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Elevated concentrations of urinary triclocarban, phenol and paraben among pregnant women in Northern Puerto Rico: Predictors and trends

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ABSTRACT

Background: Understanding important sources and pathways of exposure to common chemicals known or suspected to impact human health is critical to eliminate or reduce the exposure. This is particularly important in areas such as Puerto Rico, where residents have higher exposures to numerous chemicals, as well as higher rates of many adverse health outcomes, compared to the mainland US.

Objective: The aim of this study was to assess distributions, time trends, and predictors of urinary triclocarban, phenol, and paraben biomarkers measured at multiple times during pregnancy among women living in Northern Puerto Rico.

Methods: We recruited 1003 pregnant women between years 2010 and 2016 from prenatal clinics and collected urine samples and questionnaire data on personal care product use at up to three separate visits, between 16 and 28 weeks gestation. Urine samples were analyzed for triclocarban, seven phenols and four parabens: 2,4-dichlorophenol, 2,5-dichlorophenol, benzophenone-3, bisphenol A (BPA), bisphenol S (BPS), bisphenol F, triclosan, butylparaben, ethylparaben, methylparaben, and propylparaben.

Results: Detectable triclocarban, phenol and paraben concentrations among pregnant women were prevalent and tended to be higher than levels measured in women of reproductive age from the general US population, especially triclocarban, which had a median concentration 37 times higher in Puerto Rico participants (2.6 vs 0.07 ng/mL). A decreasing temporal trend was statistically significant for urine concentrations of BPA during the study period, while the BPA substitute BPS showed an increasing temporal trend. Significant and positive associations were found between biomarker concentrations with the products use in the past 48-h (soap, sunscreen, lotion, cosmetics). There was an increasing trend of triclocarban/triclosan urinary concentrations with increased concentrations of triclocarban/triclosan listed as the active ingredient in the bar soap/liquid soap products reported being used.

Conclusion: Our results suggest several potential exposure sources to triclocarban, phenols, and parabens in this population and may help inform targeted approaches to reduce exposure.

1. Introduction

In recent decades, a multitude of new synthetic chemicals such as environmental phenols, parabens, triclocarban and related compounds, have been introduced by industrial progress. Chemicals such as bisphenol A (BPA), triclosan, benzophenone-3, and methylparaben can be found in a wide variety of commercial products including personal care products, plastics, packaged food and drinks, and pharmaceuticals (Calafat et al., 2015; Zoeller et al., 2012). Humans are ubiquitously exposed to these chemicals through food intake, consumer product use, inhalation, dermal contact, and perinatal transmission (i.e., placenta, breast milk) (Heffernan et al., 2015; North and Halden, 2013; Soni

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et al., 2001; vom Saal and Welshons, 2014). In the United States, reports from the National Health and Nutrition Examination Survey (NHANES) showed that the majority of the U.S. population has detectable concentrations of a range of personal care product chemicals in their bodies (Centers for Disease Control and Prevention, 2009).

Exposure to environmental phenols, parabens and triclocarban has been associated with endocrine system dysfunction and increased oxidative stress in both human and animal studies (Bukowska, 2003; Diamanti-Kandarakis et al., 2009; Kang et al., 2013; Karpuzoglu et al., 2013; Kumar et al., 2009; Watkins et al., 2015), and there is growing evidence that exposure to certain environmental chemicals may contribute to the recent rise in child developmental disorders (Braun et al., 2011b; Meeker, 2012). There are particularly high rates for a number of developmental disorders in Puerto Rico, as well as elevated exposure to environmental contaminants. For example, previous research within this area suggests that pregnant women in Puerto Rico may have higher exposure to certain phenols, such as triclosan, benzophenone-3, and 2,5-dichlorophenol, compared to women of reproductive age from the U.S. general population (Meeker et al., 2013). In addition, Puerto Rico has higher rates of preterm birth, childhood obesity and asthma (Garza et al., 2011; Otero-Gonzalez and Garcia-Fragoso, 2008; Rivera-Soto et al., 2010) as well as of obesity, metabolic syndrome, and diabetes in adults (Centers for Disease Control and Prevention, 2012; Perez et al., 2008) compared to the mainland U.S.

Bisphenol S (BPS) and bisphenol F (BPF) are common alternatives to BPA (Rochester and Bolden, 2015). Their widespread use has resulted in detection in personal care products (Liao and Kannan, 2014), food (Liao and Kannan, 2013), indoor dust (Liao et al., 2012b), surface water and sediments (Fromme et al., 2002; Song et al., 2014; Yang et al., 2014). BPS and BPF have also been detected in human urine at concentrations and detection frequencies comparable to BPA (Centers for Disease Control and Prevention, 2018; Liao et al., 2012a; Vela-Soria et al., 2014; Zhou et al., 2014). *In vivo* and *in vitro* studies have indicated that BPS and BPF have similar hormonal activity as BPA (Molina-Molina et al., 2013; Owens and Ashby, 2002; Stroheker et al., 2003; Vinas and Watson, 2013) and have endocrine-disrupting effects (Ji et al., 2013; Naderi et al., 2014), therefore, they may pose similar potential health hazards as BPA. Although not a phenol, triclocarban, like triclosan, is used as a preservative and antiseptic agent primarily added to pharmaceutical and personal care products and has been detected in a wide variety of matrices worldwide (Halden, 2014). Triclocarban and triclosan are both environmentally persistent and bioaccumulate in aquatic organisms (Coogan and La Point, 2008; Meador et al., 2016). Toxicological studies suggested that triclosan can disrupt endocrine function and thyroid hormone homeostasis (Yueh and Tukey, 2016), and a recent systematic review of both animal and human studies concluded that triclosan exposure was “possibly toxic to reproductive and developmental health” (Johnson et al., 2016). Although research on the effects of triclocarban exposure is sparse (Halden et al., 2017; Rochester et al., 2017), limited studies suggest the ability to alter endocrine homeostasis, possibly by amplifying the effect of endogenous hormones (Chen et al., 2008; Witorsch and Thomas, 2010).

