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Abbreviations

BFRs brominated flame retardants

BPA bisphenol A

BMI body mass index

CDC Centers for Disease Control and Prevention

CI confidence intervals

CV coefficient of variation

DDE *p,p*' - dichlorodiphenyldichloroetheDMTP dimethylthiophosphate

GM geometric mean

GSE geometric standard error

LSGM least squares geometric mean

LOD limit of detection

MTBE Methyl *tert*-butyl ether

MEP mono-ethyl phthalate

MiBP mono-isobutyl phthalate

NHANES National Health and Nutritional Examination Survey

PBDEs polybrominated diphenyl ethers

PAHs polycyclic aromatic hydrocarbons

PFCs perfluorinated compounds

PFOS perfluorooctane sulfonic acid

PCBs polychlorinated biphenyls

VOCs volatile organic compounds

ABSTRACT

Background: We analyzed biomonitoring data from the National Health and Nutritional Examination Survey (NHANES) to characterize both individual and multiple chemical exposures in U.S. pregnant women.

Methods: We analyzed data for 163 chemical analytes in 12 chemical classes for subsamples of 268 pregnant women from NHANES 2003-2004, a nationally representative sample of the U.S. population. For each chemical analyte, we calculated descriptive statistics. We calculated the number of chemicals detected within the following chemical classes; polybrominated diphenyl ethers (PBDEs), perfluorinated compounds (PFCs), organochlorine pesticides, and phthalates, and across multiple chemical classes. We compared chemical analyte concentrations for pregnant and non-pregnant women using least square geometric means, adjusting for demographic and physiological covariates.

Results: The percent of pregnant women with detectable levels of an individual chemical ranged from 0 to 100 percent. Certain PCBs, organochlorine pesticides, PFCs, phenols, PBDEs, phthalates, polycyclic aromatic hydrocarbons (PAHs) and perchlorate were detected in 99 to 100% of pregnant women. The median number of detected chemicals by chemical class ranged from 4 (out of 12 PFCs) to 9 (out of 13 phthalates). Across chemical classes, median number ranged from 8 (out of 17 chemical analytes) to 50 (out of 71 chemical analytes). We found, generally, levels in pregnant women were similar or lower than levels in non-pregnant women, adjustment for covariates tended to increase levels in pregnant women compared to non-pregnant women.

Conclusions: Pregnant women in the U.S. are exposed to multiple chemicals. Further efforts are warranted to understand sources of exposure and implications for policy-making.

INTRODUCTION

Exposure to chemicals during fetal development can increase the risk of adverse health consequences, including adverse birth outcomes (e.g. preterm birth and birth defects), childhood morbidity (e.g. neurodevelopmental effects and childhood cancer), and adult disease and mortality (e.g. cancer and cardiovascular effects) (Gluckman and Hanson 2004; Stillerman et al. 2008). Biomonitoring studies report nearly ubiquitous exposure to many chemicals in the U.S. population, for example, bisphenol A (BPA), perchlorate, and certain phthalates and polybrominated diphenyl ethers (PBDEs) (CDC 2009a). These, along with more geographically targeted studies of pregnant women, find pregnant women are also exposed to many chemicals (Bradman et al. 2003; Swan et al. 2005). Chemicals can cross the placenta and enter the fetus, and a number of chemicals measured in maternal urine and serum have also been found in amniotic fluid, cord blood and meconium (Barr et al. 2007). In some cases, such as for mercury, fetal exposures may be higher than maternal exposure (Barr et al. 2007).

Multiple chemical exposures are of increasing concern. Studies find exposure to multiple chemicals which act on the same common adverse outcome can have a greater effect than exposure to an individual chemical. This has been recognized by the National Academy of Sciences (NAS), which recommends future efforts accounting for risks from multiple chemical exposures combine effects from chemicals acting on the same common adverse health outcome (National Research Council 2008). Subsequently, assessment of exposure to multiple chemicals has been identified as an important future research area (Kortenkamp 2007).

Since few data are available on levels of individual or multiple chemicals in pregnant women, levels in reproductive-age women have often been used as an indicator of chemical levels in pregnant women (Blount et al. 2000). Some studies have directly compared pregnant women in

their cohort and reproductive-aged women from the National Health and Nutritional Examination Survey (NHANES), a nationally representative sample of the U.S. population. For example, phthalates measured in pregnant women from three U.S. locations were lower in the study population than those measured in reproductive-aged women from NHANES (Swan et al. 2005). Numerous physiological changes occur during pregnancy, including weight gain and increases in blood and plasma volume, which can affect concentrations of chemicals (Chesley 1972; Pirani and Campbell 1973). Chemicals may also concentrate in the fetus, which could influence maternal concentrations (Takahashi and Oishi 2000). Further, behavioral changes occurring during pregnancy, such as diet modification (e.g. quantity and food type), may also influence chemical body burdens in pregnant women (Mirel et al. 2009). Understanding whether some of these factors can influence maternal concentrations of chemicals helps inform our ability to use measurements of chemicals in non-pregnant women as a surrogate for pregnant women.

We analyzed biomonitoring data for pregnant women from NHANES to characterize exposure to individual and multiple chemicals and their metabolites in pregnant women. Additionally, we evaluated the extent to which levels measured in non-pregnant women are representative of levels in pregnant women, and what factors may explain observed differences.

METHODS

Study population

NHANES, conducted by the Centers for Disease Control and Prevention (CDC), is a nationally representative survey and physical examination assessing the health and nutritional status of the civilian, non-institutionalized U.S. population. The survey also includes measurement of chemicals and their metabolites in blood and urine (Further information at (CDC 2010)) We use the term chemical analyte here to describe both chemicals and their metabolites. Due to the complex

stratified survey design, separate sample weights are assigned to each survey respondent; each participant represents approximately 50,000 other U.S. residents. Pregnant women were oversampled in the NHANES survey from 2001 to 2006 (CDC 2009b) (protocols for oversampling pregnant women are described in Supplemental Materials and in detail elsewhere (Mirel et al. 2009)). We classified pregnancy status according to the results of the urine pregnancy test administered as part of NHANES protocols.

