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Impact of Pregnancy on the Concentrations of Dichlorophenols

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Abstract

Because of the concerns that exposure to 2,4-dicholorophenol (2,4-DCP) and 2,5-dichlorophenol (2,5-DCP) may adversely affect pregnancy outcomes, this study was undertaken to evaluate the impact of pregnancy on the levels of 2,4-DCP and 2,5-DCP. Data from National Health and Nutrition Examination Survey were used to fit regression models to evaluate this association with adjustment for other factors that affect the levels of these chemicals. Non-pregnant females had higher levels of 2,4-DCP and 2,5-DCP than pregnant females but the differences were not statistically significant. Even though statistically significant trends were not detected, levels of 2,5-DCP increased over pregnancy trimesters. Non-Hispanic whites had the lowest levels of both 2,4-DCP and 2,5-DCP as compared to non-Hispanic blacks and Mexican Americans ($p < 0.01$). Smoking did not affect the levels of either 2,4-DCP or 2,5-DCP. Those who were iron deficient had statistically significantly higher levels of both 2,4-DCP and 2,5-DCP than those who were iron replete ($p <= 0.01$).

Keywords: Regression models; Smoking; NHANES; Pregnancy

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Introduction

Dichlorophenols (DCPs) are a class of compounds which are derivatives of phenol containing two chlorine atoms. They have six isomers, namely, 2,3-dicholrophenol, 2,4-dicholrophenol (2,4-DCP), 2,5-dicholrophenol (2,5-DCP), 2,6-dicholrophenol, 3,4-dicholrophenol, and 3,5-dicholrophenol. They are used as intermediates in the manufacture of more complex chemical compounds. 2,4-DCP is a photo-degradation product of the common antibacterial and antifungal agent triclosan (Singer et al., 2002, Latch et al., 2005). Liquid (molten) 2,4-DCP is readily absorbed through the skin and contact with large amounts may be fatal (Kintz et al., 1992). Exposure to 2,4-DCP may occur via absorption and/or inhalation of 2,4-DCP at workplaces where 2,4-DCP is produced or used (National Library of Medicine 2013). Exposure to 2,4-DCP may also occur by ingesting drinking water contaminated with 2,4-DCP, by ingesting fish and vegetables, or by coming in contact with vapors and other products that contain 2,4-DCP (National Library of Medicine, 2013). Workers in wood treatment plants, tanneries, textile plants, pulp and paper mills, as well as pesticide spray operators may also be exposed to 2,4-DCP as quoted in National Library of Medicine (2013).

2,5-DCP is a metabolite of para dichlorobenzene which volatilizes easily and which can be absorbed through oral, dermal, or pulmonary exposure routes (http://www.cdc.gov/biomonitoring/25D_BiomonitoringSummary.html). In a study of 538 pregnant females living in the Salinas Valley of California (Castorina et al., 2010), a highly agricultural area, over 50% of the samples were found to have 2,4-DCP as well as 2,5-DCP which according to the authors of this study, may be related to home or agricultural pesticides used in this area. In a study of 105 pregnant females in Northern Puerto Rico (Meeker et al., 2013), 2,4-DCP was detected in 97.9% of the urine samples and 2,5-DCP was detected in 100% of the urine samples and levels of 2,5-DCP among pregnant females of Puerto Rico were found to be higher than females of reproductive age in general US population (26.0 ng/mL vs. 8.4 ng/mL for NHANES 2007-2008 and 5.1 ng/mL for NHANES 2009 - 2010). In more than 90% of the air and urine samples collected from 119 adults living in Osaka, Japan, 2,5-DCP was detected (Yoshida et al., 2002). In a study

of 71 females referred for amniocentesis (Philippat et al., 2013), urine and amniotic fluid were analyzed and 2,4-DCP, 2,5-DCP, benzophenon-3 (BP-3), triclosan (TCS) among other endocrine disrupting chemicals (EDC) were detected.

