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Temporal Trends of Phenol, Paraben, and Triclocarban Exposure in California Pregnant Women during 2007–2014

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Abstract

Little is known about temporal trends of pregnant women's exposures to environmental phenols and parabens. We quantified four phenols (bisphenol A [BPA], bisphenol F, bisphenol S, triclosan), four parabens (butyl paraben, ethyl paraben [ETPB], methyl paraben [MEPB], propyl paraben [PRPB]) and triclocarban in 760 urine samples collected during 2007–2014 from 218 California pregnant women participating in a high-familial risk autism spectrum disorder cohort. We applied multiple regression to compute least square geometric means of urinary concentrations and computed average annual percent changes. We compared our urinary concentrations with those of other study populations to examine geographic variations in pregnant women's exposure

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to these target compounds. Urinary concentrations of BPA, MEPB, ETPB, and PRPB in this study population decreased over the study period [percent change per year (95% confidence interval): −5.7% (−8.2%, −3.2%); −13.0% (−18.1%, −7.7%); −5.5% (−11.0%, 0.3%); −13.3% (−18.3%, −8.1%), respectively] and were consistently lower than those in pregnant women in other U.S. regions during the same study period. In recent years, certain phenols and parabens with known adverse health effects are being regulated or replaced with alternatives, which explain decreased body burdens observed in this study population. Either the national regulations or the advocacy campaigns in California may have influenced exposures or consumer product choices.

Graphical Abstract
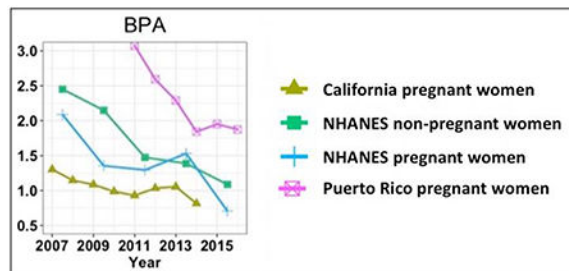
Keywords

bisphenols; geographic variations; personal care products; regulations; social forces; temporal changes

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1. INTRODUCTION

Some environmental phenols, parabens and triclocarban (TCC) are widely used in various consumer and personal care products.[1, 2] Bisphenols are used as plasticizers, and other phenols and TCC are commonly used as antimicrobial preservatives in toothpaste, soaps, and detergents.[2–4] Parabens are primarily used as preservatives in shampoos, lotions, sunscreens, deodorants, cosmetics and pharmaceutical products.[5] Because products containing phenols, parabens and TCC are widely used, they are detected in U.S. household dust [6–8] and in urine of a large, representative sample of the U.S. population as well as pregnant women, infants, and young children.[9–15]

Prenatal exposure to phenols, parabens and TCC is of public health concern because epidemiologic studies showed prenatal exposure to some phenols, parabens and TCC to be associated with adverse health effects in pregnant women or their offspring, such as poor birth outcomes,[16, 17] decreased female fecundity,[18] and increased childhood obesity.[19] Prenatal exposure to phenols, parabens and TCC is suspected to have potential adverse neurodevelopmental effects, leading to increased risk of non-typical brain development,[10] externalizing behaviors,[20] and decreased cognitive test scores.[21] Laboratory animal studies also showed that bisphenol A (BPA), bisphenol S (BPS), and bisphenol F (BPF) can disrupt female reproductive systems.[22–26] These findings, combined with the fact that phenols, parabens and TCC are detected in cord blood,[27–29] support that higher prenatal exposure

to these compounds could result in elevated risk of having adverse outcomes in pregnant women and their offspring.

Health concern and toxicity associated with prenatal exposure to some phenols, parabens and TCC led to regulatory efforts that restricted their production and inclusion in products used by women of reproductive age, infants, or young children. The U.S. Food and Drug Administration (FDA) banned the use of BPA in baby bottles and spill-proof cups, including their lids in 2012[30] and restricted the use of BPA-based epoxy resins in packaging materials used for infant formula in 2013.[31] Thus, manufacturers are replacing BPA with BPS or BPF to comply with the U.S. regulations on BPA.[32, 33] The U.S. FDA also banned the use of triclosan (TCS) and TCC in hand and body soaps in 2016.[34] Parabens are not regulated in the U. S., but after the California Safe Cosmetics Program mandates that cosmetic companies disclose chemical ingredients in beauty and personal care products sold in California since 2007,[35] exposure to parabens may have been decreased in the general U.S. population. In addition, the European Union (EU), Japan, and the Southeast Asian nations set maximum paraben concentrations in cosmetics and do not permit some parabens in any cosmetic product.[36–38] As a result of these regulations and following market changes, urinary concentrations of some phenols and parabens decreased over time in the general population of the U.S.[39] and Germany[40] and in Danish young men.[41] However, few studies examined temporal trends of pregnant women's exposure to phenols, parabens and TCC.

There are many factors that play a role in understanding pregnant women's exposure to phenols, parabens and TCC. For example, pregnant women tended to have lower urinary biomarker concentrations of these compounds than non-pregnant women,[42–44] possibly because of changes in their use in cosmetics and other personal care products after becoming pregnant. Pregnant women's exposure to these compounds differed by sociodemographic characteristics and use frequency of products potentially containing these compounds before urine collection.[45–54] In our previous study,[55] we learned that broad social forces may have influenced temporal trends and geographic variations in pregnant women's phthalate exposure. Thus, the same study approach may help identify similar broad social forces related to pregnant women's phenol, paraben and TCC exposure.