Most chemical analytes were measured in subsets of the total NHANES sample. Each subset included about one-third the total number of participants, so not all chemical analytes were measured in each participant. Further, not every group of chemical analytes was measured in each cycle. Therefore, we analyzed the 2003-2004 cycle, as it represents the cycle with highest number of chemical analytes measured across the sample of pregnant women. We limited our study population to those aged 15-44 years old to be consistent with the definition used by the National Center for Health Statistics for women of childbearing age (Chandra et al. 2005). Therefore, our study population includes 268 pregnant women and 1489 non-pregnant women aged 15-44 years included in at least one subsample for chemical analyte analysis.

Environmental chemical analyte analyses

Chemical analyte analyses were conducted at the National Center for Environmental Health laboratories (CDC, Atlanta, GA). Analytical procedures and summary statistics for the general population have been described in the Fourth National Report on Human Exposure to Environmental Chemicals and in the peer review literature (Calafat et al. 2008; Caldwell et al. 2009; CDC 2009a; Sjodin et al. 2008). We assessed 163 chemical analytes across 12 chemical classes (Table 1), measured in blood, urine and serum.

Data Analysis

We conducted analyses in SUDAAN 10.0 (Research Triangle Institute, Cary, NC) and SAS 9.2 (SAS Institute Inc., Cary, NC). SUDAAN calculates variance estimates after incorporating the non-random sampling design and the sample population weights, which account for oversampling of certain subgroups.

We examined summary statistics and distributional plots for each chemical analyte. We calculated the following descriptive statistics (analysis further described in Supplemental Materials): percent of women with levels greater than the limit of detection (LOD); geometric mean (GM); geometric standard error (GSE); median and 95th percentile estimates; and the coefficient of variation (CV, defined as the GSE divided by the GM). The GM, GSE, and CV were only calculated for chemical analytes with greater than 60% detection frequency. The median and 95th percentile were calculated for all chemical analytes. Concentrations less than the LOD were substituted by CDC with a value equal to the LOD divided by the square root of two. We present statistical results for individual chemical analytes in the main text which are representative of each chemical class (descriptive statistics and LODs for all 163 chemical analytes are presented in Supplemental Table 1). Representative chemical analytes were chosen based on public health relevance and expectation of relatively widespread exposure.

To assess extent of multiple exposures within a chemical class, we evaluated the number of individual PBDEs, perfluorinated compounds (PFCs), organochlorine pesticides and phthalates detected in each pregnant woman. We chose these chemical classes to represent banned persistent chemicals (organochlorine pesticides), persistent chemicals (PBDEs and PFCs) and currently used nonpersistent chemicals (phthalates).

We then evaluated the extent of multiple chemical exposures across chemical classes in three different subsamples. These three subsamples were the primary subsamples of the pregnant women. Pregnant women in subsample A were assessed for metals, cotinine, and PFCs (17 chemical analytes in 76 women); subsample B were assessed for metals, cotinine, organochlorine pesticides, phthalates, PBDEs, and polycyclic aromatic hydrocarbons (PAHs) (52 chemical analytes in 54 women); and subsample C were assessed for metals, phenols, PCBs, organophosphate insecticide metabolites, perchlorate, and cotinine (71 chemical analytes in 59 women) (see Supplemental Table 2 for subsample composition). Volatile organic compounds (VOCs) were only measured in a subsample of pregnant women that only partially overlapped with subsamples A, B and C. Consequently, we did not include VOCs in analyses of multiple chemical exposures.

To compare chemical analyte concentrations between pregnant and non-pregnant women, we constructed multivariate regression models, which included our main effect (binary pregnancy status variable) along with covariates. We log-transformed chemical analytes prior to regression analysis to account for the non-normal distributions. We calculated the least square geometric means (LSGM), which provide geometric mean estimates after adjustment for other covariates, from these models. For every chemical analyte in the main analysis, we used the same set of covariates. Covariates were included if they were significant predictors of more than one chemical analyte or if their inclusion in the model changed the beta coefficient for the main effect by more than 20 percent. The following covariates were evaluated: age (continuous); race/ethnicity (Mexican American, non-Hispanic white, non-Hispanic black, or other); education (high school diploma or less versus more than high school diploma); marital status (married/living with a partner, divorced/separated, or never married); parity (number of pregnancies resulting in live births; nulliparous versus one or more child); current body mass index (BMI, continuous); smoking

status (never, former, or current); serum albumin (continuous), length of food and drink fasting prior to blood collection (0-4.5 hours, 4.5-8.5 hours, or 8.5-24 hours) and urinary creatinine (continuous). All regression models were adjusted for the same covariates except for creatinine (included in models for urinary chemicals only). We excluded 12 non-pregnant women who reported fasting times greater than 24 hours. We defined statistical significance as $p<0.10$ for all analysis due to relatively small number of pregnant women sampled for each chemical analyte and consequently small degrees of freedom.

As a sensitivity analysis, we performed multivariate regression in women younger than 35 years old, since the age distribution differed between the two groups. For this analysis, we selected model covariates separately for each individual chemical analyte using the covariate selection method described above. Thus, the covariates in the sensitivity analysis may differ than what was used in the main analysis. We conducted sensitivity analysis for lead (n=215 pregnant and n=885 non-pregnant), BPA (n= 63 pregnant; n= 275 non-pregnant), and *p,p*' - dichlorodiphenyldichloroethene (DDE) (n=65 pregnant; n=380 non-pregnant).

RESULTS

While the majority of pregnant women and non-pregnant women were white, there was a higher percentage of Mexican American pregnant women compared to non-pregnant women, reflecting higher birthrates among Hispanic women in the US (Table 2) (Martin et al. 2007). Non-pregnant women were older, less likely to be married or with a partner, and more likely to smoke compared to pregnant women (Table 2). In addition, pregnant women had lower levels of albumin and shorter fasting times prior to blood collection compared to non-pregnant women.