In light of the potential impact of phenols, parabens, and triclocarban on human health, studies characterizing exposure trends and sources are needed to inform effective strategies to reduce exposure, especially among pregnant women and children. In a previous preliminary study, we reported the distribution, variability, and predictors (personal care product use) of urinary concentrations of select phenols and parabens among the first 105 participants in our study of pregnant women in Puerto Rico (Meeker et al., 2013). The detection of these biomarkers in urine samples from Puerto Rican pregnant women suggests that exposure to phenol and paraben is highly prevalent in this population. While we reported positive associations between biomarker concentrations and self-reported use of personal care products, such as liquid soap (triclosan), sunscreen (benzophenone-3), lotion (benzophenone-3 and parabens), and cosmetics (parabens), our small sample size limited our certainty in identifying specific sources of exposure within this vulnerable population. In addition, it was unclear how recent changes in the use of specific chemicals in personal care products would affect women in Puerto Rico. The present analysis greatly expands the sample size, providing more statistical power to detect associations, includes additional chemicals of concern (BPS, BPF, and triclocarban), and spans several years which enables the exploration of time trends. The aims of the present expanded study were to conduct a more robust follow-up to our previous analysis of distributions, variability, and predictors of urinary concentrations of biomarkers of triclocarban, environmental phenols and parabens measured at multiple times during pregnancy among women living in Northern Puerto Rico.

2. Methods

2.1. Study population

This study used data collected from pregnant women participating in the Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) project (Cantonwine et al., 2014; Meeker et al., 2013; Watkins et al., 2015). This prospective birth cohort was started in 2010 in the Northern Karst Region of Puerto Rico. The mission of PROTECT is to evaluate the influence of the exposure to selected environmental toxicants on the risk of preterm delivery and other adverse birth outcomes.

Study participants were recruited at seven prenatal clinics and hospitals throughout Northern Puerto Rico during 2010–2016 at approximately 14 ± 2 weeks of gestation. The present analysis reflects the 1003 women in the study to date, which is an expansion of a previous preliminary analysis that included the first 105 participants recruited into the study who had urinary biomarker data as of June 2012 (Meeker et al., 2013). All women were between the ages of 18 to 40 years. Details on the recruitment and inclusion criteria have been described previously (Cantonwine et al., 2014; Meeker et al., 2013). Spot urine samples were collected from women at three separate study visits (18 ± 2 weeks, 22 ± 2 weeks, and 26 ± 2 weeks of gestation).

The research protocol was approved by the Ethics and Research Committees of the University of Puerto Rico and participating clinics, the University of Michigan School of Public Health, and Northeastern University. The involvement of the Centers for Disease Control and Prevention (CDC) laboratory was determined not to constitute engagement in human subject research. The study was described in detail to all participants, and informed consent was obtained prior to study enrollment.

2.2. Measurement of triclocarban, phenols and parabens in urine

Urine samples were collected in polypropylene containers, divided into aliquots, and frozen at −80 °C until shipped overnight to the CDC for analysis. All urine samples were analyzed for triclocarban, seven phenols: BPA, BPS, BPF, 2,4-dichlorophenol, 2,5-dichlorophenol, benzophenone-3, triclosan, and four parabens: butylparaben, ethylparaben, methylparaben, propylparaben by online solid-phase extraction-high-performance liquid chromatography-isotope dilution tandem mass spectrometry (Watkins et al., 2015; Ye et al., 2005; Ye et al., 2006). To monitor accuracy and precision, each analytical run included calibration standards, reagent blanks, and quality control materials of high and low concentrations. Details of the analytical method, which was also used to analyze NHANES samples (Centers for Disease Control and Prevention, 2014), were described previously (Meeker et al., 2013). Biomarker concentrations below the limit of detection (LOD) were replaced by LOD/√2 (Hornung and Reed, 1990).

2.3. Questionnaire

The product use questionnaire, which was adapted from questionnaires used in other studies of adults (Meeker et al., 2013), was developed to capture information on potential exposure sources to which the pregnant women may have been in contact. The questionnaire was administered by a study nurse at each urine sample collection to gather demographic information as well as data on self-reported product use. The personal care product use section contained yes/no questions about the use of different products in the 48-h preceding urine sample collection, in addition to questions on the usual frequency of using these personal care products (not at all, < once/month, 1–3 times/month, once/week, few times/week, every day). The questionnaire asked about the use of the following personal care products: bar soap, cologne/perfume, colored cosmetics, conditioner, deodorant, fingernail polish, hair cream, hairspray/hair gel, laundry products, liquid soap, lotion, mouthwash, other hair products, shampoo, and shaving cream. Following each yes/no question regarding the use of personal care product, the participants were also asked to report the specific brand of the product.