In this study, we quantified four phenols (BPA, BPF, BPS, TCS), four parabens (butyl paraben (BUPB), ethyl paraben (ETPB), methyl paraben (MEPB), and propyl paraben (PRPB)), and TCC to assess temporal trends of their urinary concentrations in California pregnant women during 2007–2014. To understand whether broad social forces affected exposure to the target study compounds in the U. S., we compared our measured urinary concentrations with those of other pregnancy cohorts in Massachusetts and Puerto Rico as well as those of pregnant and non-pregnant women in the U.S. National Health and Nutrition Examination Survey (NHANES).

2. METHODS

2.1. Study population

This study included women participating in MARBLES (Markers of Autism Risk in Babies – Learning Early Signs), a pregnancy cohort study in California beginning in 2006.[56]

MARBLES enrolls pregnant women who have a child with autism spectrum disorder (ASD) and thus are at high risk (~20%) for delivering another infant who develops ASD.[57] MARBLES families are recruited from lists of children receiving services for ASD through the California Department of Developmental Services, from other studies, by self- or other referrals and various clinics. Details of study design, eligibility criteria for inclusion, recruitment, exposure data, sample size, and developmental diagnosis are available elsewhere.[56]

For the current study, we selected 218 women who provided first morning voids (FMVs) and/or 24-hour urine samples during pregnancy between 2007 and 2014. Among 218 women, 15 women participated in this study for two different pregnancies. All urine samples included in this study were collected from a total of 233 unique pregnancies from 218 women. This study was approved by the institutional review boards for the State of California and the University of California Davis (UC Davis). Participants provided informed consent prior to collection of data.

2.2. Urine sample collection

Women in the MARBLE Study were instructed to collect three FMVs (taken one week apart) and one 24-hour urine sample during each trimester of pregnancy. Participants were asked to place their urine samples in home freezers or refrigerators; these biosamples were collected during home visits and then transported to UC Davis, where they were thawed, aliquoted, and stored at −80 °C until analysis. To reduce sample analysis cost, for women who provided three or more samples within a trimester, we selected the first FMV as an individual sample and pooled remaining samples (including 24-hour samples if any) for that trimester.[43, 58] After pooling, 760 samples (383 FMVs, 116 24-hour samples, 261 pools) from 233 pregnancies remained for chemical analysis. Although all women were asked to collect four samples (i.e., three FMVs and one 24-hour samples) per trimester, many did not. Thus, only 116 24-hour samples were available from 233 pregnancies. The details of collecting urine samples and methods for pooling multiple samples are described elsewhere.[43, 58] The type and number of urine samples collected and analyzed in this study are summarized in the Supporting Information (SI, Figure S1).

2.3. Biomarker quantification

We shipped the urine samples in a 1-mL aliquot to the Laboratory of Exposure Assessment and Development for Environmental Research (LEADER), Rollins School of Public Health, at Emory University for biomarker analysis. At Emory University, we quantified urinary concentrations for our nine target compounds using two liquid chromatographic-tandem mass spectrometric (LC-MS/MS) methods. Details of analytical methods are described elsewhere[10] and are also presented in the SI.

In the current study, the average relative percent difference (RPD) of repeated measures of quality controls (QCs) was below 11%, depending on the analyte and QC concentration. The laboratory also analyzed 16 blind duplicates for quality assurance. Replicate analyses for individual pairs of duplicate samples exhibited good agreement. The average RPD of 8 pairs of blind duplicates was 15%, ranging from 9% to 22%, depending on the analyte. The limits

of detection (LOD) for BPA, BPF, BPS, TCC, TCS, BUPB, ETPB, MEPB, and PRPB were 0.8, 2.5, 0.5, 1.0, 15.0, 1.5, 0.5, 0.5, and 1.0 nanograms per milliliter (ng/mL), respectively (Table 1).

2.4.   Correction for urinary dilution

We measured specific gravity (SG) of each analyzed urine sample with a digital handheld refractometer (Atago Co., Ltd., Tokyo, Japan) at UC Davis. We then corrected urinary concentrations of our target compounds for urinary dilution using the following formula:[59] $C_{SG} = C[(1.012 - 1)/(SG-1)]$, where C_{SG} is the SG-corrected urinary concentration (in ng/mL), C is the measured urinary concentration (in ng/mL), 1.012 is the median SG of all analyzed urine samples, and SG is the specific gravity of each sample.

2.5.   Statistical analysis

We performed all statistical analyses using R version 3.6.1[60] and several packages.[61–63] For all analyzed compounds, we provided summary statistics of SG-corrected urinary concentrations. For all other statistical analyses requiring sufficient detection of the samples, we only included compounds detected in 50% or greater of all samples. For concentrations below the LOD, we assigned a value of the LOD divided by the square root of 2.[64, 65]