Higher levels of 2,5-DCP were detected among workers exposed to 1,4-dichlorobenzene along with higher white blood cell count and serum alanine aminotransferase levels (Hsiao et al., 2009). Buttke et al. (2012) found an inverse association between the levels of 2,5-DCP and age at menarche in a study of 12 - 16 years old girls. Adjusted birth weight was found to decrease by 77 grams and 49 grams with 1 unit increase in log transformed values of 2,4-DCP and 2,5-DCP concentrations in maternal urine respectively (Philippat et al., 2012). In a study of 404 females (Wolff et al., 2008) in New York City during their third trimester of pregnancy, high prenatal exposure to 2,5-DCP was associated with relatively lower birth weight by 210 grams in boys. Concentrations of 2,4-DCP and 2,5-DCP were found to be lower in pregnant females than in their children (Casas et al. 2011). Association of lower birth weights with prenatal exposure to 2,5-DCP and 2,4-DCP (Wolf et al., 2008, Phillipat et al., 2012) should be of concern because low birth weight is associated with adverse developmental outcomes.

The adverse health effects associated with the exposures to 2,4-DCP and 2,5-DCP should of particular concern for the developing fetus. While, there have been a few studies which have assessed the effect of prenatal exposure to 2,4-DCP and 2,5-DCP as reviewed above, we do not know of a study done in the general US population to delineate the differences in the concentrations of DCP in pregnant and non-pregnant females. Consequently, this study was undertaken to evaluate the impact of pregnancy on the concentrations of DCP among females aged 20 - 44 years. The data from NHANES (www.cdc.gov/nchs/nhanes.htm) for the period 2005-2010 were used for this purpose. This communication extends the previous work using the same data to evaluate the impact of pregnancy on the levels of phthalates (Jain, 2014), triclosan (Jain, 2015), sunscreen agent benzophenone-3 (Jain, 2016a), and parabens and bisphenol-A (Jain, 2016b).

Materials and Methods

Data source and data description

Data were downloaded from demographic (http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/DEMO_D.htm), DCP-data files (http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/PP_D.htm), serum cotinine, body measures, and pregnancy files (http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/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, non-institutionalized U.S. 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 non-response, and post-stratification.

Data were available for 2,4-DCP, 2,5-DCP, 2,4,5-Trichlorophenol (2,45,-TCP), 2,4,6-TCP, and O-phenyl phenol. Urine samples for which concentrations of 2,4,5-TCP, 2,4,6-TCP, and O-phenyl phenol were found to be below the limit of detection (LOD) were 77%, 76%, and 83.2% respectively, thus it was not feasible to include these compounds in the study due to small sample size. For, 2,4-DCP and 2,5-DCP, urine sample concentrations were found to be below LOD in 16.7% and 2% of samples respectively. Therefore, 83.3% and 98% of urine samples had concentrations of 2,4-DCP and 2,5-DCP that were ≥ LOD. Traditionally, at least for the data reported from NHANES, when concentrations are below the LOD, they are imputed as LOD ÷ √2 before proceeding to analyze data. However, when a large percentage of samples have concentrations below LOD, the substitution of unknown concentrations by a constant LOD ÷ √2 can lead to inaccurate or unreliable results. Many researchers, particularly those at the U.S. Centers for Disease Control, though somewhat arbitrarily, have taken the stance that unless at least 60% of the samples have concentrations ≥ LOD, the statistical analysis is too unreliable to be carried out. This approach has been used by other authors such as Wang and Jain (2009) and Jain (2013a), and therefore, in this study, we adopted this approach. Therefore, statistical analysis was carried out for 2,4-DCP and 2,5-DCP only. It should, however, be noted that if the only interest lies in analyzing the frequency of detecting a specific chemical, not in its concentrations, the 60% rule as specified above is irrelevant.

Sample selection

This study was limited to those females who were aged 20 - 44 years. After removing 70 females from the data set for whom either the smoking status and/or the iron storage status were missing, a total of 1147 participants (149 pregnant and 998 non-pregnant females) were available for analysis. The sample size details are given in Table 1.