2.4. Statistical methods

For some statistical analyses, biomarker concentration values were corrected for urinary specific gravity (SG) using the following equation: $Pc = P[(SGp - 1)/(SGi - 1)]$ where Pc is the SG corrected biomarker concentration (μg/L), P is the measured biomarker concentration, SGp is the median urinary specific gravity (1.019), and SGi is the individual's urinary specific gravity. Distribution of urinary biomarkers (geometric means and selected percentiles) were calculated and compared to the concentrations measured NHANES (2009–2010, 2011–2012, 2013–2014) among women aged between 18 and 40 years ($n = 1185$). The relationships between the various biomarkers were assessed by calculating Spearman rank correlations. To test whether there were differences in geometric mean biomarker concentrations between study visits (i.e., time points in gestation), linear mixed effect models were used which account for repeated measurements from individuals. We assessed the proportion of variance attributed to between-person variability across the three-time points in pregnancy using intra-class correlation coefficients (ICCs) and their 95% confidence intervals (Hankinson et al., 1995). ICC, ranging between 0 (no reproducibility) and 1 (perfect reproducibility), is interpreted as reflecting a poor degree of reliability when below 0.40, a moderate to good reliability when ranging between 0.40 and 0.75, and an excellent reliability when above 0.75 (Rosner, 2015).

Next, to examine the changes in urinary biomarker concentrations over time among the study population, tests of linear trend across increasing visit-years were conducted by modeling the geometric mean of each biomarker and visit-year as a continuous variable and assessing significance using the Wald test.

We examined the association between urinary biomarker concentrations and categories of demographic variables (maternal age, maternal education, marital status, household income, parity, and pre-pregnancy body mass index (BMI)), as well as with repeated 48-h recall of the use of different products (yes/no questions mentioned above). With compound symmetry covariance structure, we used linear mixed effects models to account for the intra-individual correlation and variation of repeated measures over time. SG-corrected urinary biomarker concentrations were log-transformed and modeled as the dependent variable, with separate models for each demographic and product use variable. Data were analyzed using R version 3.2.2 and SAS 9.4 (SAS Institute Inc., Cary, NC).

Finally, based on the associations between product use and urine biomarker concentrations, we examined frequencies of the active ingredient (percentage if available) in different brands of bar soap and liquid soap use reported in the 48-h recall questionnaire in relation to triclosan and triclocarban concentrations among soap users. We searched the active ingredient and ingredient content level of the most commonly reported soap brands by women in the study, using the Environmental Working Group (EWG)'s Skin Deep Cosmetic Database which contains 72,454 products (Environmental Working Group, 2018), the U.S. National Library of Medicine Household Products Database (National Library Of Medicine, 2010), and web-based search engines (i.e., Google). For brands containing triclocarban or triclosan, we presented triclosan and triclocarban distribution corresponding to the specific soap brand users in comparison to those who did not report any soap use in the recall.

3. Results

Statistical analysis was conducted for both uncorrected and SG-corrected biomarker concentrations on a total of 2166 urine samples from 1003 women, and results were highly consistent between the two approaches. The results for models utilizing uncorrected biomarker concentrations also remained the same when we excluded 152 samples without available SG data. Therefore, only results for SG-corrected concentrations are presented.

3.1. Demographics

The mean age of the participants was 26.6 years and nearly all women were non-smokers during pregnancy. Other demographic characteristics of the women in our study are shown in Table 3. Most women in our study had an education above high school and were employed, married or in a domestic partnership.

3.2. GM and percentiles

Distributions of urinary biomarker concentrations among women in our study and distributions among women 18 to 40 years old from the NHANES 2009–10, 2011–12 and 2013–14 are presented in Table 1. BPA, benzophenone-3, both dichlorophenols, methylparaben, and propylparaben were detected in between 95% and 100% of samples from the PROTECT cohort. Triclocarban and triclosan were detected in 93% and 87% of samples, respectively, while BPS was detected in 90%, butylparaben was detected in 55%, and BPF was in 41% of the samples. Women in our study had higher geometric mean concentrations of 2,4-dichlorophenol, 2,5-dichlorophenol, BPA, butylparaben, triclocarban, and triclosan, compared with NHANES women. PROTECT women had a median concentration of triclocarban that was 37 times greater than NHANES. Median concentrations of butylparaben, triclosan, and 2,5-dichlorophenol among Puerto Rico women were 2-,2- and 4-fold greater, respectively, compared to women in NHANES. For 2,4-dichlorophenol and BPA median concentrations were similar in the two cohorts, but geometric mean concentrations were higher among PROTECT women. Distribution of benzophenone-3 and BPS were similar between the two populations, while the remaining parabens (ethylparaben, methylparaben, propylparaben) and BPF were lower among women in this study compared to NHANES. There was a moderate to strong correlation between 2,4-dichlorophenol and 2,5-dichlorophenol (Spearman $r = 0.65$), between 2,4-dichlorophenol and triclosan (Spearman $r = 0.46$), and between the four parabens, particularly between methylparaben and propylparaben ($r = 0.78$). There were also weak to moderate ($r = 0.25$ to 0.4) but statistically significant correlations between benzophenone-3 and the parabens (SI Table S1).

