, Research Triangle Park, North Carolina, USA). All analyses used appropriate weights as provided in the data files. SUDAAN Proc DESCRIPT was used to compute unadjusted geometric means and percent of participants at or above the limit of detection. SUDAAN Proc REGRESS was used to fit linear regression models. A total of five regression models, one each for BPA, BUP, EPB, MPB, and PPB, were fitted. The dependent variable in each model was the log10 transformed values of BPA or the parabens. The independent variables were age, race/ethnicity (Non-Hispanic White (NHW), Non-Hispanic Black (NHB), Mexican American (MA), and other unclassified races/ethnicities (OTH)), pregnancy status (pregnant, nonpregnant), smoking status (nonsmoker,

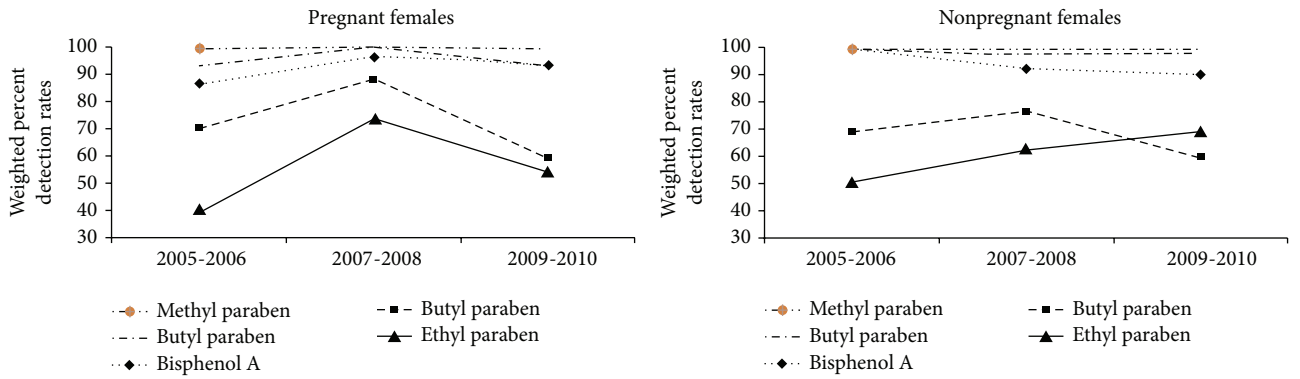

Figure 1: Weighted percent detection rates for bisphenol A and butyl, ethyl, methyl, and propyl parabens for pregnant and nonpregnant females.

smoker), iron storage status (absent, deficient, and replete), body mass index, NHANES study year to adjust for any changes over time, urine albumin, and urine creatinine. Iron storage status was defined as being absent if the values of serum ferritin were <16.5 ng/mL. Those with serum ferritin values between 16.5 and 26.5 ng/mL were defined as being iron deficient and those with >26.5 ng/mL as iron replete. This classification has previously been used by Jain [20]. First-order interaction terms between race/ethnicity, smoking status, iron storage status, and pregnancy status were considered for all models but were retained in the final models only if they were statistically significant at $\alpha = 0.05$. In addition, univariate analyses using SUDAAN Proc DESCRIPT were also done to compare BPA, BUP, EPB, MPB, and PPB levels across the three pregnancy trimesters.

The data were available for a total of 1217 participants (159 pregnant and 1058 nonpregnant females). The sample size details are given in Table 1. After deleting 70 females for whom the smoking status and/or the iron storage status were not available, 1127 females remained available for analysis. However, actual sample sizes used for regression models were much smaller ($N = 949$) because of missing values for other independent variables like urine creatinine, body mass index, and so forth.

Table 1: Unweighted sample sizes by race/ethnicity, smoking status, iron storage status, pregnancy status, and pregnancy trimester. Data from the National Health and Nutrition Examination Survey 2005–2010.