To test for significant changes in urinary concentrations of the target compounds over our study period, we selected *a priori* six population characteristics that may influence exposure to our target compounds:[45–54] race/ethnicity (non-Hispanic White, Hispanic, others), age at delivery (≤35 years, >35 years), education (less than college degree, Bachelor's degree, graduate or professional degree), pre-pregnancy body mass index (BMI) (underweight/normal, overweight, obese), parity (1, >1), and homeownership (yes, no). Then, we performed multiple linear regression analyses. We used natural log-transformed urinary concentrations in the regression to account for their skewed distributions. To estimate the least square mean (LSM) which is the mean of natural log-transformed urinary concentrations for each sampling year, we used the estimated regression coefficients and the computed yearly-specific fractions or average of the selected covariates. Then, we computed the least square geometric mean (LSGM) of urinary concentrations for each sampling year as exp(LSM), with 95% confidence intervals (CIs) as $exp(LSM ± 1.97·SE_{LSM})$, where SE_{LSM} is the standard error of the LSM.[66] We also computed average annual percent changes of LSGMs, using the equation $[exp(β) – 1] × 100\%$ with 95% CIs as $[exp(β ± 1.97·SE_β) – 1]$, where β is the time-related regression coefficient and $SE_β$ is the standard error of the time-related regression coefficients.[66]

We examined differences in urinary concentrations among three types of urine samples (i.e., FMV, 24-hour, pool) and among subgroups of population characteristics (e.g., race/ethnicity, age at delivery). To test for monotonic (or unadjusted) temporal trends in urinary concentrations over our study period, we performed the Mann-Kendall test and computed the Kendall's tau correlation coefficient (τ) between sampling dates and urinary concentrations.

One of our study goals is to understand broad social forces that may influence exposure to our target compounds in the United States. Thus, to compare urinary concentrations in our study population with those in other study populations, we computed geometric means (GMs) of urinary concentrations for MARBLES pregnant women and NHANES's pregnant and non-pregnant women (20 to 50 years of age).[67] For pregnant women in Massachusetts, we used GMs during 2007–2009 from the LIFECODES cohort.[68] For pregnant women in Puerto Rico, we used GMs during 2011–2016 from the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) cohort.[45] Sampling time, sample size, participants' age range, LODs, and GMs of urinary concentrations for each cohort are available in Table S1. Although the PROTECT, LIFECODES, and MARBLES studies measured SG-corrected concentrations while the NHANES studies did not conduct any correction, other studies have demonstrated that medians and temporal variability among SG-corrected concentrations and uncorrected concentrations are similar.[69, 70]

3.   RESULTS

3.1.   Population characteristics

The average age of the participating women at delivery was 34.9 years old, ranging from 20.5 to 49.2 years old (Table S2). The women included in the study were 55% White, 21% Hispanic, and 24% other (3% Black, 18% Asian, and 3% multiracial). Approximately 43% of the women were normal or underweight and 44% of the women did not have a bachelor's degree or a higher degree. Summary statistics of other population characteristics are available in Table S2.

3.2.   Urinary concentrations of target compounds

Among the nine studied analyte compounds, four compounds were detected in 50% or more of all urine samples: BPA (59%), MEPB (96%), ETPB (50%), and PRPB (78%) (Table 1). The other five compounds (i.e., BPF, BPS, TCC, TCS, BUPB) were detected in less than 35% of the samples. For BPA, MEPB, ETPB and PRPB, concentrations were not significantly different (p-value > 0.05) in pair-wise comparisons of the three sample types (i.e., FMV versus pool, FMV versus 24-hour, pool versus 24-hour), indicating that FMVs can be interpreted together with 24-hour samples and pools in the current study. The detection frequency of BPA decreased from 67% to 42%, while that of BPS increased from 0% to 32% during the study period (Table 2). The detection frequency of MEPB, ETPB, and PRPB varied during the study period: 91–98% for MEPB, 40–61% for ETPB, and 71–88% for PRPB (Table 2). The highest median of SG-corrected concentrations was observed for MEPB (38.9 ng/mL), followed by PRPB, BPA, and ETPB (8.3, 1.0, and 0.7 ng/mL, respectively).

3.3.   Temporal trends of urinary phenol and paraben concentrations in California pregnant women in a high-familial risk ASD cohort

After adjusting for the selected covariates, the LSGMs of BPA, MEPB, ETPB, and PRPB in California pregnant women in a high-familial risk ASD cohort decreased over the study period [average percent change of the LSGM per year (95% CI): −5.7% (−8.2%, −3.2%); −13.0% (−18.1%, −7.7%); −5.5% (−11.0%, 0.3%); −13.3% (−18.3%, −8.1%), respectively]

(Figure 1). For MEPB and PRPB, larger than 60% and 50% of the LSGM decrease occurred from 2007 to 2008, respectively. Temporal trends of unadjusted concentrations from the Mann-Kendall trend test were similar to those of adjusted concentrations from the regression (Figure S2). Urinary concentrations of BPA ($\tau = -0.11$, p-value <0.01), MEPB ($\tau = -0.14$, p-value <0.01), ETPB ($\tau = -0.06$, p-value = 0.01), and PRPB ($\tau = -0.13$, p-value <0.01) decreased over the study period.