3.3. Between visit comparison

Box plots comparing the biomarker concentration distributions between study visits are shown in SI Fig. S1. Statistically significant differences were observed between SG-corrected concentrations at the three visits for the biomarkers 2,5-dichlorophenol ($p = 0.02$), BPA

Table 1
Uncorrected urinary biomarker concentrations (ng/mL) in n = 1003 pregnant women from Puerto Rico[a] in 2010–2016 and comparison with U.S. population-based samples of women ages 18–40 from NHANES.[b,c]

	Cohort	LOD	% > LOD	GM	GSD	25%	50%	75%	95%	p Value[d]
2,4-Dichlorophenol	PROTECT	0.1	97.2	1.1	3.5	0.5	0.9	2.1	10.4	< 0.01**
	NHANES	0.1	95.9	0.8	4.0	0.3	0.7	1.5	9.6	
2,5-Dichlorophenol	PROTECT	0.1	99.9	12.7	5.4	3.9	9.9	29.7	394.9	< 0.01**
	NHANES	0.1	98.0	3.9	8.7	0.9	2.7	10.8	256.4	
Benzophenone-3	PROTECT	0.4	99.7	39.1	6.6	10.3	26.5	124.0	1585.9	0.37
	NHANES	0.4	99.2	36.6	8.3	8.1	25.9	128.0	2337.8	
BPA	PROTECT	0.2–0.4	98.7	2.0	2.5	1.1	2.0	3.5	9.7	< 0.01**
	NHANES	0.2–0.4	92.8	1.7	3.1	0.8	1.7	3.5	10.2	
BPF	PROTECT	0.2	41.1	0.3	2.9	0.1	0.1	0.4	2.1	< 0.01**
	NHANES	0.2	67.2	0.5	4.3	0.1	0.4	1.1	8.8	
BPS	PROTECT	0.1	89.8	0.5	3.2	0.2	0.4	0.9	3.5	0.30
	NHANES	0.1	88.8	0.5	3.5	0.2	0.5	1.3	4.0	
Triclosan	PROTECT	1.7–2.3	86.6	21.3	8.7	3.5	14.9	128.3	824.8	< 0.01**
	NHANES	1.7–2.3	78.1	12.4	6.6	2.7	8.4	40.0	485.0	
Triclocarban	PROTECT	0.1	93.1	3.5	11.1	0.5	2.6	28.6	153.6	< 0.01**
	NHANES	0.1	43.0	0.2	4.0	0.1	0.07	0.2	4.1	
Methylparaben	PROTECT	1.0	99.4	73.4	5.3	22.9	86.3	243.8	913.2	< 0.01**
	NHANES	1.0	99.7	108.3	5.4	34.0	121.5	380.2	1387.0	
Ethylparaben	PROTECT	1.0	55.4	2.6	6.8	0.7	1.3	8.3	109.8	< 0.01**
	NHANES	1.0	63.2	4.1	6.5	0.7	2.5	15.7	159.9	
Propylparaben	PROTECT	0.1	99.0	14.5	7.7	3.1	16.7	75.0	295.4	< 0.01**
	NHANES	0.2	98.7	19.3	8.0	4.7	24.1	94.7	402.7	
Butylparaben	PROTECT	0.1	55.1	0.5	7.7	0.1	0.2	1.8	28.6	< 0.01**
	NHANES	0.2	51.8	0.4	6.0	0.1	0.1	1.3	15.0	

[a] Includes biomarker concentrations for up to 3 repeated samples per woman (n = 2166 samples).
[b] Females 18–40 years of age; n = 1185 for biomarkers measured in 2009–2010, 2011–2012, and 2013–2014 NHANES.
[c] NHANES, National Health and Nutrition Examination Survey; LOD, limit of detection; GM, geometric mean, GSD, geometric standard deviation.
[d] p Value for two sample t-test comparing geometric mean of chemical concentration in two cohorts.
** $p < 0.01$.

Table 2
Intraclass correlation coefficients (ICCs) and 95% confidence for ln-transformed urinary concentrations of biomarkers[a].

	Uncorrected	SG_corrected[b]
Urinary biomarker	ICC (95% CI)	ICC (95% CI)
2,4-Dichlorophenol	0.19 (0.15,0.24)	0.20 (0.21,0.30)
2,5-Dichlorophenol	0.22 (0.18,0.27)	0.29 (0.25,0.34)
Benzophenone-3	0.53 (0.49,0.57)	0.54 (0.50,0.57)
BPA	0.12 (0.08,0.19)	0.09 (0.05,0.16)
BPS	0.03 (0.01,0.14)	0.02 (0.00,0.16)
Triclosan	0.52 (0.48,0.57)	0.59 (0.55,0.63)
Triclocarban	0.72 (0.68,0.76)	0.69 (0.64,0.73)
Methylparaben	0.23 (0.18,0.30)	0.16 (0.11,0.21)
Ethylparaben	0.29 (0.24,0.34)	0.40 (0.36,0.45)
Propylparaben	0.43 (0.38,0.49)	0.35 (0.30,0.41)
Butylparaben	0.55 (0.49,0.60)	0.57 (0.51,0.62)

[a] Among 1003 women, 405 had data from all three visits, 353 had data from two visits, and 245 had data from one visit.
[b] Specific gravity corrected concentration.

($p < 0.01$), butylparaben ($p = 0.02$), and ethylparaben ($p = 0.01$), where the concentration at first visit was higher than at later visits. For 2,4-dichlorophenol and benzophenone-3, geometric mean concentrations at the three visits were statistically different ($p < 0.05$) before correcting for specific gravity (the first visit had the highest concentration), but after correcting for specific gravity there was no difference (SI Table S2). ICCs of uncorrected and SG-corrected biomarker were presented in Table 2. Reproducibility varied widely between biomarkers and ranged from weak (BPS = 0.02) to good. A moderate to good reproducibility was observed for all four parabens, triclocarban, triclosan, benzophenone-3, and butylparaben, with ICC ranging from 0.54 to 0.69, after correcting for specific gravity. On the other hand, 2,4-dichlorophenol, 2,5-dichlorophenol, BPA, BPS, and methylparaben presented a poor degree of reliability with low ICC (0.02–0.29), while ethylparaben was intermediate (0.40).