	Pregnant	Nonpregnant	Total
Total	159	1058	1217
Non-Hispanic White	61	451	648
Non-Hispanic Black	20	218	325
Mexican American	55	211	304
Others	23	178	322
Nonsmoker	131	730	861
Smoker	18	274	292
Missing			64
Iron absent	50	187	237
Iron deficient	37	151	188
Iron replete	62	662	724
Missing			68
Pregnancy trimester			
Trimester I	23		
Trimester II	53		
Trimester III	56		

3. Results

3.1. Univariate Analysis. Unadjusted geometric means (UGMs) in ng/gm creatinine with 95% confidence intervals are provided in Table 2. Levels of BPA did not differ by race/ethnicity, iron storage status, smoking status, or pregnancy status. NHB had the lowest UGMs for BUP and they were statistically significantly lower than the UGMs for NHW, MA, and OTH. Smokers had statistically significantly lower UGM for BUP than nonsmokers (0.61 ng/mg creatinine versus 1.17 ng/mg creatinine for a difference of about 100%). Levels of EPB did not differ by race/ethnicity, iron storage status, smoking status, or pregnancy status. MPB were observed at the highest levels and PPB at the second highest levels. For both MPB and PPB, statistically significant differences were observed among pairs of racial/ethnic groups except between NHB and OTH and between MA and NHB. NHB had the highest levels and NHW the lowest levels. For both MPB and PPB, nonsmokers had statistically significantly higher levels than smokers. Pregnancy and iron storage status did not affect UGMs for BUP, MPB, EPB, or PPB even though pregnant females had more than 40% higher BUP than nonpregnant females (1.45 ng/mg creatinine versus 0.96 ng/mg creatinine, Table 2). Those Mexican Americans who were born in the USA as compared to those who were born in Mexico had statistically significantly higher levels for BPA ($p = 0.048$), BUP ($p = 0.018$), MPB ($p = 0.044$), and PPB ($p = 0.002$, Table S1 in Supplementary Material available online at http://dx.doi.org/10.1155/2016/1529071). For PPB, UGMs for those who were born in the USA were more than twice the UGMs for those who were born in Mexico (59.2 ng/mL versus 23.3 ng/mL).

The weighted percent detection rates for EPB among pregnant females rose from 40.3% in 2005-2006 to 54.3%

Table 2: Unadjusted geometric means in ng/mg creatinine with 95% confidence intervals for selected endocrine disrupting chemicals for females aged 20–44 years. Data from the National Health and Nutrition Examination Survey 2005–2010[#].

	Bisphenol A	Butyl paraben	Ethyl paraben	Methyl paraben	Propyl paraben
Total	2.12 (2.01–2.24)	0.98 (0.86–1.13)	3.74 (3.17–4.41)	130.66 (113.25–150.74)	25.89 (21.95–30.55)
Non-Hispanic White (NHW)	2.14 (1.99–2.31)	1.03 (0.87–1.23)*	3.82 (3.07–4.74)	106.89 (88.72–128.77)^	22.86 (18.21–28.7)^
Non-Hispanic Black (NHB)	2.17 (1.97–2.39)	0.58 (0.41–0.82)*,**,***	3.74 (2.87–4.88)	238.67 (207.44–274.59)^	40.96 (33.98–49.37)^
Mexican American (MA)	2.11 (1.87–2.38)	1.2 (0.95–1.5)**	3.34 (2.73–4.1)	198.4 (170.13–231.36)^	37.04 (28.58–48)^
Others (OTH)	2.01 (1.65–2.45)	1.11 (0.77–1.58)***	3.7 (2.84–4.83)	135.74 (105.15–175.22)^	22.97 (16.8–31.41)^
Nonsmokers	2.13 (2.01–2.25)	1.17 (0.97–1.4)*	4.05 (3.34–4.92)	142.46 (121.05–167.66)*	29.56 (24.25–36.03)*
Smokers	2.12 (1.88–2.38)	0.61 (0.45–0.85)*	2.99 (2.31–3.88)	102.92 (79.87–132.63)*	17.97 (13.63–23.7)*
Iron absent	1.99 (1.74–2.29)	0.79 (0.61–1.02)	4.11 (3.15–5.37)	149.87 (120.61–186.23)	30.43 (23.05–40.16)
Iron deficient	2.33 (2.03–2.67)	1.18 (0.79–1.77)	4.44 (2.77–7.11)	132.19 (99.76–175.16)	32.36 (23.82–43.95)
Iron replete	2.11 (1.97–2.27)	1 (0.83–1.21)	3.5 (2.89–4.24)	125.56 (105.58–149.33)	23.51 (19.02–29.06)
Pregnant	1.94 (1.64–2.3)	1.45 (0.87–2.42)	3.76 (2.39–5.93)	132.41 (89.32–196.3)	23.5 (13.95–39.58)
Nonpregnant	2.14 (2.02–2.26)	0.96 (0.83–1.11)	3.74 (3.18–4.4)	130.54 (112.74–151.15)	26.07 (22.06–30.8)