3.4. Temporal trends of urinary concentrations of phenols, parabens and TCC in all study populations

Overall, GM concentrations of BPA, MEPB, ETPB, and PRPB in California pregnant women in a high-familial risk ASD cohort were consistently lower than those in NHANES pregnant and non-pregnant women as well as pregnant women in Massachusetts and Puerto Rico during the same study period (Figure 2). Compared to NHANES non-pregnant women, GM concentrations in NHANES pregnant women were lower for BPA during most of the NHANES cycles. Puerto Rico pregnant women had higher GM concentrations of BPA, TCC, TCS, and BUPB than the current study population or NHANES pregnant and non-pregnant women during the same study period, while they had lower GM concentrations of BPF and BPS than NHANES non-pregnant women. Compared to other study populations, Puerto Rico pregnant women had relatively fast decreasing trends in GM concentrations of BPA, MEPB, ETPB, and PRPB, while they had relatively fast increasing trends in GM concentrations of BPS. MEPB and ETPB had a sharp decrease between 2007 and 2009 in our study and in other studies from the same time period. PRPB sharply declined in the earlier part of the study period in our study but did not decline much in other studies. Note that because of the relatively small sample size of NHANES pregnant women for each sampling year (Table S1), the results on their temporal trends and GM concentrations should be interpreted with caution.

3.5. Urinary concentrations with different subgroups of population characteristics

For the four compounds detected in 50% or greater of the samples in the current study (i.e., BPA, MEPB, ETPB, PRPB), medians of urinary concentrations differed by several population characteristics (Table S3). Hispanic women had the highest median for three parabens (p-value < 0.05). Women with pre-pregnant BMI in a normal/underweight range had the highest median of BPA, MEPB, ETPB and PRPB. Women without a college degree had the highest median of BPA and PRPB. Women who owned a home (considered as a proxy of higher socioeconomic status) had lower medians for three parabens and a higher median for BPA than those who did not.

When examining trends in urinary concentrations of the four compounds (i.e., BPA, MEPB, ETPB, PRPB) within specific subgroups of population characteristics during the study period, three parabens (MEPB, ETPB, PRPB) did not change in Hispanic women or in women with pre-pregnant BMI in an overweight range (Table 3). BPA did not change in women with pre-pregnant BMI in an obese range or in women with a graduate or professional degree. ETPB also did not change in women in other race/ethnicity group, in women with pre-pregnant BMI in a normal/underweight range, in women without a college degree, in women who delivered at older ages (> 35 years old) or in women who did not

own a home. Both ETPB and MEPB did not change in women with one parity. However, because the sample size for each demographic variable is not equally distributed over the years, these findings need to be interpreted with caution.

4.   DISCUSSION

In the current study, we examined temporal trends of urinary concentrations of phenols, parabens and TCC in California pregnant women participating in a high-familial risk ASD cohort. We observed that GM decreased from 1.44 to 0.78 (46%) for BPA, from 111.42 to 21.18 (81%) for MEPB, from 2.02 to 1.15 (43%) for ETPB, and from 18.00 to 5.39 (70%) for PRPB between 2007 and 2014. The detection frequency of BPS, a BPA replacement, increased from 0% to 32% during the same study period. When comparing our urinary concentrations with those in other study populations, urinary concentrations of BPA, MEPB, ETPB, and PRPB in California pregnant women were lower than those in other study populations during the same study period.

Overall, the decreasing trends of BPA, MEPB, and PRPB urinary concentrations in California pregnant women were also observed in NHANES's non-pregnant women (Figure 2). Although we did not test differences in urinary concentrations among studies for each calendar year, we observed that the GMs of these three compounds and ETPB in California pregnant women were lower than those in NHANES women, both pregnant and non-pregnant, during the same period. Beause our participating women already have a child with ASD, they may have more concerns about products they were using such as personal care products or cosmetics. Thus, this comparision needs to be interpreted with caution. In addition, because California has been leading in protecting human health from chemical exposure via advocacy campaigns or legislation,[35, 71] it is possible that California women may have been choosing products that do not contain chemicals such as our target compounds more frequently than women in other U.S. states. The decreasing trends of BPA in California pregnant women and NHANES's women might be attributed to regulations against the use of BPA in cell phone cases, certain food contact polycarbonate products and thermal papers.[72] Regulations enforced in other countries (e.g., EU, Japan) since the late 2000s may also play a role, at least in part, in the decreasing trends of urinary paraben concentrations among U.S. pregnant women, because the U.S. is the second largest importer for cosmetics in the world and approximately half of the imported cosmetics are originated from EU or Japan where some parabens are currently under regulations.[73] Decreasing trends of MEPB, ETPB, and BUPB were observed in Massachusetts pregnant women,[68] but this result should be interpreted cautiously because of a relatively short period of sample collection (i.e., 2007–2009). Note that BUPB was detected in fewer than 10% of the samples in the current study. Ashrap et al. also observed decreasing trends of two phenols (i.e., BPA, TCS) and four parabens (i.e., MEPB, ETPB, PRPB, BUPB) during 2011–2016 in pregnant women of Puerto Rico, a part of the U.S. territory.[45] Thus, the decreasing trends in urinary concentrations of some phenols and parabens among U.S. study populations correspond temporally with domestic and/or international legislative actions or advocacy campaigns for reducing exposure to these compounds.