3.4. Distribution by year

Fig. 1 shows urinary biomarker concentration distributions in the study population stratified by year. For all biomarkers, urinary concentrations were lower in participants from the later year cycle compared to those from the earlier year cycle (P for trend < 0.01), with the exception of BPS (P for trend < 0.01) which has an increasing trend, and benzophenone-3 (P for trend = 0.95), BPF (P for trend = 0.54) and triclocarban (P for trend = 0.15) which stayed constant.

3.5. Demographics and biomarkers

Associations between urinary biomarker concentrations and demographic variable categories are presented in Table 3. There were trends for increasing concentration of benzophenone-3, triclosan and four parabens with increasing age categories, where BPA and triclocarban concentration had a decreasing trend with increasing age categories. Benzophenone-3, triclosan, and the four paraben concentrations were higher among women with > 12 years of education. There were decreasing trends in triclocarban concentrations and education categories. 2,5-Dichlorophenol, methylparaben, and triclocarban concentrations were associated with marital status, where concentrations among women who were either married or in a domestic partnership were significantly lower ($p = 0.04$, 0.04 and $p = 0.05$, respectively) compared to women who reported their marital status as single. There were trends for increasing concentrations of benzophenone-3, butylparaben, BPF, ethylparaben with increasing income categories, whereas 2,5-dichlorophenol and triclocarban concentrations had decreasing trends in relation to increasing income categories. There was an increasing trend between triclocarban concentration and pre-pregnancy BMI and a decreasing trend between butylparaben concentrations and increased

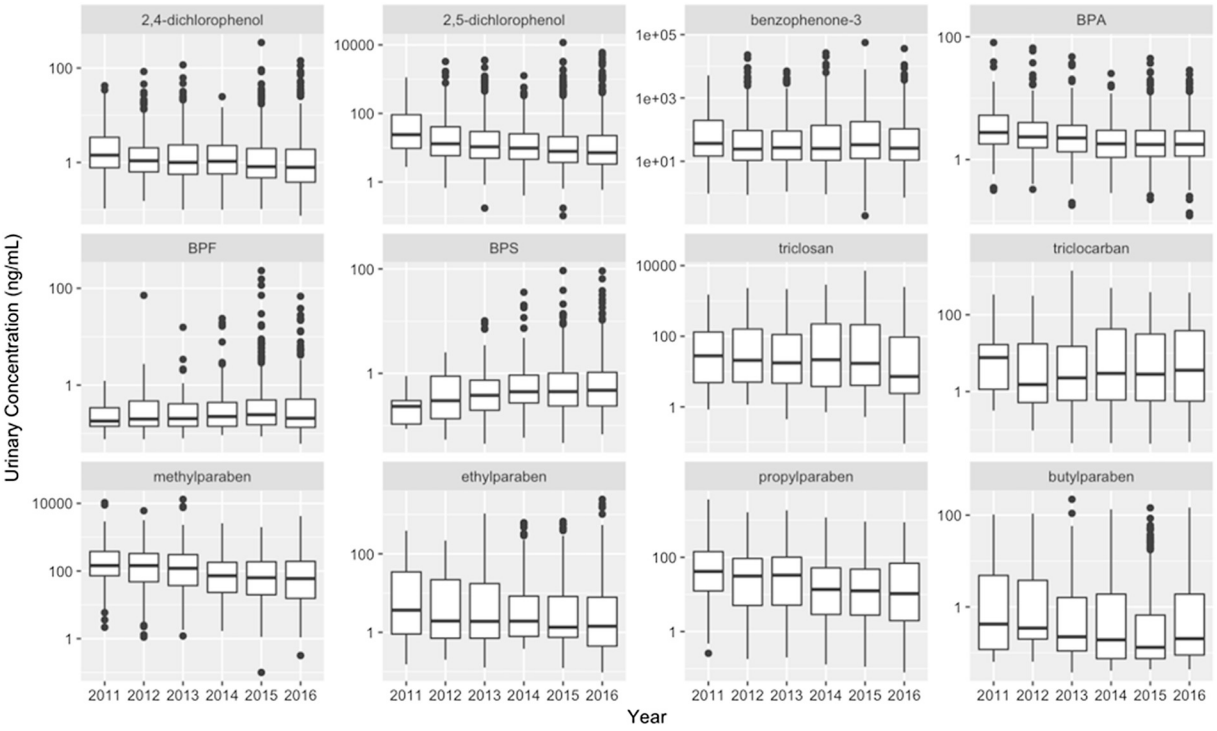

Fig. 1. Distribution of urinary biomarker concentrations (ng/mL) among 1003 pregnant women in Puerto Rico over study years (2010–2016)[a].
[a]Number of participants in each year during 2011–2016 were 136, 364, 354, 240, 447, and 499, respectively.

parity. Finally, concentrations of benzophenone-3, triclosan and three parabens (butylparaben, methylparaben, propylparaben) were lower, and triclocarban concentrations higher, among women who were not currently employed.