Summary statistics of pregnant women for: 1) select chemical analytes are in Table 3; and 2) all 163 chemical analytes are in Supplemental Table 1. Descriptive statistics of select chemical analytes for

non-pregnant women are in Table 3. We found 0 to 100 percent of pregnant women had a detectable level across the individual chemical analytes. Eight of 12 classes of chemicals included individual chemical analytes detected in 99 to 100% of pregnant women (PFCs, PBDEs, PCBs, organochlorine pesticides, phenols, phthalates, PAHs, and perchlorate). Four classes (VOCs, PFCs, PCBs, and organochlorine pesticides) included at least one individual chemical analyte not detected in any pregnant women (Supplemental Table 1). In general, organophosphate metabolites, VOCs, and dioxins and furans were less frequently detected in pregnant women than the other chemical classes except for dimethylthiophosphate (DMTP), toluene and methyl *tert*-butyl ether (MTBE).

Among pregnant women, DDE had the highest GM concentration (GM= 140.4 ng/g lipid) of the persistent, lipophilic compounds measured in serum (PCBs, PBDEs and organochlorine pesticides), while concentrations of most of the other measured chemical analytes in these classes were an order of magnitude lower (4 to 8 ng/g lipid for PCBs, 5 to 23 ng/g lipid for PBDEs). Perfluorooctane sulfonic acid (PFOS) had the highest GM among the persistent chemical analytes which do not accumulate in lipids (e.g. lead, cadmium, and PFCs). Of the nonpersistent chemical analytes measured in urine (organophosphate metabolites, phenols, phthalates, PAHs, and perchlorate), triclosan, benzophenone-3, and mono-ethyl phthalate (MEP) had the highest GMs (17.00, 25.49, and 226.53 µg/L respectively).

While the GM for cotinine was below 1 µg/L, the range of concentrations spanned three orders of magnitude (CV = 0.31). Variability in other chemical analyte levels measured in pregnant women was generally low (CV < 0.25), with the exception of some phenols (CV=0.25-0.51), phthalates (CV=0.22-0.35), MTBE (CV=0.40), triclosan (CV=0.51) and PBDE-153 (CV=0.31).

Figure 1 shows the numbers of individual PFC, PBDE, organochlorine pesticide and phthalate chemical analytes detected in individual pregnant women. At least two organochlorine pesticides,

one PBDE, two PFCs and four phthalates were measured in each pregnant woman. The median number of chemicals detected for organochlorine pesticides, PBDEs, PFCs and phthalates were 6, 6, 4 and 9, respectively. For PBDEs and phthalates, 7% and 2% respectively, had detectable levels of 90% or more of the chemical analytes in the class.

The median number of chemical analytes detected among women in subsamples A, B, and C were: 8 (Range: 4-12), 37 (Range: 28-45), and 50 (Range: 35-60), respectively (Figure 2). We found generally that the overall number of chemicals detected was not dominated by detects within a particular chemical class (Figure 3 of subsample B, other subsamples were similar). For example, several participants in subsample B at the median detected level (37 chemicals), had 10 phthalates, 10 PAHs, 7 PBDEs, 6 organochlorine pesticides, 3 metals and cotinine detected.

GM and median levels for most chemicals were similar or lower in pregnant compared to non-pregnant women, except for PBDEs, DMTP, triclosan, and perchlorate (Table 3). About half the LSGM estimates for pregnant women (Table 4) increased after adjusting for covariates (Tables 3 and 4). For a few chemicals, the LSGM estimates for pregnant women decreased after adjustment such as PBDEs, some phthalates, perchlorate, and BPA. In general, adjusted LSGMs were comparable between pregnant and non-pregnant women (Table 4). Non-pregnant women had significantly higher levels of cadmium, lead, PFOS, BPA, and cotinine, but pregnant women had significantly higher levels of DDE, DMTP, MTBE, and perchlorate (Table 4). The most pronounced differences between pregnant and non-pregnant women were for MTBE and DMTP (pregnant women about two times greater concentrations) and cotinine (pregnant women about half the levels of nonpregnant women).

Serum albumin influenced the comparison between pregnant and non-pregnant women for 28 of the 32 compounds evaluated in regression analysis (the beta coefficient changed by more than 20%);

however, direction of the effect varied by type of compound. In general, for chemical analytes measured in blood, effect estimates for albumin were positive, and their inclusion increased the LSGMs for pregnant women; whereas, for nonpersistent urinary chemical analytes, the albumin effect estimates were more often negative and their inclusion decreased the LSGMs for pregnant women (data not shown). Smoking influenced comparison of LSGMs between pregnant and non-pregnant women for 75% of chemicals. Maternal age and BMI changed the LSGMs for persistent organic pollutants such as PCBs, and creatinine influenced LSGMs for most chemical analytes measured in urine. Other variables, such as race/ethnicity and education, were often significant predictors of chemical analyte concentrations but generally did not change LSGM comparisons in Table 4.

Compared to estimates based on women of all ages, LSGMs for lead and DDE for both pregnant and non-pregnant women were reduced when analyses were restricted to younger women (<35 years of age). However, relative differences in adjusted estimates between pregnant and nonpregant women were not substantially affected. LSGMs for BPA increased for both groups in the restricted analysis, and the difference in LSGM estimates between pregnant and non-pregnant women were no longer statistically significant (LSGM=2.16 (pregnant) vs. 3.03 µg/L (non-pregnant), p=0.24).

DISCUSSION

We found widespread exposure to pregnant women in the U.S. to multiple chemical analytes, including both banned and contemporary contaminants. While we did not make any direct connection to potential adverse health consequences, many of these chemical analytes were similar to levels measured in epidemiologic studies finding an association with adverse reproductive and developmental outcomes. These include: phthalates (prenatal exposures have been associated with increased risk of adverse male reproductive outcomes (Swan et al. 2005)); mercury and

developmental neurological outcomes (Lederman et al. 2008), PBDEs and neurodevelopmental outcomes (Herbstman et al. 2009); and PCBs and maternal thyroid hormone disruption during pregnancy (Chevrier et al. 2008) .

Additionally, pregnant women were exposed to multiple chemical analytes at one time, many of which can affect the same common adverse outcomes. Examples include maternal thyroid hormone disruption (e.g. perchlorate, PCBs, PBDEs, and triclosan (Crofton 2008)), male reproductive development (multiple phthalates); and the developing brain (mercury, lead, PCBs) (National Research Council 2008). The NAS has recommended risk assessment of multiple chemicals expand to account for chemicals acting on a common adverse outcome (National Research Council 2008). While the NAS focused on grouping chemicals contributing to disturbances of androgen action, they also proposed this approach for chemicals affecting brain development (National Research Council 2008).