When comparing our annual average urinary concentrations of the target compounds with those observed in other study populations, we found that the levels and temporal trends of the concentrations were different across regions within the U.S. during the same period (Figure 2). For example, pregnant women in Puerto Rico had higher BPA, MEPB, ETPB, and PRPB concentrations than California pregnant women. In addition, compared to NHANES's women, pregnant women in Puerto Rico had higher TCC, TCS, and BUPB concentrations but had lower concentrations of BPF, a substitute for BPA. Puerto Rico is a U.S. territory, but its median household income in 2019 was low (~$20,000) compared to that of California (~$80,000) and the entire U.S. (~$65,000).[74] In addition, racial composition was different between California (39.4% Hispanic) and Puerto Rico (98.7% Hispanic).[75] Thus, the considerable difference in household income and racial composition between Puerto Rico and other U.S. states may have contributed to the differences in exposure patterns (e.g., cosmetic use frequencies) and the magnitude of exposure sources (e.g., type of products containing BPA, MEPB, ETPB, and PRPB) for the study compounds. Two states, California and Massachusetts, had comparable median household incomes in 2019 ($78,105, $87,707, respectively), however, the Hispanic population was approximately three times higher in California (39.4%) than Massachusetts (12.4%). Nevertheless, we observed that Massachusetts pregnant women had higher MEPB, ETPB, and PRPB concentrations than California pregnant women during the same study period.

Trends in detection frequencies or urinary concentrations for BPA versus BPS were in opposite directions among all study populations, including the current study, NHANES women, and Puerto Rico pregnant women. These trends may have been influenced by nationwide regulatory efforts for reducing exposure to BPA [30, 31] and corresponding emergence of BPS as a substitute of BPA.[32, 33] As experimental research showed that prenatal exposure to BPS has a neurotoxicity potential and abnormal behavioral function,[76] monitoring the trend of pregnant women's BPS exposure such as this study may help open up avenues for potential intervention of BPS exposure in the vulnerable populations (e.g., women of reproductive age, infants). For BPF, a clear trend was not observed in the detection frequency in California pregnant women during 2007–2014 (Table 2) and in the urinary concentrations in Puerto Rico pregnant women during 2011–2016 (Figure 2), but we observed a decreasing trend in NHANES's women during 2013–2016 (Figure 2).

We observed potential determinants affecting urinary concentrations and their temporal trends of BPA and three parabens (Table S3, Table 3). For example, Hispanic pregnant women tended to have higher concentrations of three parabens (i.e., MEPB, ETPB, PRPB) than pregnant women in the two other subgroups of race/ethnicity, which was observed in a previous study of the U.S. general population using NHANES data.[77] Compared to non-Hipanic White pregnant women, Hispanic pregnant women in our study had a lower rate of owning a home (54% versus 64%) or having at least a bachelor's degree (28% versus 64%). In addition, because we observed higher BPA concentrations among women who owned a home than those who did not, exposures to our target compounds might be associated with socioeconomic status. Women with pre-pregnancy BMI in a normal/ underweight range had the highest concentrations of three parabens (i.e., MEPB, ETPB, PRPB), which was observed in other studies,[78, 79] which may have reflected differences in paraben metabolism between women with differing BMI and/or exposure (e.g., diet or

product use).[79] We observed higher ETPB concentrations in older women (> 35 years old) than in younger women (≤ 35 years old). These differences may be due to increased use of personal care products and cosmetics with age[80] or from decreased metabolic or execretion rates with age.[81, 82]

Strengths of this study include concentrations of phenols, parabens and TCC in urine collected from pregnant women over a relatively long sample collection time (during 2007–2014). This enabled us to observe temporal trends in pregnant women's exposure to these compounds after regulations or advocacy campaigns since the late 2000s to mid 2010s. In addition, from comparison of these compounds among mutiple U.S. study populations including NHANES women, we could find the potential effect of socioeconomic status, racial composition and broad social forces such as state advocacy campagins on pregnant women's exposure to phenols, parabens and TCC. When comparing urinary concentrations between NHANES pregnant women and non-pregnant women, we found that pregnant women had consistently lower concentrations of BPA, BPF, and BPS than non-pregnant women during most of the NHANES study cycles. We note that the NHANES pregnant women data need to be interpreted cautiously because of their small sample size. However, this might be further evidence that pregnant women may have changed their use in cosmetics and other personal care products after becoming pregnant.[42–44]

Some limitations should be noted for this study. First, the exposure levels observed in our pregnancy cohort may not be representative of other U.S. pregnancy cohorts and California pregnant women, because our study participants may have changed their use of personal care products or cosmetics to reduce the risk of having another child with ASD. Second, because over two thirds of our urine samples were FMVs, which were collected a long time after product use or the last meal (i.e., approximately 9 hours of sleeping),[83] this may have resulted in lower concentrations of BPA, MEPB, ETPB, and PRPB in our populations than NHANES women. In addition, the LODs were approximately 5 to 12 times higher in the current study than the other three studies (Table S1). Thus, it is likely that BPF, BPS, TCC, TCS, and BUPB were less frequently detected in our samples than the other three studies. Lastly, the relationship between several population characteristics and urinary concentrations (Table S3) should be interpreted with caution, because our target compounds are quickly excreted in urine with elimination half-lives of less than one day.[84, 85]