[#]Pairs within the same category with the same symbol $*$, $**$, or $***$ were statistically significant at $\alpha = 0.05$.
^All pairwise differences were statistically significant at $\alpha = 0.05$ except between NHW and OTH and between NHB and MA.

Table 3: Unadjusted geometric means with 95% confidence intervals in ng/mg creatinine for selected endocrine disrupting chemicals by pregnancy trimester. Data from the National Health and Nutrition Examination Survey 2005–2010.

	Trimester		
	I	II	III
Bisphenol A	1.62 (0.95–2.75)	1.89 (1.42–2.5)	2.17 (1.73–2.7)
Butyl paraben	1.24 (0.48–3.16)	1.46 (0.81–2.63)	1.68 (0.52–5.41)
Ethyl paraben	2.04 (1.16–3.58)	3.76 (1.95–7.26)	5.74 (1.9–17.33)
Methyl paraben	117.84 (81.9–169.57)	143.58 (95.26–216.42)	177.21 (81.42–385.7)
Propyl paraben	32.53 (19.67–53.82)	16.55 (5.85–46.79)	33.72 (15.85–71.75)

in 2009-2010 (Figure 1) and from 51.2% to 69.4% for nonpregnant females. Percent detection rates for BPA among pregnant females were 86.7% in 2005-2006 and 93.7% in 2009-2010 (Figure 1). These rates among nonpregnant females were 92.7% and 90.3% for 2005-2006 and 2009-2010, respectively. Percent detection rates for MPB for both pregnant and nonpregnant females were very close to 100% for the entire study period (Figure 1).

The unweighted sample sizes for which data were available by pregnancy trimester were 23, 53, and 56 for the first, second, and third trimester, respectively. UGMs for BPA, BUP, EPB, and MPB rose as the pregnancy progressed from the first trimester to the third trimester. For example, UGM for MPB rose from 117.8 ng/mg creatinine in the first trimester to 177.2 ng/mg creatinine, an increase of more than 50%. Similarly, UGMs for EPB rose from 2.0 ng/mg creatinine in the first trimester to 5.7 ng/mg creatinine, an increase of more than 150%. However, because of relatively small sample sizes, statistical significance could not be reached except for EPB between the first and third trimester (Table 3, $p = 0.049$).

3.2. Multivariate Regression Analysis. R^2 for the models fitted for BPA, BUP, EPB, MPB, and PPB were 28.4%, 10.7%, 12.1%, 18%, and 14.5%, respectively, and unweighted sample size used in each case was 949. No interaction terms were found to be statistically significant for the models for BPA, MPB, and PPB. For BUP, interaction between race/ethnicity and smoking status was found to be statistically significant ($p < 0.05$). For EPB, interaction between iron storage status and pregnancy status was found to be statistically significant ($p < 0.05$).