Levels of chemicals measured during pregnancy can be influenced by physiological (e.g. changes in BMI, plasma volume expansion, and bone mobilization) and behavioral factors. For example, previous research finds an inverse relationship between weight gain during pregnancy and levels of persistent organic pollutants in pregnant women (Bradman et al. 2006). We found that plasma volume expansion, using the level of albumin as a surrogate, may also influence chemical levels measured in pregnant women. Plasma volume begins to expand in pregnant women around 8 weeks gestation, increases progressively until 30 to 34 weeks gestation when it plateaus. This expansion may dilute environmental chemical concentrations in blood (Faupel-Badger et al. 2007). Accurately measuring plasma volume expansion is expensive, and ideally requires multiple measurements throughout pregnancy (Faupel-Badger et al. 2007). However, albumin measurements may provide a reasonable surrogate as previous studies suggest blood volume

expansion dilutes circulating levels of albumin during pregnancy (Honger 1968). We found that, in general, adjusting for albumin increased GM estimates of persistent compounds, such as DDE, in pregnant women suggesting the concentration is diluted by increased plasma volume. However, adjustment for albumin generally decreased estimates for nonpersistent compound, such as BPA, in pregnant women suggesting that lower albumin may be associated with an increased clearance of environmental contaminants. Albumin may affect metabolism and transport of chemicals by mechanisms other than plasma volume expansion. For example, previous research has shown that PFCs actually bind to albumin in the blood (Jones et al. 2003). BPA also binds to plasma proteins, such as albumin, in humans (Teeguarden et al. 2005), so reduced albumin during pregnancy may influence the amount of BPA which undergoes phase II conjugation and subsequent elimination through urine. The role of albumin, and other transport proteins, in the transport and metabolism of environmental chemicals, particularly during pregnancy, is an important topic and requires further research.

We found that, generally, the levels in pregnant women were similar or lower than levels measured in non-pregnant women. Adjusting for physiologic factors that may influence levels of chemicals in pregnant women tended to increase the levels in pregnant women compared to non-pregnant women. This suggests that generally levels of chemicals in non-pregnant reproductive-age women are reasonably representative of levels found pregnant women. However, for several chemicals, levels in pregnant women remain lower than those in non-pregnant women. There may be behavioral factors that explain this difference (e.g. cotinine and smoking) or other physiological factors may be important (e.g. chemical levels concentrating in the fetus such as for BPA (Takahashi and Oishi 2000)).

The NHANES study design, where groups of chemicals were analyzed in approximate one third size subsamples, meant we could not evaluate more than 71 chemical analytes in any individual pregnant women, about 44% of chemical analytes measured during 2003-2004. This also limited our ability to assess exposures to multiple chemical analytes that may be acting on the same common adverse outcome (e.g. PBDEs and PCBs which can affect neurodevelopment were not measured in the same women). Given that there several chemical analytes within each of the classes that were detected fairly ubiquitously, pregnant women have more detectable chemical analytes than we could assess in any individual participant in this analysis.

Other methodological changes between cycles make it challenging to compare data across NHANES cycles. For example, the number and types of chemicals sampled changes by cycle. Another challenge is detection limits vary among the cycles. Mostly they decrease, such as with PCBs, which can increase the number of chemicals detected. However, a few LODs have increased, for example, certain urinary phthalate esters, such as MEHP and MEP, increased between 2003-2004 and 2005-2006.

Chemical analyte concentrations in NHANES participants should be representative of typical US concentrations. As such, highly exposed subpopulations may be underrepresented. For example, women living in the agricultural Salinas Valley of California had higher measurable levels of several pesticides compared to those measured among NHANES pregnant women (Castorina et al. 2010). Other subpopulations may have non-representative exposure patterns, such as high fish consumption, or higher use of certain personal care products.

Our analysis indicates high variability in exposures for some chemical analytes, shown by the relatively high CV for phenols, phthalates, cotinine and MTBE. For some of these analytes, with almost an order of magnitude difference between the median and the 95th percentile, variation may

reflect geographic variability in exposure sources. For example, MTBE was used in reformulated gasoline starting in 1995. Reformulated gasoline was required for use in cities year round with significant smog problems (Energy Information Administration 2008), so it was not used in every U.S. location. Thus the geographic variation in MTBE usage may play a role in the wide exposure variability (Energy Information Administration 2008). PBDE-153 is another example of how geographic use variation can influence exposures levels. The 95th percentile of PBDE-153 levels is 15 times greater than the median, and previous research has found PBDE concentrations to be around two times higher in Californians than in others in the US, likely due to California's unique flammability standard (Zota et al. 2008). Variation in exposure to chemical analytes used in consumer and personal care products (e.g., triclosan, where the 95th percentile is 35 times greater than the median) could be driven by unique product uses (Allmyr et al. 2009). Although biomonitoring studies can demonstrate variation in exposures within populations, they generally are limited in their ability to identify sources of exposures. Consequently, additional exposure assessment research is needed to identify the dominant sources of exposure among pregnant women and the general population.

Our analysis of the NHANES pregnancy data finds ubiquitous exposure to multiple chemicals during a sensitive period of development. The NAS recommends accounting for both multiple exposures and exposures that occur during vulnerable developmental periods in improved approaches for assessing chemical risks across the population, which includes shifting to a risk assessment approach that presumes no threshold of effect among the population unless shown otherwise (National Academy of Science 2008). Data, such as from NHANES, should be used to enhance our understanding of risks among the U.S. population and to inform further policy and research activities.

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Table 1. Chemical classes measured in biological tissue of pregnant women, NHANES 2003-2004[a].