In summary, this study showed decreasing trends in urinary concentrations of BPA, MEPB, ETPB, and PRPB and increasing detection frequencies of BPS, a substitute for BPA, in California pregnant women during 2007–2014. This may reflect the U.S. nationwide regulation efforts and/or California advocacy campaigns since the late 2000s to mid 2010s for reducing exposure to phenols, parabens and TCC in women of reproductive age and infants. Comparison of our urinary concentrations with those in other U.S. study populations allowed us to observe geographic variations in pregnant women's exposure to some phenols and parabens, which may be associated with differences in regulatory status, socioeconomic status, and racial composition as well as potential changes in product use after being pregnant. As other BPA alternatives that were not targeted for analysis in the current study (i.e., bisphenol A bis (2,3-dihydroxypropyl) ether, bisphenol A (3-chloro-2-hydroxypropyl) (2,3-dihydroxypropyl) ether, and bisphenol AF) were detected in U.S. residential indoor

dust collected during 2015–2016,[6, 8] future studies may benefit by measuring those BPA alternatives to gain insight into trends in total bisphenol exposure. As transparent product composition information is not readily available from all manufacturers, characterizing comprehensive temporal biomarker trends of phenols, parabens, and TCC in pregnant women will help us to understand the effects of regulations or advocacy compaigns on exposure trends and to identify chemicals with similar use or functions in products that are increasing over time.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Synopsis:

This study showed that body burden of some phenols and parabens in the U.S. pregnant women decreased over time, which appeared to reflect regulations or campaigns.
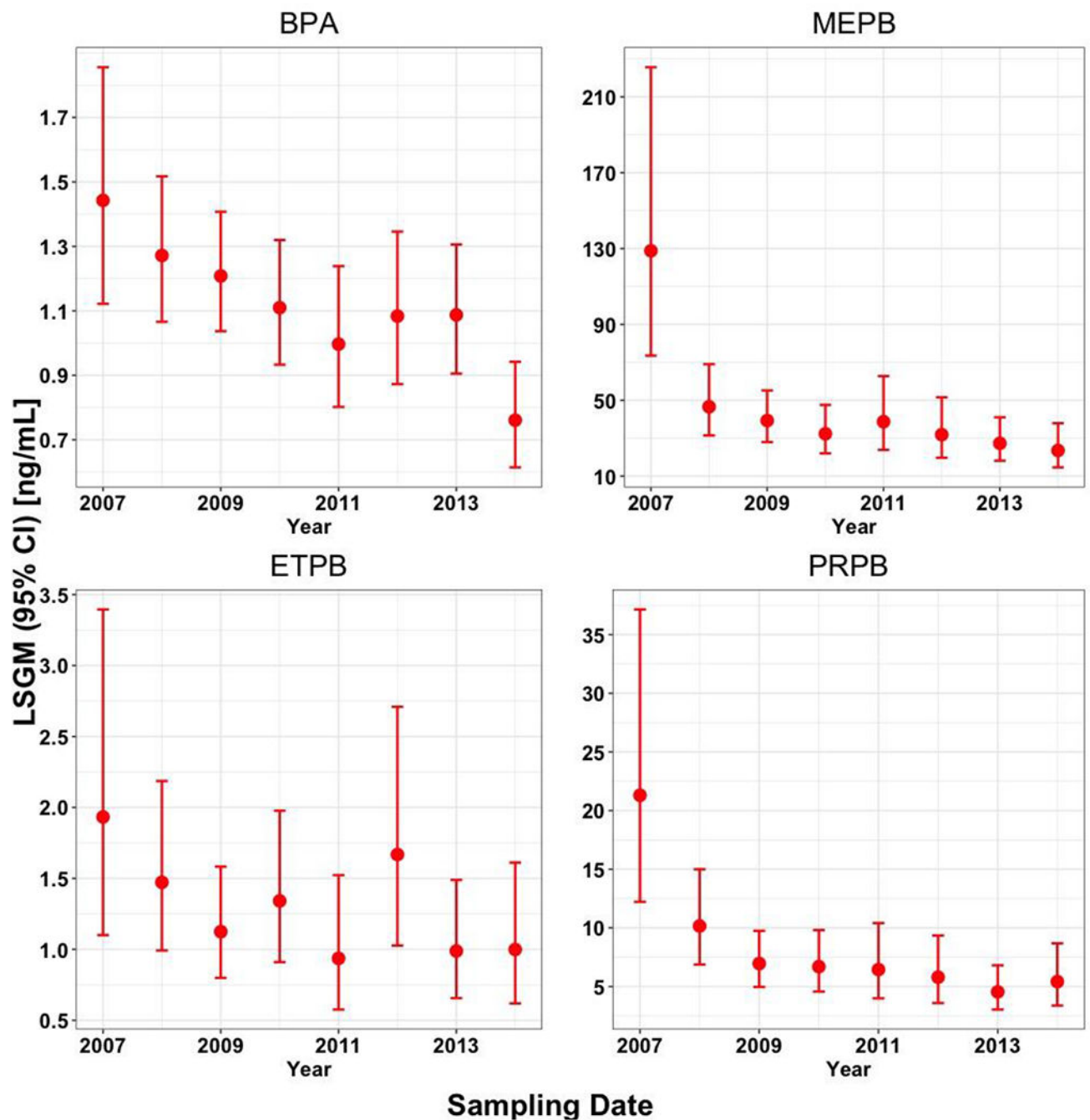
Figure 1.