Levels of BPA decreased with increase in age ($\beta = -0.0054$, $p = 0.04$, Table 4). The levels of any of the four parabens were not affected by age. Levels of all four parabens, namely, BUP, EPB, MPB, and PPB, decreased with increase in BMI ($p \leq 0.001$, Table 4) but BMI did not affect the levels of BPA. Number of live births or parity did not affect the levels of BPA for any of the four parabens. Levels of BUP decreased over the study period of 2005–2010 ($\beta = -0.086$, $p = 0.03$, Table 4) but the levels of EPB increased over the same period ($\beta = 0.099$, $p = 0.02$, Table 4). There was a negative association between the levels of urinary albumin and EPB ($\beta = -0.0001$, $p < 0.001$, Table 4). There was a positive association between the levels of BPA and all four parabens and urinary creatinine ($p < 0.001$, Table 4).

Adjusted geometric means (AGM) for BPA were not affected by race/ethnicity, smoking status, or pregnancy status. However, statistically significantly lower AGM was observed for BPA when iron was absent as compared to when iron was deficient (1.87 ng/mL versus 2.43 ng/mL, Table 5). NHB had statistically significantly lower AGM for BUP as compared to MA (0.74 ng/mL versus 1.34 ng/mL, Table 5), and smokers had statistically significantly lower BUP levels than nonsmokers (0.61 ng/mL versus 1.1 ng/mL,

Table 4: Regression slopes with p values for selected endocrine disrupting chemicals (EDC) for females aged 20–44 years. Data from the National Health and Nutrition Examination Survey 2005–2010.

	Endocrine disrupting chemical				
	Bisphenol A	Butyl paraben	Ethyl paraben	Methyl paraben	Propyl paraben
Age	−0.00538 (0.044)	0.00183 (0.715)	−0.00234 (0.561)	0.00668 (0.178)	0.00466 (0.444)
Body mass index	0.00287 (0.191)	−0.01665 (0.001)	−0.01738 (<0.001)	−0.01312 (<0.001)	−0.01705 (<0.001)
Number of live births	0.00813 (0.572)	0.00513 (0.859)	0.01704 (0.461)	−0.01812 (0.44)	−0.01733 (0.517)
Survey year	0.00204 (0.91)	−0.0855 (0.03)	0.09916 (0.016)	−0.04819 (0.206)	−0.06213 (0.182)
Urine albumin	0.00002 (0.12)	0 (0.978)	−0.00008 (<0.001)	−0.00004 (0.325)	−0.00003 (0.577)
Urine creatinine	0.00327 (<0.001)	0.00259 (<0.001)	0.0029 (<0.001)	0.00292 (<0.001)	0.00346 (<0.001)

Table 5: Adjusted geometric means in ng/mL with 95% confidence intervals for selected endocrine disrupting chemicals for females aged 20–44 years. Data from the National Health and Nutrition Examination Survey 2003–2010[#].

	Bisphenol A	Butyl paraben	Ethyl paraben	Methyl paraben	Propyl paraben
Non-Hispanic White	2.02 (1.85–2.2)	0.94 (0.78–1.14)	3.69 (3.01–4.53)*	99.23 (81.92–120.19)^	22.42 (17.81–28.22)^^
Non-Hispanic Black	2.14 (1.9–2.41)	0.74 (0.53–1.04)*	4.64 (3.43–6.28)&	288.53 (235.53–353.45)^	48.76 (37.27–63.78)^^
Mexican American	2.17 (1.86–2.53)	1.34 (0.9–2)*	3.22 (2.47–4.21)	205.37 (167.67–251.56)^	37.35 (27.41–50.91)^^
Others	2.11 (1.69–2.64)	0.84 (0.64–1.09)	2.73 (2.14–3.49)*,&	122.16 (91.92–162.34)^	19.84 (13.68–28.77)^^
Nonsmokers	2.06 (1.91–2.22)	1.1 (0.9–1.35)*	3.88 (3.21–4.68)	130.87 (109.02–157.11)	28.66 (22.9–35.85)
Smokers	2.07 (1.79–2.38)	0.61 (0.47–0.79)*	2.93 (2.29–3.75)	112.06 (86.13–145.79)	18.86 (13.67–26.03)
Iron absent	1.87 (1.56–2.24)*	0.75 (0.57–0.98)	4.08 (3.03–5.49)	118.19 (94.16–148.34)	26.5 (18.47–38.01)
Iron deficient	2.43 (2.1–2.82)*	1.03 (0.66–1.6)	4.09 (2.59–6.47)	127.74 (93.06–175.35)	32.6 (23.6–45.03)
Iron replete	2.03 (1.86–2.22)	0.96 (0.79–1.17)	3.33 (2.76–4.01)	126.78 (108.43–148.24)	23.8 (19.55–28.98)
Pregnant	1.78 (1.41–2.24)	1.59 (0.92–2.76)*	3.64 (2.09–6.32)	138.83 (89.64–214.99)	27.31 (16.88–44.2)
Nonpregnant	2.08 (1.94–2.23)	0.9 (0.79–1.04)*	3.56 (3.08–4.12)	124.61 (109.29–142.09)	25.41 (21.73–29.72)