3.6. Product use and biomarkers

Urinary biomarker concentrations in relation to self-reported product use are presented in Table 4. The geometric mean concentration of benzophenone-3, triclosan, and all parabens were 2- to 3-fold higher among women who reported recent use of hand or body lotion compared to women who did not. Similar associations (2–3 fold difference) between benzophenone-3 and all paraben biomarker concentrations and self-reported cosmetic use were also observed. Use of sunscreen was associated with 5-fold higher geometric mean concentrations of benzophenone-3. Triclosan and triclocarban geometric mean concentrations were 2- and 4-fold higher among women reporting the use of liquid soap and bar soap, respectively, compared to those who did not. Use of perfume and nail polish were associated with significant increase in butylparaben. There were no associations between any of the questionnaire variables and 2,5-dichlorophenol, BPA, BPF or BPS concentrations. We also found an unexpected decrease in butylparaben concentration associated with the use of fabric softener, detergent and paint, and 2,4-dichlorophenol concentration was lower among women who reported recent use of pet grooming product compared to women who did not.

3.7. Soap brands and triclocarban, triclosan

Self-reported use of several brands of bar soap and liquid soap in the 48 h preceding urine sample collection and corresponding urinary triclocarban and triclosan concentrations are presented in Fig. 2 and SI Fig. S2, respectively. There is a decreasing trend of triclocarban concentration with decreasing active ingredient concentration (triclocarban) in the bar soaps. Geometric mean concentrations of triclocarban among women who reported recent use of triclocarban-containing brand 1 containing 1.2% triclocarban (from Fig. 2 x-axes label) and brand 2 containing 0.6% triclocarban were 61.2 ng/mL and 34.3 ng/mL, and the concentrations were 64 and 36 times higher compared to women who did not report the use of bar soap, respectively. Users of products containing triclosan also showed higher levels of urinary triclosan levels than non-users (SI Fig. S2). Geometric mean concentrations of triclosan among women who reported recent use of triclosan-containing brand 1 (triclosan 0.3%, urinary triclosan GM = 66.7 ng/mL) and brand 2 (triclosan 0.15%, urinary triclosan GM = 29.0 ng/mL) were 3.5 and 2 times higher compared to women who did not report the use of liquid soap, respectively.

4. Discussion

4.1. GM and percentiles

The main purpose of our study was to examine the distribution, variability, time trends, and predictors of urinary concentrations of triclocarban, and select phenols and parabens in repeated urine samples collected from pregnant women in Puerto Rico. We found that Puerto Rican pregnant women are widely exposed to these chemicals. Concentrations of a majority of biomarkers among this population were higher compared to women of similar age in the U.S. general population, especially triclocarban, which had a median concentration 37 times higher in PROTECT participants. Concentrations of benzophenone-3 and BPS were similar in the two populations. The biomarkers that were significantly lower in the PROTECT population when compared to the concentrations found in women of reproductive age from the 2009–2014 NHANES study were the remaining parabens (ethylparaben, methylparaben, propylparaben) and BPF, though caution must be taken for the BPF comparison since there was low detection frequency for BPF in the PROTECT study (41%).

As shown in Table 5, other pregnancy cohort studies from around the globe have also reported concentrations of these urinary biomarkers. We have also reported SG-corrected concentration of urinary biomarker in our Study in Table 5 to make better comparison with other

Table 3
Demographic characteristics of $n = 1003$ pregnant women from Puerto Rico (2010–2016) and geometric means of specific gravity corrected urinary concentrations of triclocarban and selected[a] phenols and parabens according to demographic, and maternal factors.