Temporal trends in measured urinary concentrations (ng/mL) of bisphenol A (BPA), methyl paraben (MEPB), ethyl paraben (ETPB), and propyl paraben (PRPB) in 760 urine samples collected from California pregnant women in a high-familial risk ASD cohort during 2007–2014. The urinary concentrations were adjusted for SG, sampling year, race/ethnicity, pre-pregnancy body mass index (BMI), education, age at delivery, homeownership, and parity. Data points represent LSGMs (least square geometric means or adjusted geometric means) and error bars represent 95% confidence intervals (CIs).
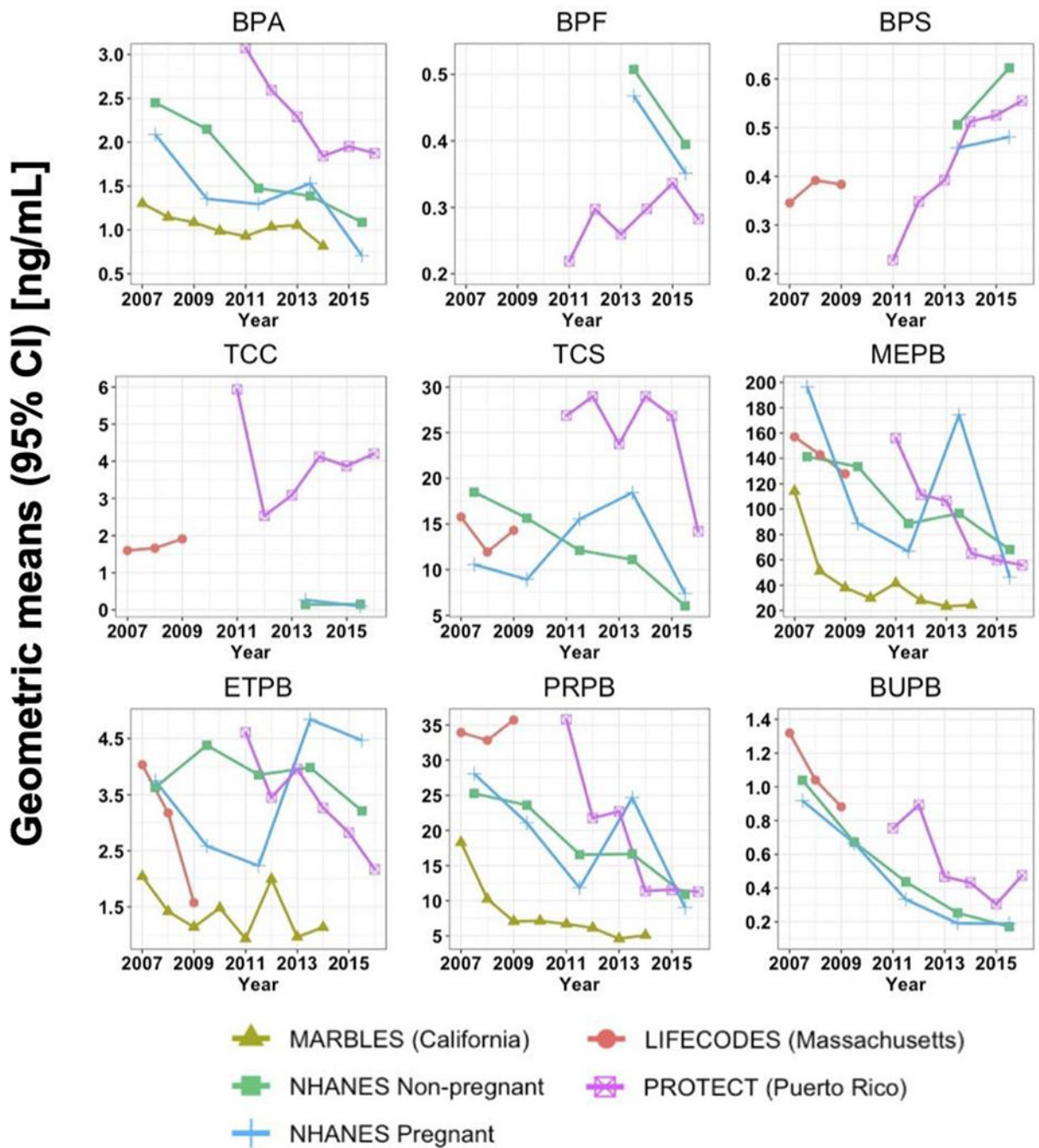
Figure 2.
Geometric means (GMs) of urinary concentrations of bisphenol A (BPA), bisphenol F (BPF), bisphenol S (BPS), triclocarban (TCC), triclosan (TCS), methyl paraben (MEPB), ethyl paraben (ETPB), propyl paraben (PRPB), and butyl paraben (BUPB) [ng/mL] among different study cohorts between 2007 and 2016. GMs for MARBLES, PROTECT and LIFECODES were only adjusted for specific gravity and those for NHANES were not adjusted. Only non-pregnant women aged 20 to 50 years were included in U.S. NHANES non-pregnant women. Urinary concentrations for NHANES pregnant women were only

available in a small sample size (range: 18–26 pregnant women), depending on the NHANES cycle, and thus should be interpreted with caution. BPS, BPF, TCC, TCS and BUPB were detected in less than 50% of the samples in MARBLES. BPA and BPF were not measured in LIFECODES. BPF, BPS, TCC were not measured in the NHANES during 2007–2012.

Table 1.

Distribution of specific gravity-corrected concentrations of phenols, parabens and TCC [ng/mL] in 760 urine samples (383 FMVs, 116 24-hour samples, 261 pools) collected from 233 pregnancies.