	Number of chemical analytes measured in each matrix			
Chemical class	Blood	Serum	Urine	Total
Cotinine		1		1
Environmental phenols			4	4
Metals	4			4
Organochlorine pesticides		13		13
Organophosphate insecticides			6	6
Perchlorate			1	1
Phthalates			13	13
Polybrominated diphenyl ethers (PBDEs) and other brominated flame retardants (BFRs)		11		11
Polychlorinated biphenyls (PCBs) and dioxin-like chemicals		55		55
Polycyclic aromatic hydrocarbons (PAHs)			10	10
Perfluorinated compounds (PFCs)		12		12
Volatile organic compounds (VOCs)	33			33

[a] See Supplemental Materials for individual chemical analytes included in each chemical class

Table 2. Characteristics of reproductive-aged women by pregnancy status, NHANES 2003-2004

	Pregnant women (N=268)	Non-pregnant women (N=1489)
Demographic characteristics		
Age, years (mean, (SE))**	27 (0.8)	30 (0.37)
Age, years (%)**		
15-17	4	10
18 -24	30	23
25-29	31	13
30-34	25	17
35-44	11	37
Race/Ethnicity (%)**		
Non-Hispanic White	56	67
Non-Hispanic Black	18	14
Mexican American	17	10
Other Hispanic	2	5
Other	6	5
Education (%)		
< High school diploma	26	24
High school diploma	15	22
> High school diploma	59	54
Marital status (%)**		
Married or living with partner	79	50
Divorced, separated, or widowed	2	12
Never married	19	38
Parity (%)**		

0	45	44

Table 2 (cont.))

	Pregnant women (N=268)	Non-pregnant women (N=1489)
1	34	14
≥ 2	21	42
Smoking status (%)**		
Never	59	60
Former	31	11
Current	9	30
Trimester		
1st Trimester	31	
2nd Trimester	32	
3rd Trimester	37	
Biochemical measurements		
Serum albumin, (mean (SE), g/dL)**	3.46 (0.04)	4.23 (0.01)
Urinary creatinine, (mean (SE), mg/dL)	127.81 (6.00)	130.86 (3.27)
Sampling characteristics		
Duration of food and drink fasting prior to blood collection, (mean (SE), hours)**	8.40 (0.73)	10.67 (0.10)

Data were missing for: parity (n=18), education (n=3), smoking (n=6), trimester (n=41), and length of fasting (n=2) in pregnant women. Data were missing for: parity (n=160), education (n=46), smoking (n=151), and length of fasting (n=25) in non-pregnant women.

**p<0.01

Table 3. Descriptive statistics for chemical analytes in pregnant and non-pregnant women from NHANES 2003-2004[a].

Chemical analyte	N	Reproductive status	LOD[a]	Percent greater than LOD	GM (GSE)	50th	95th	CV
Metals (blood; µg/L)								
Cadmium**	253	Preg	0.14	66	0.22 (0.01)	0.2	0.8	0.07
	1396	Nonpreg		79	0.33 (0.01)	0.3	1.6	0.03
Lead (µg/dL)**	253	Preg	0.28	94	0.68 (0.04)	0.6	1.8	0.06
	1396	Nonpreg		99	0.96 (0.04)	0.9	2.4	0.04
Mercury (total)*	253	Preg	0.20	89	0.67 (0.07)	0.7	3.4	0.10
	1396	Nonpreg		92	0.80 (0.05)	0.8	4.4	0.06
Volatile organic compounds (VOCs) (blood; µg/L)								
Benzene	89	Preg	0.024	38	—[b]	<LOD	0.2	—[b]
	389	Nonpreg		53	—[b]	<LOD	0.3	—[b]
1,4-Dichlorobenzene	89	Preg	0.12	40	—[b]	<LOD	20.0	—[b]
	373	Nonpreg		47	—[b]	<LOD	4.1	—[b]
Methyl tert-butyl ether (MTBE)	85	Preg	0.002	86	0.01 (0.01)	0.02	0.1	0.40

Table 3 (cont.)

Chemical analyte	N	Reproductive status	LOD[a]	Percent greater than LOD	GM (GSE)	50th	95th	CV
	373	Nonpreg		78	0.01 (0.002)	0.01	0.1	0.20
Toluene**	90	Preg	0.025	94	0.07 (0.01)	0.1	0.2	0.07
	387	Nonpreg		95	0.10 (0.01)	0.1	0.5	0.10
Cotinine (serum; µg/L)								
Cotinine**	249	Preg	0.015	66	0.07 (0.02)	0.03	68.8	0.31
	1369	Nonpreg		83	0.54 (0.13)	0.1	318.0	0.24
Perfluorinated compounds (PFCs) (serum; µg/L)								
Perfluorooctanoic acid	76	Preg	0.1	99	2.39 (0.24)	2.6	5.6	0.10
(PFOA)*	400	Nonpreg		99	3.19 (0.16)	3.2	8.4	0.05
Perfluorooctane sulfonic acid	76	Preg	0.4	99	12.29 (1.02)	12.0	21.8	0.08
(PFOS)**	400	Nonpreg		100	16.26 (0.84)	15.5	44.0	0.05
Polybrominated diphenyl ethers (PBDEs) (serum; ng/g lipid)								

Table 3 (cont.)

Chemical analyte	N	Reproductive status	LOD[a]	Percent greater than LOD	GM (GSE)	50th	95th	CV
PBDE-47	75	Preg	4.2	99	23.90 (2.21)	23.7	100.0	0.09
	441	Nonpreg		98	21.15 (2.03)	21.2	114.0	0.10
PBDE-99	75	Preg	5.0	87	5.51 (0.81)	5.1	21.8	0.15
	434	Nonpreg		68	5.04 (0.42)	4.4	31.5	0.08
PBDE-100*	75	Preg	1.4	99	6.06 (0.91)	6.6	23.2	0.15
	443	Nonpreg		96	4.00 (0.43)	3.8	25.2	0.11
PBDE-153	75	Preg	2.2	100	9.90 (3.04)	7.8	127.0	0.31
	442	Nonpreg		93	5.18 (0.53)	4.5	43.9	0.10
Polychlorinated biphenyls (PCBs) (serum; ng/g lipid)								
PCB-118	75	Preg	0.6	100	4.31 (0.95)	3.6	14.3	0.22
	415	Nonpreg		100	4.46 (0.28)	4.3	16.9	0.06
PCB-138 & 158	75	Preg	0.4	100	7.70 (1.24)	7.3	20.2	0.16
	416	Nonpreg		100	8.95 (0.55)	8.3	37.0	0.06

Table 3 (cont.)