[#]Levels for two groups within the same category with the same symbol ∗ or & were statistically significantly different at $\alpha = 0.05$.
^All pairwise differences were statistically significant at $\alpha = 0.05$ except between Non-Hispanic White and others.
^^All pairwise differences were statistically significant at $\alpha = 0.05$ except between Non-Hispanic White and others and between Non-Hispanic Black and Mexican American.

a difference of more than 40%, Table 5). However, when interaction between race/ethnicity and smoking status is taken into account, among smokers, only NHW and MA had statistically significantly higher levels of BUP than OTH (0.68 ng/mL and 1.47 ng/mL versus 0.25 ng/mL, $p < 0.001$, Figure 2(a)). In addition NHB smokers almost had statistically significantly lower BUP than MA (0.45 ng/mL versus 1.47 ng/mL, $p = 0.053$, Figure 2(a)). In addition NHB and OTH nonsmokers only had statistically significantly higher levels of BUP than NHB and OTH smokers, respectively (Figure 2(a)). The same almost applied to NHW nonsmokers versus smokers ($p = 0.054$). Pregnant females were found to have statistically significantly higher adjusted levels of BUP than nonpregnant females (1.59 ng/mL versus 0.9 ng/mL, a difference of more than 60%, Table 5). Both NHW and NHB had statistically higher levels of EPB than OTH (Table 5). Other than this, EPB levels were not affected by smoking, iron storage, and pregnancy status even though pregnant females did have slightly higher EPB levels than nonpregnant females (3.64 ng/mL versus 3.56 ng/mL, Table 5). However, when statistically significant interaction between iron storage status and pregnancy status is taken into account, for pregnant females, EPB levels were found to be statistically significantly higher when iron was deficient than when iron was absent ($p = 0.045$, Figure 2(b)) and EPB levels were almost higher when iron was replete than when iron was deficient ($p = 0.056$). The order in which adjusted levels of MPB were observed was NHB (288.5 ng/mL) > MA (205.4 ng/mL) > OTH (122.2 ng/mL) > NHW (99.2 ng/mL) and all pairwise differences were statistically significant except between NHW and OTH. It is noticeable that NHB had almost three times the adjusted levels of MPB compared to NHW. The adjusted levels of PPB were observed in the order NHB (48.8 ng/mL) > MA (37.4 ng/mL) > NHW (22.4 ng/mL) > OTH (19.8 ng/mL) and all pairwise differences were statistically significant except those between NHW and OTH and between NHB and MA. Neither the levels of MPB nor the levels of PPB were affected by smoking, iron storage, or the pregnancy status even though pregnant females did have somewhat higher levels of both MPB (138.8 ng/mL versus 124.6 ng/mL) and PPB (27.3 ng/mL versus 25.4 ng/mL).