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

	Pregnant		Non-pregnant		Total	
	N	%	N	%	N	%
Total	149	100.0	998	100.0	1147	100.0
Non-Hispanic White	58	38.9	432	43.3	490	42.7
Non-Hispanic Black	20	13.4	197	19.7	217	18.9
Mexican American	52	34.9	195	19.5	247	21.5
Others	19	12.8	174	17.4	193	16.8
Nonsmoker	131	87.9	727	72.8	858	74.8
Smoker	18	12.1	271	27.2	289	25.2
Iron absent	50	33.6	187	18.7	237	20.7
Iron deficient	37	24.8	151	15.1	188	16.4
Iron replete	62	41.6	660	66.1	722	62.9
Pregnancy trimester						
I trimester	24	16.1				
II trimester	53	35.6				
III trimester	56	37.6				

Laboratory methods

Laboratory methods to measure DCPs are provided by the Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/PP_D.htm#Description_of_Laboratory_Methodology). Briefly, the method used solid phase extraction coupled on-line to high performance liquid chromatography and tandem mass spectrometry. Laborato-

ry methodology to test for pregnancy is also provided by the Centers for Disease Control and Prevention (http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/UCPREG_D.htm#Description_of_Laboratory_Methodology). Briefly, the methods use the Icon 25 hCG kit, a rapid chromatographic immunoassay for the qualitative detection of human chorionic gonadotropin.

Outcome variables

Log10-transformed values of 2,4-DCP and 2,5-DCP were used as the two outcome or dependent variables for this study.

Covariates

The independent variables/covariates used for this study were: age, race/ethnicity (non-Hispanic white (NHW), non-Hispanic black (NHB), Mexican American (MA), and other unclassified race/ethnicities (OTH)), pregnancy status (pregnant, non-pregnant), smoking status (nonsmoker, smoker), iron storage status (absent, deficient, replete), body mass index, and NHANES study year to adjust for any changes over time, urine albumin, and urine creatinine. Urine creatinine was used for hydration correction. Specific gravity of the urine is another measure that has been used for hydration correction but since NHANES does not provide data on specific gravity of the urine, urine creatinine was used for this study.

Non-smokers 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. 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 (2013b). Number of live births was also considered as one of the independent variables but, in a preliminary analysis, this was not found to have statistically significant association with either of the two dependent variables.

Statistical Analysis

One multivariate regression model each for 2,4-DCP and 2,5-DCP with dependent and independent as listed before were fitted. 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 $\alpha = 0.05$.

All analyses were done using SAS version 9.2 (www.sas.com, SAS, Cary, North Carolina, USA) and SUDAAN version 11.0 (www.rti.org/SUDAAN, Rsearch Triangle Institute International, Research Triangle Park, North Carolina, USA). All analyses used appropriate weights as provided in the data files. First, unadjusted geometric means (UGM)for 2,4-DCP and 2,5-DCP and percent participants ≥ LOD were computed using SUDAAN Proc DESCRIPT and t-tests were used to compare UGMs across pregnancy status, smoking status, iron storage status, gender, and race/ethnicity. Next, UGMs for 2,4-DCP and 2,5-DCP were computed across three pregnancy trimesters and pair-wise comparisons were made by t-test. Next, multivariate linear regression models with dependent and independent variables as previously described were fitted by using SUDAAN Proc REGRESS. Finally, adjusted geometric means (AGM) for 2,4-DCP and 2,5-DCPas computed during the regression modeling producers were compared across three pregnancy trimesters and pair-wise comparisons were made by t-test. It should be noted that actual sample sizes used for regression models were slightly smaller than those listed in Table 1 because of missing values for other independent variables like body mass index etc.

Results

Univariate analysis

Detection rates for pregnant females for 2,4-DCP increased slightly from 94.5% in 2005 - 2006 to 98.2% in 2009 - 2010 but for non-pregnant females, they remained the same throughout the study period. Detection rates for 2,5-DCP for pregnant females were above 92% for both 2005 - 2006 and 2007 - 2008 but decreased to 61.7% for 2009 - 2010; and for non-pregnant females, detection rates were above 89% for both 2005 - 2006 and 2007 - 2008 but decreased slightly to 82% for 2009 - 2010.