Variable	Count (percent)	N[b]	2,5-Dichlorophenol	Benzophenone-3	BPA	BPF	Triclosan	Triclocarban	Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben
Overall	1003	2166	13.5	41.6	2.1	0.3	22.7	3.8	78.2	2.8	15.4	0.5
Maternal age (years)												
< 25	395 (39.6%)	828	14.8	**25.6**	**2.3**	0.3	**19.0**	**7.2**	**64.7**	**2.2**	**11.1**	**0.4**
25–30	362 (36.3%)	810	12.5	**44.4**	**2.1**	0.3	**23.1**	**2.5**	**82.9**	**3.2**	**17.9**	**0.5**
> 30	241 (24.1%)	519	13.1	**81.5**	**2.0**	0.3	**29.6**	**2.6**	**97.1**	**3.4**	**21.0**	**0.7**
Missing[c]	5	9	9.0	36.2	2.6	0.3	10.0	10.4	50.7	0.7	5.8	0.3
p Value[d]			0.32	< **0.01****	**0.02****	0.05	**0.01***	< **0.01****	< **0.01****	< **0.01****	< **0.01****	< **0.01****
Maternal education (years)												
< 12	80 (8.3%)	165	15.9	**21.8**	2.1	0.3	**16.0**	**7.5**	**59.6**	**1.4**	**8.6**	**0.4**
12	129 (13.4%)	270	13.0	**21.9**	2.2	0.2	**16.2**	**9.2**	**53.5**	**2.3**	**9.5**	**0.3**
> 12	757(78.4%)	1676	13.4	**49.5**	2.1	0.3	**25.1**	**3.0**	**85.3**	**3.1**	**17.7**	**0.5**
Missing[c]	37	55	10.5	33.5	2.3	0.2	15.0	3.5	79.4	1.9	13.9	0.5
p-Value[d]			0.33	< **0.01****	0.73	0.05	< **0.01****	< **0.01****	< **0.01****	< **0.01****	< **0.01****	**0.01***
Marital status												
Single	201(20.7%)	420	**17.1**	35.3	2.2	0.3	26.2	**5.2**	**95.5**	3.3	18.4	0.5
Married or living together	768 (79.3%)	1698	**12.8**	43.5	2.1	0.3	22.1	**3.5**	**74.2**	2.7	14.8	0.5
Missing[c]	34	48	10.2	35.2	2.4	0.2	15.7	3.7	84.5	2.4	13.7	0.7
p-Value[d]			**0.04***	0.06	0.38	0.34	0.35	**0.05***	**0.04***	0.54	0.13	0.94
Income status (us $)												
< $20,000	291 (29%)	597	**15.52**	**31.02**	2.22	**0.28**	**20.82**	**5.90**	84.37	**2.73**	14.99	**0.43**
≥ $20,000 to < $40,000	189 (18.8%)	403	**15.57**	**52.00**	2.27	**0.31**	**32.47**	**2.99**	93.68	**3.45**	21.33	**0.55**
≥ $40,000	155 (15.5%)	339	**11.4**	**81.9**	2.16	**0.4**	**41.0**	**1.8**	97.6	**4.0**	18.7	**0.62**
Missing[c]	368	827	10.5	33.5	2.3	0.2	15.0	3.5	79.4	1.9	13.9	0.5
p-Value[d]			**0.01***	< **0.01****	0.61	< **0.01****	< **0.01****	< **0.01****	0.19	**0.02***	0.06	**0.04***
Parity												
0	377 (42.8%)	839	13.4	43.0	2.2	0.3	25.8	3.3	82.5	3.0	16.7	**0.5**
1	380 (43.2%)	812	15.8	40.8	2.1	0.3	22.2	3.7	83.3	3.1	17.8	**0.5**
> 1	123 (14%)	261	12.5	38.0	2.2	0.3	20.9	5.0	68.4	1.9	10.9	**0.4**
Missing[c]	123	254	8.8	43.4	1.8	0.3	17.4	4.4	61.2	2.4	10.8	0.5
p-Value[d]			0.52	0.51	0.91	0.13	0.26	0.13	0.26	0.15	0.07	**0.01***
Prepregnancy BMI (kg m − 2)												
≤ 25	351 (53%)	746	15.1	41.2	2.2	0.3	27.8	**3.1**	97.1	3.6	20.5	0.5
> 25 to ≤ 30	200 (30.2%)	403	16.1	44.3	2.2	0.3	24.4	**4.3**	93.6	3.8	19.3	0.6
> 30	111 (16.8%)	221	18.4	40.2	2.5	0.3	26.9	**5.1**	80.2	2.3	14.7	0.4
Missing[c]	341	796	10.2	41.0	1.9	0.3	17.3	3.8	57.9	2.3	10.7	0.4
p-Value[d]			0.07·	0.90	0.18	0.79	0.65	**0.02***	0.26	0.07	0.15	0.62
Employment status												
Unemployed	378 (37.7%)	817	13.7	**29.6**	2.2	0.3	**18.6**	**7.0**	**66.9**	2.5	**12.1**	**0.4**
Employed	585 (58.3%)	1289	13.5	**52.2**	2.1	0.3	**26.2**	**2.5**	**86.9**	3.1	**18.4**	**0.6**
Missing[c]	40	60	10.0	32.0	2.2	0.2	16.8	7.1	66.0	1.9	9.9	0.5
p-Value[d]			0.98	< **0.01****	0.70	0.10	**0.01***	< **0.01****	< **0.01****	0.12	< **0.01****	**0.01***

[a] Results shown for associations with *p*-value < 0.05.
[b] = 2166 total number of total responses.
[c] Missing values were treated as missing at random for the statistical analysis.
[d] *p*-Values from linear mixed effects models accounting for within-person correlations.
* *p* from 0.05 to 0.01.
** $p < 0.01$.

Table 4
Frequencies of product use reported in the 48-h recall questionnaire and selected[a] SG-corrected geometric mean concentrations of chemical biomarkers (ng/mL) associated with self-reported use or nonuse.