Chemical analyte	N	Reproductive status	LOD[a]	Percent greater than LOD	GM (GSE)	50th	95th	CV
PCB-153	75	Preg	1.1	100	8.74 (1.29)	8.8	22.5	0.15
	415	Nonpreg		100	11.07 (0.64)	10.2	44.0	0.06
PCB-180*	75	Preg	0.4	96	4.61 (0.99)	6.8	13.2	0.21
	416	Nonpreg		99	7.42 (0.44)	7.5	33.3	0.06
Organochlorine (OC) pesticides (serum; ng/g lipid)								
DDT	71	Preg	7.8	62	— [c]	— [c]	37.4	0.16
	426	Nonpreg		63	— [c]	—[c]	13.3	0.06
DDE	71	Preg	7.8	100	140.39 (29.72)	99.9	850.0	0.21
	424	Nonpreg		99	151.04 (16.03)	141.0	815.0	0.11
Hexachlorobenzene*	70	Preg	7.8	100	11.27 (1.08)	10.4	25.7	0.10
	428	Nonpreg		99	14.34 (0.39)	14.3	25.7	0.03
Organophosphate (OP) insecticide metabolites (urine; µg/L)								
Dimethylphosphate (DMP)	89	Preg	0.5	44	— [b]	<LOD	13.7	— [b]

Table 3 (cont.)

Chemical analyte	N	Reproductive status	LOD[a]	Percent greater than LOD	GM (GSE)	50th	95th	CV
	483	Nonpreg		48	—[b]	<LOD	14.3	—[b]
Diethylphosphate (DEP)	89	Preg	0.1	33	—[b]	<LOD	10.8	—[b]
	474	Nonpreg		49	—[b]	<LOD	14.8	—[b]
Dimethylthiophosphate	89	Preg	0.5	83	2.43 (0.43)	2.7	16.0	0.18
(DMTP)*	483	Nonpreg		73	1.81 (0.17)	1.7	28.3	0.09
Diethylthiophosphate (DETP)	87	Preg	0.2	57	—[b]	0.2	2.2	—[b]
	478	Nonpreg		46	—[b]	<LOD	2.6	—[b]
Dimethyldithiophosphate	86	Preg	0.1	56	—[b]	0.2	3.2	—[b]
(DMDTP)	475	Nonpreg		34	—[b]	<LOD	4.0	—[b]
Environmental phenols (urine; µg/L)								
Bisphenol-A	86	Preg	0.4	96	2.53 (0.63)	2.7	15.0	0.25
	489	Nonpreg		96	2.89 (0.29)	3.0	17.6	0.10
Triclosan	86	Preg	2.3	87	17.00 (8.74)	8.2	283.0	0.51

Table 3 (cont.)

Chemical analyte	N	Reproductive status	LOD[a]	Percent greater than LOD	GM (GSE)	50th	95th	CV
	489	Nonpreg		81	14.65 (0.97)	11.1	411.0	0.07
Benzophenone-3	86	Preg	0.3	100	25.49 (6.52)	16.9	353.0	0.26
	489	Nonpreg		98	37.14 (6.44)	31.4	1530.0	0.17
Phthalates (urine; µg/L)								
Mono-benzyl phthalate	91	Preg	0.1	100	15.12 (3.79)	17.8	86.8	0.25
(MBzP)	497	Nonpreg		100	14.77 (0.79)	15.5	99.9	0.05
Mono-isobutyl phthalate	91	Preg	0.3	99	3.47 (0.84)	4.4	19.5	0.24
(MiBP)	497	Nonpreg		98	4.21 (0.27)	4.5	21.1	0.06
Mono-n-butyl phthalate	91	Preg	0.4	99	18.83 (4.11)	17.1	143.8	0.22
(MnBP)	497	Nonpreg		99	24.64 (1.16)	25.7	132.2	0.05
Mono-ethyl phthalate (MEP)	91	Preg	0.4	100	226.53 (79.03)	265.7	2263.0	0.35
	497	Nonpreg		100	246.06 (29.56)	234.5	2992.6	0.12
Polycyclic Aromatic Hydrocarbons (PAHs) (urine; µg/L)								

Table 3 (cont.)

Chemical analyte	N	Reproductive status	LOD[a]	Percent greater than LOD	GM (GSE)	50th	95th	CV
9-Hydroxyfluorene	85	Preg	0.005	100	0.21 (0.04)	0.2	0.8	0.19
	478	Nonpreg		100	0.30 (0.03)	0.2	1.1	0.11
2-Naphthol	91	Preg	0.031	100	2.49 (0.59)	2.4	14.7	0.24
	492	Nonpreg		100	3.68 (0.31)	3.3	28.7	0.08
2-Hydroxyphenanthrene	87	Preg	0.005	100	0.06 (0.01)	0.05	0.2	0.17
	479	Nonpreg		99	0.06 (0.004)	0.06	0.3	0.07
1-Hydroxypyrene	86	Preg	0.005	100	0.08 (0.02)	0.08	0.5	0.25
	481	Nonpreg		99	0.09 (0.007)	0.09	0.6	0.07
Perchlorate (urine; µg/L)								
Perchlorate*	89	Preg	0.05	100	4.17 (0.84)	4.3	34.0	0.07
	492	Nonpreg		100	2.68 (0.21)	2.8	11.0	0.08

*p<0.10; **p<0.01 (P values calculated using univariate regression analysis)

GM=Geometric mean; GSE= geometric standard error; CV= coefficient of variation; Preg= pregnant women; Nonpreg= non-pregnant women

Sample sizes for chemical classes are approximate since sample sizes vary slightly by chemical

[a] For most chemicals, the LOD is constant across samples. However, for persistent organic pollutants (PBDEs, PCBs, and organochlorine pesticides), each individual sample has its own LOD because the available sample volume differed by sample, and a higher sample volume results in a lower LOD. For chemicals with sample-specific LODs, the maximum LOD is reported in the table. In general, the average LOD is approximately 40-50% of the maximum LOD (CDC, 2009).

[b] GM ,GSE, or CV could not be calculated because detection frequency is less than 60%.