UGM for 2,4-DCP concentrations for NHW was less than half of what it was for MA and more than 25% lower than what it was for NHB (0.69 vs. 1.43 and 1.23 ng/mg creatinine, $p < 0.01$, Table 2). Smokers had lower UGM for 2,4-DCP concentrations than nonsmokers (0.76 vs. 0.88 ng/mg creatinine, Table 2) but the differences were not statistically significant. UGM for 2,4-DCP concentrations was higher when iron was absent as compared to when iron was replete (0.99 vs. 0.79 ng/mg creatinine, Table 2). Non-pregnant females had somewhat higher UGM than pregnant females (0.85 vs. 0.79 ng/mg creatinine, Table 2) but the differences were not statistically significant. UGM for 2,4-DCP concentrations rose by more than 25% from 0.69 (0.51 – 0.94) ng/mg creatinine during first trimester to 0.94 (0.61 – 1.43) ng/mg creatinine during second trimester and then dropped by more than 20% to 0.77 (0.53 – 1.13) ng/mg creatinine (Table 3) but the differences were not statistically significant.

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 National Health and Nutrition Examination Survey 2005 - 2010.

	2,4-dichlorophenol	Statistically Significant Differences	2,5-dichlorophenol	Statistically Significant Differences
Total	0.85 (0.77 - 0.94)		7.17 (5.99 - 8.57)	
Non-Hispanic White (NHW)	0.69 (0.62 - 0.76)	NHW < NHB ($p < 0.01$), NHW < MA ($p < 0.01$), NHW < OTH ($p < 0.01$)	4.64 (3.84 - 5.6)	NHW < NHB ($p < 0.01$), NHW < MA ($p < 0.01$), NHW < OTH ($p < 0.01$)
Non-Hispanic Black (NHB)	1.23 (0.98 - 1.54)		20.02 (14.25 - 28.12)	NHB > OTH ($p = 0.03$)
Mexican American (MA)	1.43 (1.08 - 1.9)		18.59 (11.54 - 29.93)	MA > OTH ($p = 0.03$)
Others (OTH)	1.05 (0.84 - 1.31)		9.62 (6.87 - 13.46)	
Nonsmokers	0.88 (0.8 - 0.98)		7.22 (6 - 8.68)	

Smokers	0.76 (0.62 - 0.93)		7.02 (5.27 - 9.34)	
Iron Absent	0.99 (0.79 - 1.25)		9.4 (6.58 - 13.44)	IA > IR (p = 0.3)
Iron Deficient	0.98 (0.76 - 1.27)		8.84 (6.24 - 12.54)	ID > IR (p = 0.04)
Iron Replete	0.79 (0.7 - 0.88)		6.33 (5.27 - 7.61)	
Pregnant	0.79 (0.61 - 1.02)		7.42 (4.39 - 12.54)	
Non-pregnant	0.85 (0.77 - 0.95)		7.15 (5.96 - 8.57)	

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

	Trimester		
	I	**II**	**III**
2,4-dichlorophenol	0.69 (0.51 - 0.94)	0.94 (0.61 - 1.43)	0.77 (0.53 - 1.13)
2,5-dichlorophenol	3.85 (1.56 - 9.53)	9.1 (4.07 - 20.33)	8.49 (4.44 - 16.24)

Both MA and NHB had statistically significantly higher UGM for 2,5-DCP concentrations than NHW (20.0 and 18.6 vs. 4.6 ng/mg creatinine respectively, $p < 0.01$, Table 2). Smokers had lower UGM for 2,5-DCP concentrations than nonsmokers (7.02 vs. 7.22 ng/mg creatinine, Table 2). When iron storage was absent or deficient, the UGM levels were higher than when iron storage was replete (9.4 and 8.44 ng/mg creatinine vs. 6.33 ng/mg creatinine, $p <= 0.04$, Table 2). Non-pregnant females had somewhat lower UGM than pregnant females (7.15 vs. 7.42 ng/mg creatinine, Table 2) but the differences were not statistically significant. UGMs for 2,5-DCP concentrations were more than twice during second and third trimester than what they were during first trimester (9.1 and 8.49 vs. 3.85 ng/mg creatinine respectively, Table 3) but differences were still not statistically significant.