Compounds	LOD [ng/mL]	% detect	All samples Percentiles			FMV	Pool	24-hr	FMV versus pools [a]	FMV versus 24-hr [a]	24-hr versus pools [a]
			5th	50th	95th	50th	50th	50th			
BPA	0.8	59	<LOD	1.0	4.5	1.0	1.1	1.0	0.42	0.35	0.17
BPF	2.5	17	<LOD	<LOD	9.9	<LOD	<LOD	<LOD	-	-	-
BPS	0.5	14	<LOD	<LOD	2.8	<LOD	<LOD	<LOD	-	-	-
TCC	1.0	5	<LOD	<LOD	2.8	<LOD	<LOD	<LOD	-	-	-
TCS	15.0	32	<LOD	<LOD	285.5	<LOD	<LOD	<LOD	-	-	-
MEPB	0.5	96	0.6	38.9	388.0	36.2	41.4	48.9	0.78	0.60	0.58
ETPB	0.5	50	<LOD	0.7	44.3	0.7	0.8	0.7	0.90	0.54	0.54
PRPB	1.0	78	<LOD	8.3	98.6	8.5	7.8	8.2	0.34	0.94	0.43
BUPB	1.5	8	<LOD	<LOD	7.5	<LOD	<LOD	<LOD	-	-	-

Abbreviation: limit of detection (LOD), bisphenol A (BPA), bisphenol F (BPF), bisphenol S (BPS), triclocarban (TCC), triclosan (TCS), methyl paraben (MEPB), ethyl paraben (ETPB), propyl paraben (PRPB), butyl paraben (BUPB)

[a] P-value from the Wilcoxon rank-sum test of the null hypothesis that two populations have the same distribution with the same median.

Table 2.

Detection frequencies of phenols, parabens and TCC and the number of samples for each sampling year.

Year	No. of all samples	% of FMVs	% of Pools	% of 24-hour samples	Detection frequency (%)								
					BPA	BPF	BPS	TCC	TCS	MEPB	ETPB	PRPB	BUPB
2007	51	51	38	11	67	22	0	12	25	96	61	88	8
2008	121	58	34	8	63	22	5	3	30	98	56	88	11
2009	181	54	30	16	58	18	9	4	38	96	46	71	9
2010	112	48	35	17	59	13	14	4	38	96	51	82	5
2011	67	48	38	14	55	10	6	3	33	96	40	76	7
2012	65	46	31	24	62	17	26	5	43	95	54	78	11
2013	106	49	36	15	62	17	26	2	22	94	46	72	5
2014	57	36	47	17	42	9	32	14	23	91	51	77	4

Abbreviation: bisphenol A (BPA), bisphenol F (BPF), bisphenol S (BPS), triclocarban (TCC), triclosan (TCS), methyl paraben (MEPB), ethyl paraben (ETPB), propyl paraben (PRPB), butyl paraben (BUPB)

Table 3.

Trends in SG-corrected urinary concentrations [ng/mL] in 760 urine samples collected during 2007–2014.

Characteristics	n	BPA		MEPB		ETPB		PRPB	
		tau [a]	p-value [b]	tau	p-value	tau	p-value	tau	p-value
Race/ethnicity									
White (non-Hispanic)	425	−0.07	**0.03**	−0.19	**<0.01**	−0.14	**<0.01**	−0.15	**<0.01**
Hispanic	173	−0.18	**<0.01**	0.02	0.74	0.06	0.24	−0.06	0.23
Other [c]	162	−0.14	**0.01**	−0.15	**0.01**	0.00	0.95	−0.15	**0.01**
Pre-pregnancy BMI									
Normal/ underweight	335	−0.08	**0.04**	−0.15	**<0.01**	−0.07	0.05	−0.19	**<0.01**
Overweight	241	−0.20	**<0.01**	−0.07	0.09	0.03	0.50	−0.02	0.62
Obese	172	−0.02	0.68	−0.20	**<0.01**	−0.15	**<0.01**	−0.15	**<0.01**
Education									
Less than college degree	361	−0.14	**<0.01**	−0.08	**0.02**	0.01	0.77	−0.08	**0.02**
Bachelor's degree	278	−0.11	**0.01**	−0.19	**<0.01**	−0.12	**<0.01**	−0.16	**<0.01**
Graduate or professional degree	121	−0.10	0.12	−0.20	**<0.01**	−0.16	**0.01**	−0.18	**<0.01**
Age at delivery									
35 years old	404	−0.13	**<0.01**	−0.15	**<0.01**	−0.08	**0.02**	−0.14	**<0.01**
> 35 years old	356	−0.09	**0.02**	−0.12	**<0.01**	−0.02	0.56	−0.11	**<0.01**
Homeownership									
Yes	280	−0.12	**<0.01**	−0.12	**<0.01**	−0.10	**0.02**	−0.09	**0.03**
No	466	−0.12	**<0.01**	−0.13	**<0.01**	−0.02	0.56	−0.15	**<0.01**
Parity									
1	49	−0.26	**0.01**	−0.12	0.24	−0.02	0.84	−0.22	**0.02**
>1	697	−0.10	**<0.01**	−0.14	**<0.01**	−0.06	**0.01**	−0.13	**<0.01**

[a] The number of missing values for pre-pregnancy BMI, homeownership, and parity are 12, 14, and 14, respectively.

[b] Kendall's tau from the Mann-Kendall trend test: negative and positive tau represent decrease and increase in urinary concentrations, respectively, over time.

[c] P-values from the Mann-Kendall trend test less than 0.05 are highlighted in bold.

[d] Includes Black (3%), Asian (18%), and multiracial (3%).