[c] Geometric mean or percentile estimate is not reported because it is less than the maximum LOD.

Table 4. Comparison of chemical analyte concentrations between pregnant and non-pregnant women after adjustment for covariates[a]. Effect estimates (β coefficients and 90% confidence intervals (90% CI) and least square geometric means (LSGM and 90% CI) are calculated from multivariate regression models.

		Pregnant women		Non-pregnant women	
Chemical analyte	β (90% CI)[b]	LSGM	90% CI	LSGM	90% CI
Metals (blood; µg/L)		N=225		N=1091	
Cadmium	-0.20 (-0.36, -0.04)*	0.27	0.23-0.31	0.33	0.31-0.35
Lead (µg/dL)	-0.16 (-0.27, -0.06)*	0.80	0.72-0.89	0.94	0.89-0.99
Mercury (total)	-0.11 (-0.33, 0.10)	0.71	0.57-0.89	0.79	0.72-0.88
VOCs (blood; µg/L)		N = 82		N = 334	
MTBE	0.97 (0.03, 1.90)*	0.02	0.01-0.06	0.008	0.005-0.01
Toluene	0.15 (-0.14, 0.43)	0.11	0.08-0.14	0.09	0.08-0.10
Cotinine (serum; µg/L)		N = 225		N = 1091	
	-0.94 (-1.39, -0.48)**	0.19	0.13-0.28	0.49	0.42-0.58

Table 4 (cont.)		Pregnant women		Non-pregnant women	
Chemical analyte	β (90% CI)[b]	LSGM	90% CI	LSGM	90% CI
PFCs (serum; µg/L)		N = 70		N = 313	
PFOA	-0.18 (-0.37, 0.02)	2.69	2.18-3.32	3.22	2.95-3.52
PFOS	-0.23 (-0.35, -0.12)**	12.81	11.94-13.74	16.28	15.18-17.46
PBDEs (serum; ng/g lipid)		N= 68		N = 366	
PBDE-47	0.02 (-0.32, 0.35)	21.76	16.73-28.30	21.33	18.21-24.97
PBDE-99	-0.11 (-0.47, 0.26)	4.62[c]	3.37-6.33	5.10	4.44-5.87
PBDE-100	0.24 (-0.22, 0.70)	5.21	3.60-7.52	4.10	3.38-4.97
PBDE-153	0.51 (-0.10, 1.12)	8.85	5.05-15.50	5.31	4.46-6.33
PCBs (serum; ng/g lipid)		N = 66		N = 334	
PCB-118	-0.02 (-0.31, 0.28)	4.39	3.20-6.02	4.44	3.99-4.93
PCB-138 & 158	-0.07 (-0.33, 0.19)	8.25	6.57-10.36	8.85	7.96-9.83
PCB-153	-0.11 (-0.39, 0.17)	9.87	7.73-12.62	11.02	9.92-12.25

PCB-180	-0.27 (-0.65, 0.11)	5.64	3.97-8.01	7.39	6.77-8.07
Table 4 (cont.)		Pregnant women		Non-pregnant women	
Chemical analyte	β (90% CI)[b]	LSGM	90% CI	LSGM	90% CI
OC pesticides (serum; ng/g lipid)		N = 64		N = 354	
DDT	-0.10 (-0.32, 0.13)	3.49[c]	2.78-4.38	3.86[c]	3.60-4.14
DDE	0.33 (0.12, 0.53)*	198.34	160.72-244.78	142.59	126.13-161.21
Hexachlorobenzene	-0.02 (-0.14, 0.10)	13.74	12.36-15.26	14.01	13.53-14.51
OP insecticide metabolites (urine; µg/L)		N = 74		N = 370	
DMTP	0.85 (0.34, 1.35)*	4.39	2.74-7.05	1.88	1.60-2.20
Environmental phenols (urine; µg/L)		N = 72		N = 371	
Bisphenol-A	-0.55 (-0.97, -0.13)*	1.63	1.13-2.36	2.83	2.42-3.31
Triclosan	0.47 (-0.60, 1.54)	23.81	8.17-69.36	15.03	13.06-17.29
Benzophenone-3	-0.07 (-1.26, 1.12)	38.09	14.02-103.46	40.85	29.28-57.00

Phthalates (urine; µg/L)		N = 75		N = 377	
Mono-benzyl (MBzP)	-0.02 (-0.53, 0.50)	14.73	8.86-24.49	15.03	13.77-16.41

Table 4 (cont.)		Pregnant women		Non-pregnant women	
Chemical analyte	β (90% CI)[b]	LSGM	90% CI	LSGM	90% CI
Mono-isobutyl (MiBP)	-0.37 (-0.76, 0.03)	2.83	1.89-4.23	4.06	3.65-4.50
Mono-n-butyl (MnBP)	-0.26 (-0.62, 0.11)	18.36	12.93-26.07	23.81	21.81-25.99
Mono-ethyl (MEP)	-0.13 (-0.93, 0.66)	221.41	98.85-495.90	254.68	206.36-314.30

PAHs (urine; µg/L)			N=74			N=372
9-Hydroxyfluorene	-0.15 (-0.50, 0.19)		0.20	0.14-0.28	0.23	0.21-0.26
2-Naphthol	-0.15 (-0.57, 0.27)		3.00	1.97-4.58	3.49	3.20-3.81
2-Hydroxyphenanthrene	-0.12 (-0.27, 0.02)		0.05	0.04-0.06	0.06	0.05-0.06
1-Hydroxypyrene	-0.14 (-0.46, 0.19)		0.08	0.06-0.10	0.09	0.08-0.09

Perchlorate (urine; µg/L)		N = 74		N = 374	
	0.25 (0.05, 0.45)*	3.35	2.67-4.21	2.61	2.31-2.95

*p<0.10; **p<0.01

[a] Models adjusted for age, race/ethnicity, education, smoking, parity, BMI, albumin, duration of fasting before specimen collection, and creatinine (only urinary chemical analytes adjusted for creatinine).