4. Discussion

Given the evidence that is provided by the current literature including some of the studies reviewed in the Introduction, there is the possibility that prenatal exposure to BPA has adverse consequences for the developing fetus as well as children during at least the early childhood. The adverse consequences include miscarriages [21], low birth weight

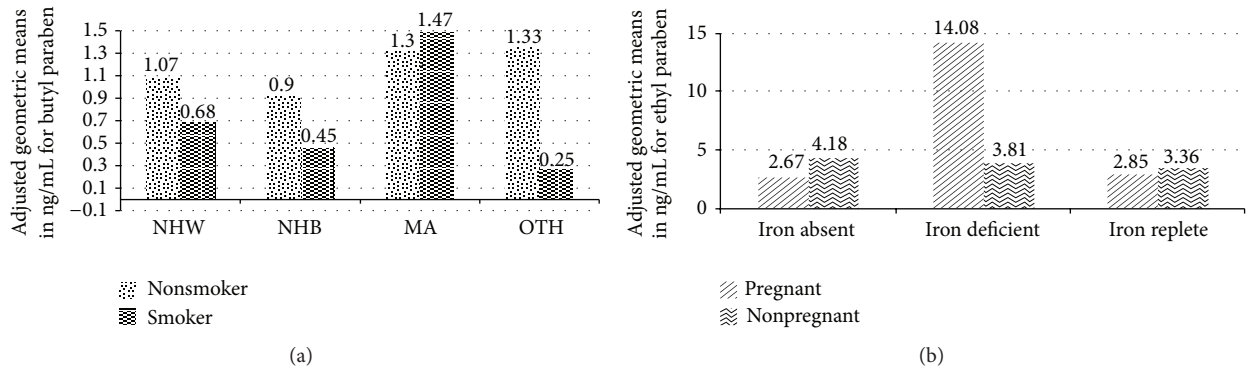

Figure 2: Adjusted geometric means in ng/mL for (a) butyl paraben by race/ethnicity (NHW = Non-Hispanic White, NHB = Non-Hispanic Black, MA = Mexican American, and OTH = other unclassified races/ethnicities) and smoking status and (b) ethyl paraben by iron storage status and pregnancy status.

[16, 18], obesity [22, 23], overweight [14], impaired fetal growth [17], reduced gestation [11], wheezing [24], and behavioral problems like anxiety/depression and aggressive behavior [25]. In this study, the percent of pregnant females for whom BPA was detected rose from 86.7% in 2005-2006 to 96.8% in 2007-2008 and dropped slightly to 93.7% in 2009-2010 (Figure 1) even though the lower limit of detection remained the same at 0.4 ng/mL for the entire study period. Thus, exposure to BPA among pregnant females remains a substantial risk factor for the fetus and children. Another concern that should be considered here is the fact that, in spite of the absence of statistical significance (which, in the opinion of this author, is primarily due to small sample sizes), the levels of PBA rose consistently as the pregnancy progressed from 1.24 ng/mg creatinine in the first trimester to 1.89 ng/mg creatinine during the second trimester and then finally to 2.17 ng/mg creatinine during the third trimester. There may be several reasons for this observation. First, the rate at which BPA is passed through the placenta to the fetus may slow down as the pregnancy progresses. However, this is in contradiction to what was found by Valvi et al. [14] who found the BPA levels to have decreased to 2.0 μg/g creatinine during the third trimester from 2.6 μg/g during the first trimester. Secondly, though unlikely, additional BPA exposure during the second and third trimester of pregnancy may explain the increase in the observed BPA levels from the first to the third trimester. Third, ongoing physiological changes and associated processes as the pregnancy progresses may have slowed down the clearance of BPA from the body meaning upward changes in half-life of BPA. While there is a vast amount of literature on metabolism and toxicokinetics of BPA, for example, as provided in http://www.who.int/foodsafety/chem/chemicals/4_metabolism_and_toxicokinetics.pdf, the question we have raised may not have been answered yet. The issue of statistical significance has been complicated by lack of enough data on pregnant females provided by NHANES. For the dataset of this study, there were 113 pregnant females for 2005-2006; there were only 20 and 26 pregnant females for 2007-2008 and 2009-2010, respectively. The reason for this lies in the fact that while pregnant females were oversampled in NHANES until the 2005-2006 cycle, oversampling of pregnant females was discontinued starting the 2007-2008 cycle of NHANES (http://www.cdc.gov/nchs/data/nhanes/analyticnote_2007-2010.pdf). Also, there is no reason to assume that the samples of pregnant females available for analyses during their first, second, and third trimester were, in fact, random samples of all pregnant females during their first, second, and third trimesters, respectively. In fact, the overall sample of pregnant females may also not be a random sample of pregnant females.