Multivariate Regression Analysis

None of the interaction terms were found to be statistically significant at $\alpha = 0.05$ for either 2,4-DCP or 2,5-DCP. The actual sample size used in the analysis was 1035. R^2 was 29.1% for the model for 2,4-DCP, and 29% for the model for 2,5-DCP. Age did not affect the concentrations of 2,4-DCP or 2,5-DCP. Concentrations of 2,5-DCP ($\beta = 0.0084$, $p = 0.04$, Table 4) increased with increase in BMI but concentrations of 2,4-DCP were not associated with BMI. Concentrations of 2,5-DCP decreased during the study period ($\beta = -0.1235$, $p = 0.008$, Table 4). Urine creatinine was positively associated with the concentrations of 2,4-DCP as well as 2,5-DCP ($p < 0.001$, Table 4).

Table 4: Regression slopes with p-values for 2,4-DCP and 2,5-DCP for females aged 20-44 years. Data from National Health and Nutrition Examination Survey 2005 - 2010.

	2,4-DCP	**2,5-DCP**
Age	-0.00024 (0.925)	-0.00301 (0.412)
Body Mass Index	0.00158 (0.535)	0.00835 (0.038)
Survey Year	-0.03436 (0.158)	-0.12349 (0.008)
Urine Albumin	0.00002 (0.356)	0.00003 (0.461)
Urine Creatinine	0.00343 (< 0.001)	0.00394 (< 0.001)

NHW had statistically significantly lower AGM for 2,4-DCP concentrations than NHB, MA, and OTH (0.65 vs. 1.2, 1.43, and 1.06 ng/mL respectively, $p < 0.001$, Table 5). Smoking did not affect the concentrations of 2,4-DCP. AGM for 2,4-DCP concentrations was statistically significantly lower when iron was replete as compared to when iron was deficient (0.76 vs. 1.06 ng/mL, $p = 0.01$, Table 5). AGM for 2,4-DCP concentrations was about 20% higher among non-pregnant females than among pregnant females (0.83 vs. 0.64 ng/mL, Table 5) but the differences were not statistically significant.

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 National Health and Nutrition Examination Survey 2005 - 2010.

	2,4-dichlorophenol	**Statistically Significant Differences**	**2,5-dichlorophenol**	**Statistically Significant Differences**
Non-Hispanic White (NHW)	0.65 (0.6 - 0.72)	NHW < NHB (p < 0.01), NHW < MA (p < 0.01), NHW < OTH (p < 0.01)	4.42 (3.66 - 5.34)	NHW < NHB (p < 0.01), NHW < MA (p < 0.01), NHW < OTH (p < 0.01)
Non-Hispanic Black (NHB)	1.2 (0.96 - 1.49)		17.38 (12.4 - 24.35)	NHB > OTH (p = 0.03)
Mexican American (MA)	1.43 (1.11 - 1.84)		18.68 (12.18 - 28.64)	MA > OTH (p = 0.03)
Others (OTH)	1.06 (0.84 - 1.33)		10.24 (7.2 - 14.56)	
Nonsmokers (NSM)	0.83 (0.76 - 0.9)		6.58 (5.63 - 7.68)	
Smokers (SM)	0.81 (0.65 - 0.99)		7.88 (5.98 - 10.38)	
Iron Absent (IA)	0.87 (0.69 - 1.09)		7.56 (5.45 - 10.49)	
Iron Deficient (ID)	1.06 (0.82 - 1.37)	ID > IR (p = 0.01)	9.84 (6.98 - 13.88)	ID > IR (p < 0.01)
Iron Replete (IR)	0.76 (0.69 - 0.84)		6.2 (5.3 - 7.26)	
Pregnant	0.64 (0.47 - 0.88)		5.32 (3 - 9.43)	
Non-pregnant	0.83 (0.77 - 0.91)		7.02 (6.04 - 8.16)	