[b] Reference group = non-pregnant women, Chemical analyte concentrations are log-transformed

[c] LSGM estimates are below the LOD (see Table 3)

Sample sizes for chemical classes are approximate since sample sizes vary slightly by chemical

Figure Captions

Figure 1: Distribution of the number of chemicals detected in US pregnant women for four chemical classes (organochlorine pesticides (n=71), PBDEs (n=75), PFCs (n=76) and phthalates (n=91)).

Figure 2: Distribution of the number of chemicals detected in US pregnant women across multiple chemical classes

Figure 3. Number of chemicals detected by chemical class in US pregnant women (NHANES subsample B (metals, cotinine, organochlorine pesticides, phthalates, flame retardants and PAHs), 2003-2004)

Figure 1.

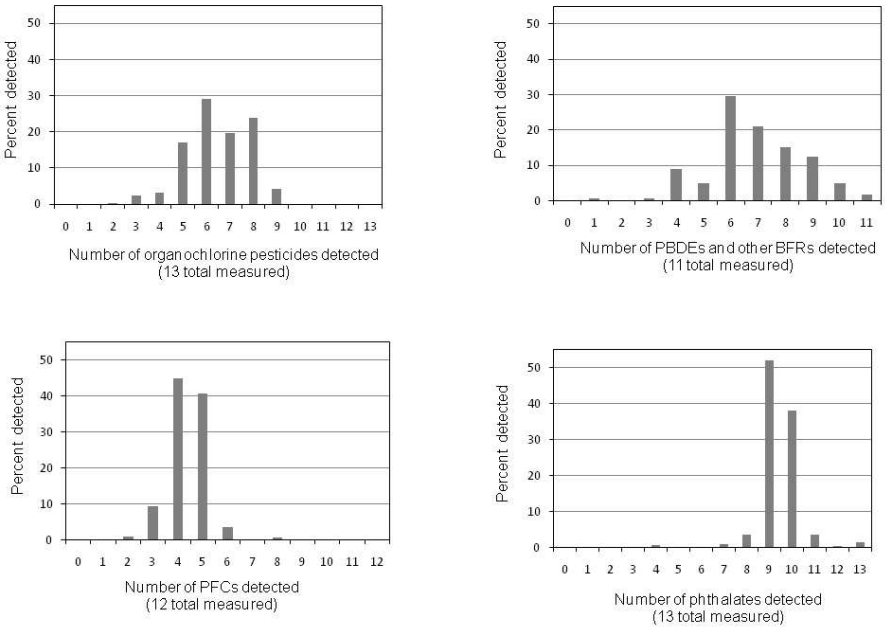

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Figure 2.

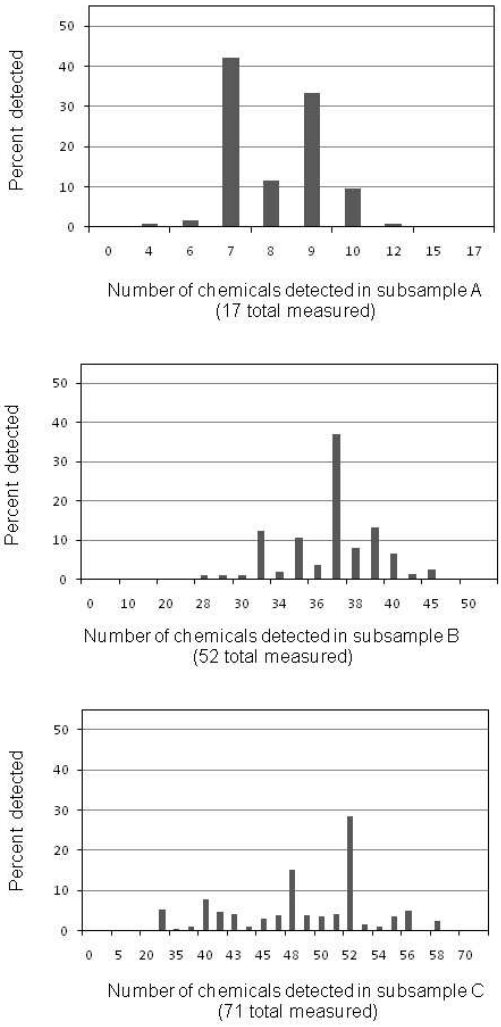

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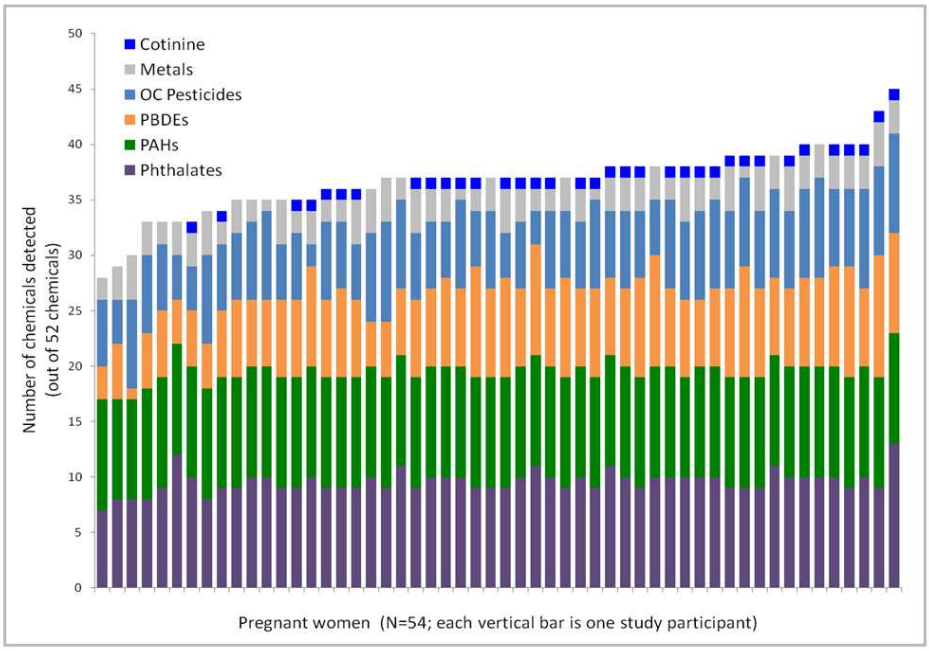
Figure 3.



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