Calafat et al. [26] found adjusted BPA levels to be significantly lower in Mexican Americans than in Non-Hispanic Blacks ($p = 0.006$) and Non-Hispanic Whites ($p = 0.007$) using NHANES 2003-2004 data. These results could not be confirmed in this study. We did not find any racial/ethnic differences in the levels of BPA. This may be due to the differences in study design and the population studied. Casas et al. [27] found smoking to be associated with higher levels of BPA. This finding was not confirmed in this study. However, in our study age was found to be negatively associated with BPA levels (Table 3) as was also found by Casas et al. [27].

There was a consistent increase in the levels of BUP, EPB, and MPB from the first trimester to the third trimester of pregnancy (Table 3). For BUP, the rise from the first trimester to the third trimester was about 35% from 1.24 ng/mg creatinine to 1.68 ng/mg creatinine; for EPB, it was about 182% from 2.04 ng/mg creatinine to 5.74 ng/mg creatinine; and for MPB, it was about 50% from 117.84 ng/mg creatinine to 177.21 ng/mg creatinine (Table 3). As previously discussed in the context of a similar rise for BPA, increasing levels of these toxicants as pregnancy progresses from the first trimester to the third trimester may be due to increasing exposure to these toxicants during pregnancy or due to decelerating excretion of these toxicants from the body as pregnancy progresses or due to the decreased rate at which parabens are passed through the placenta to the fetus as the pregnancy progresses. The cross-sectional nature of data along with small sample sizes defies any reasonable answers to these questions. On the other hand, a consistent trend of the observed magnitude like this cannot be ignored. A longitudinal dataset from the same females followed from prepregnancy through the

full pregnancy and beyond with urine samples collected at various time points during the pregnancy will provide a better data foundation and any answers that are sought from it. Right now, judgment may be reserved but these data cannot be dismissed outright.

Levels of both MPB and PPB among NHB were found to be more than 2.5 times higher than in NHW (Table 4) which is similar to what was found by Smith et al. [5]. This may be due to the differences in how parabens are metabolized by different racial/ethnic groups. Smith et al. [5] also found levels of MPB and PPB to be 25–45% lower during pregnancy than before the pregnancy but, in this study, pregnant and nonpregnant females did not differ in their levels of MPB and PPB. This is due to differences in the study design. Smith et al. [5] measured MBP and PPB levels in the same females before and during pregnancy. We used cross-sectional data, not longitudinal data, to compare levels of MPB and PPB between pregnant and nonpregnant females.

New to this study, we found levels of BUP to be higher among nonsmokers than smokers (1.1 ng/mL versus 0.61 ng/mL, Table 4). It is possible that constituents in tobacco smoke may induce enzymes that accelerate clearance of BUP from the body resulting in lower levels of BUP among smokers. Pregnant females were found to have more than 60% higher levels of BUP than nonpregnant females (1.59 ng/mL versus 0.9 ng/mL, Table 4). This should be of concern for the developing fetus in view of the finding by Ali and Elgoly [4] in an animal study that exposure to BUP during pregnancy is related to neurodevelopmental disorders in the offspring.

In conclusion, pregnancy affects the levels of urinary BPA and parabens thus exposing the developing fetus to these toxicants and any associated adverse health consequences. In addition, concentrations of these toxicants vary as pregnancy progresses from the first trimester to the third trimester.

Data Access

All data used in this research are available free of charge from http://www.cdc.gov/nchs/nhanes/index.htm.

Competing Interests

The author declares that he has no financial or any other competing interests that could have affected the conclusions arrived at in this paper.

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