The order in which AGMs for 2,5-DCP concentrations by race/ethnicity were seen was MA > NHB > OTH > NHW and all pairwise differences except between NHB and MA were statistically significant ($p <= 0.03$, Table 5). AGMs for both NHB and MA were more than four times of what they were for NHW (17.4, 18.7 vs. 4.4 ng/mL respectively, $p < 0.01$, Table 5). Smoking and pregnancy statuses did not affect the adjusted concentrations of 2,5-DCP. AGM was statistically significantly higher when iron storage was deficient then when iron storage was replete (9.84 vs. 6.2 ng/ml, $p < 0.01$, Table 5). AGM for 2,5-DCP concentrations was more than 20% higher among non-pregnant females than among pregnant females (7.0 vs. 5.3 ng/mL, Table 5) but the differences were not statistically significant.

Discussion

Non-pregnant females had 29.7% higher AGM for 2,4-DCP concentrations than pregnant females, yet the differences were not found to be statistically significant. Pregnant females had 32% lower AGM for 2,5-DCP concentrations than non-pregnant females and the differences were not statistically significant. These results are somewhat surprising. It looks like large standard errors of AGMs may be the reason for non-significant differences observed between pregnant and non-pregnant females. Standard errors of AGMs for pregnant females for 2,5-DCP were 2.4 times greater than those for non-pregnant females (1.58 vs. 0.646, data not shown). Standard errors of AGMs for pregnant females for 2,4-DCP were 1.5 times greater than those for non-pregnant females (0.069 vs. 0.045, data not shown). The reason for relatively larger changes in concentrations of these chemicals among pregnant females is likely to be due to ongoing physiological changes and associated processes as pregnancy progresses from the first to third trimesters. These changes as pregnancy progresses are reflected in the trimester wise chemical concentration data provided in Table 3.

Concentrations of 2,5-DCP were more than twice as high during third trimester as compared to first trimester (8.49 vs. 3.85 ng/mg creatinine, Table 3) and yet, no statistically significant differences were observed. Consequently, we went back and looked at the relative standard errors of unadjusted log transformed means over the three trimesters. However, differences as large as were seen for 2,5-DCP over time as the pregnancy progresses, cannot be totally ignored. These differences may be due to the effect of possibly, varying half-life of these chemicals. At this point in time, this is just a conjecture and there are no available trimester wise data to confirm or refute this conjecture. This is an area which requires future scientific investigations. The observed increasing concentrations of 2,5-DCP and possibly 2,4-DCP (Table 3) during pregnancy, could potentially be due to modification of drug half-life. Although there is no specific evidence that the compounds studied here have altered half-life during pregnancy, there is evidence that similar processes occur with human pharmaceuticals. Changes in physiology during pregnancy which begin during the first trimester and are most marked during the third trimester alter the pharmacokinetics of many drugs leading to changes in how drugs are absorbed, distributed, and finally eliminated from the body (Dawes and Chowienczyk, 2001). For example, clearance of anti-convulsive drugs like carbamazepine during pregnancy is accelerated while those of drugs like theophylline are impaired (Dawes and Chowienczyk, 2001). Elimination half-life of caffeine in healthy adults is about 4.9 hours; among women taking oral contraceptives about 5 - 10 hours, among pregnant women about 9 - 11 hours, and as much as 96 hours among individuals with severe liver disease (http://www.news-medical.net/health/Caffeine-Pharmacology.aspx). Behavioral changes during pregnancy may also affect exposure to chemicals, and therefore chemical burden. Caution must be exercised to understand and interpret these results. Toxicant concentrations are dynamic and can dramatically change with various metabolic states within the body. In this study, data from only single urine samples were available and as such may not be reflective of the true toxicant concentrations in the body. Observed toxicant concentrations may be affected by activity concentration, time of the day, dietary intake, and many other variables. However, Meeker et al. (2013) also did not report any statistically significant changes in the levels of either 2,4-DCP or 2,5-DCP over three samples collected at 20 ± 2, 24 ± 2, and 28 ± 2 weeks of gestation among Puerto Rican pregnant females aged 18 - 40 years.

Further, these results were generated using cross-sectional data. As such, the trimester wise data analyzed were from different pregnant females. In addition, while NHANES data do provide representative samples for certain combinations of age, gender, and racial/ethnicity, the data may not represent a representative sample of pregnant and non-pregnant females. Also, there was an imbalance in the size of data for pregnant and non-pregnant females over the study period. The number of pregnant females in the data for the years 2005 - 2006, 2007 - 2008, and 2009 - 2010 were 106, 20, and 23 respectively. The number of non-pregnant females in the data for the years 2005 - 2006, 2007 - 2008, and 2009 - 2010 were 266, 336, and 396 respectively. This is because while pregnant females were oversampled until the NHANES cycle 2005 - 2006, oversampling of pregnant females was discontinued starting the NHANES cycle 2007 - 2008 (http://www.cdc.gov/nchs/data/nhanes/analyticnote_2007-2010.pdf). However, total sample size of 203 for pregnant females and 998 for non-pregnant females is still large enough by any statistical standards. In addition to the data quality, the outcome of any statistical analysis also depends up on natural characteristics of the data. In this case, non-representative and non-longitudinal nature of the data did affect the data quality. Relatively larger variability in the data for pregnant females is probably natural but it did affect the outcome of statistical analysis and the power of statistical tests. If the sample size for pregnant females were 5 or 10 times larger than they were, it is unknown but certainly possible that the power of statistical test could have increased. Finally, in order to truly understand the differences in how these chemicals are metabolized over the pregnancy period, longitudinal data on same females from pre-pregnancy to beyond the lactational period are required. However, a longitudinal study of the size of NHANES may be prohibitively expensive.

For both, 2,4-DCP and 2,5-DCP, NHW had statistically significantly lower concentrations than both NHB and MA (Table 2). These results are in concurrence with the results in a study by Ye et al., (2014) in spite of the differences in designs of this and Ye et al., (2014) study. Racial/ethnic differences in the observed concentration concentrations are probably due to the differences in exposure to these chemicals in addition to yet unknown factors.

Inability to store adequate iron has been associated with higher concentrations of toxic metals like cadmium and lead in blood among pregnant and non-pregnant females (Jain, 2013b). In this study, statistically significantly higher concentrations of 2,4-DCP were associated with iron storage deficiency (Table 2). The same was true for the concentrations of 2,5-DCP but the statistical significance was not reached. To the best of our knowledge, we do not know if anyone has studied the effect of inadequate iron storage on the concentrations of 2,4-DCP and 2,5-DCP.

Since this research was based on data obtained from spot urine samples, adjustments were made to account for this by including urine creatinine concentrations in all regression models and not surprisingly, statistically significant positive correlation between the concentrations of urine creatinine with 2,4-DCP as well as 2,5-DCP were observed (Table 3). Similarly urine albumin concentrations were used in all regression models to adjust for changes in albumin concentrations because of any disease or disorder.

Using data from NHANES for the period 2003-2010, Ye et al. (2014) found AGMs for both 2,4-DCP and 2,5-DCP concentrations for the age group 20-59 years to be lower than for the age groups 6 - 11 years and 60+ years. In comparison, this study was restricted to females aged 20 - 44 years old and age was not found to affect the concentrations of either 2,4-DCP or 2,5-DCP (Table 4). The concentrations of both 2,4-DCP and 2,5-DCP declined over the study period 2005 - 2010 (Table 4) but the decline was not statistically significant for 2,4-DCP. These results are in agreement with those in Ye et al. (2014) indicating decline in exposure to these two chemicals. While the concentrations of 2,4-DCP were not affected by body mass index, the concentrations of 2,5-DCP increased with increase in body mass index.

In summary, (i) pregnant females, possibly, had lower concentrations of 2,4-DCP and 2,5-DCP than non-pregnant females but the differences were not found to be statistically significant, (ii) as compared to other racial/ethnic groups, non-Hispanic whites had the lowest concentrations of 2,4-DCP and 2,5-DCP, and (iii) females in second and third trimester of their pregnancy, possibly, had higher concentrations of 2,5-DCP than females in first trimester of their pregnancy.

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