	Use	n = 1003[b]	N = 2166[c]	2,4-Dichlorophenol	Benzophenone-3	Triclosan	Triclocarban	Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben
Cleaning products											
Laundry	Yes	539	1186	1.2	39.0	21.9	4.2	78.1	3.0	15.3	**0.4**
detergent	No	361	790	1.1	45.5	24.8	3.5	79.0	2.5	15.8	**0.6**
p-Value[d]				0.36	0.52	0.76	0.18	0.87	0.70	0.62	**0.02***
General cleaner	Yes	505	1174	1.2	41.0	21.1	4.0	82.1	3.0	17.0	0.5
	No	392	800	1.1	42.0	26.2	3.7	73.5	2.5	13.6	0.5
p-Value[d]				0.88	0.99	0.26	0.65	0.83	0.19	0.28	0.51
Fabric softener	Yes	453	985	1.2	37.8	22.1	4.0	77.7	2.9	15.8	**0.4**
	No	447	992	1.1	45.5	23.9	3.8	79.3	2.7	15.3	**0.5**
p-Value[d]				0.14	0.19	0.79	0.35	0.98	0.75	0.89	**0.01***
creams and lotions											
Hand/body	Yes	687	1569	1.2	**47.0**	**24.3**	3.5	**91.8**	**3.0**	**18.6**	**0.5**
lotion	No	212	404	1.1	**25.3**	**18.8**	5.5	**43.0**	**2.0**	**7.7**	**0.3**
p-Value[d]				0.40	< **0.01****	**0.02***	0.27	< **0.01****	< **0.01****	< **0.01****	**0.01***
Shaving cream	Yes	73	152	1.1	64.0	26.5	3.9	74.8	4.6	16.2	0.5
	No	827	1824	1.2	40.1	22.8	3.9	78.8	2.7	15.4	0.5
p-Value[d]				0.95	0.34	0.74	0.78	0.44	0.13	0.72	0.56
Sunscreen	Yes	30	64	1.3	**187.2**	19.4	1.8	130.0	4.7	24.9	0.7
	No	869	1910	1.1	**39.5**	23.2	4.0	77.4	2.8	15.3	0.5
p-Value[d]				0.65	< **0.01****	0.72	0.70	0.42	0.29	0.73	0.72
Toiletries and cosmetics											
Perfume/	Yes	743	1651	1.2	43.2	22.0	3.9	81.3	2.9	16.3	**0.5**
cologne	No	156	324	1.1	33.9	29.0	3.8	66.0	2.1	12.2	**0.3**
p-Value[d]				0.55	0.06	0.16	0.65	0.32	0.33	0.21	**0.01****
Cosmetic	Yes	680	1468	1.2	**51.2**	23.8	3.4	**100.9**	**3.6**	**22.4**	**0.7**
	No	220	508	1.0	**22.5**	20.7	5.7	**38.2**	**1.3**	**5.4**	**0.2**
p-Value[d]				0.49	< **0.01****	0.59	0.87	< **0.01****	< **0.01****	< **0.01****	< **0.01****
Liquid soap	Yes	779	1766	1.1	42.0	**23.5**	3.8	78.6	2.8	15.6	0.5
	No	120	210	1.2	37.6	**19.4**	4.3	77.4	2.8	14.7	0.5
p-Value[d]				0.38	0.85	**0.04***	0.54	0.36	0.69	0.37	0.75
bar soap	Yes	825	1808	1.2	39.7	22.4	**4.4**	76.8	2.8	15.3	0.5
	No	74	167	1.1	67.7	31.0	**1.0**	97.4	2.9	18.1	0.6
p-Value[d]				0.83	0.09·	0.14	< **0.01****	0.25	0.88	0.76	0.08·
Mouth wash	Yes	410	977	1.2	46.4	23.1	3.5	82.4	2.8	15.9	0.5
	No	490	1000	1.1	37.2	22.9	4.3	74.9	2.8	15.2	0.5
p-Value[d]				0.63	0.21	0.54	0.43	0.74	0.92	0.65	0.86
Hair and nail products											
Hairspray	Yes	279	609	1.2	40.4	25.0	4.5	83.8	2.9	15.3	0.5
	No	617	1363	1.1	42.0	22.1	3.7	76.5	2.7	15.6	0.5
p-Value[d]				0.26	0.29	0.14	0.05·	0.53	0.63	0.72	0.86
Shampoo	Yes	640	1398	1.2	41.3	23.5	3.6	82.4	3.0	16.4	0.5
	No	260	578	1.1	42.1	21.9	4.7	70.1	2.4	13.5	0.5
p-Value[d]				0.22	0.54	0.45	0.79	0.74	0.23	0.53	0.37
conditioner	Yes	625	1369	1.2	41.0	23.9	3.6	81.6	2.9	16.1	0.5
	No	274	606	1.1	42.7	21.1	4.6	72.2	2.5	14.3	0.5
p-Value[d]				0.47	0.52	0.25	0.55	0.90	0.62	0.88	0.26
Other hair	Yes	130	136	1.3	49.3	24.3	3.2	**110.0**	**5.1**	**26.1**	0.7
product	No	586	605	1.2	41.6	22.5	3.9	**74.7**	**3.0**	**15.0**	0.5
p-Value[d]				0.24	0.25	0.75	0.64	**0.02***	**0.02***	**0.01***	0.07
Nail polish	Yes	245	521	1.1	42.6	18.4	4.3	89.7	**3.9**	18.3	**0.6**
	No	655	1454	1.2	41.2	24.9	3.8	75.0	**2.5**	14.6	**0.5**
p-Value[d]				0.07	0.52	0.12	0.46	0.29	< **0.01****	0.21	**0.01***
Vinyl products											
Vinyl curtain	Yes	569	1260	1.2	42.0	22.1	4.1	81.6	2.8	15.7	0.5
	No	331	717	1.1	40.7	24.8	3.5	73.4	2.7	15.2	0.5
p-Value[d]				0.47	0.93	0.11	0.76	0.61	0.71	0.86	0.35
Vinyl gloves	Yes	88	172	1.2	54.5	31.8	3.2	82.7	3.0	16.9	0.5
	No	812	1805	1.1	40.4	22.3	4.0	78.1	2.8	15.4	0.5
p-Value[d]				0.34	0.34	0.46	0.60	0.70	0.38	0.29	0.86
Furniture and care, pet											
Paint	Yes	23	68	1.4	30.3	40.9	4.1	90.5	1.9	14.3	**0.4**
	No	877	1909	1.1	42.0	22.6	3.9	78.1	2.8	15.6	**0.5**
p-Value[d]				0.71	0.51	0.06	0.59	0.97	0.08	0.48	**0.03***
Pesticide use	Yes	51	131	1.3	40.9	29.5	3.0	93.9	3.7	21.6	0.5
	No	849	1846	1.1	41.5	22.6	3.9	77.5	2.7	15.1	0.5
p-Value[d]				0.24	0.67	0.48	0.85	0.37	0.79	0.17	0.38

(*continued on next page*)

Table 4 (*continued*)

	Use	$n = 1003$[b]	$N = 2166$[c]	2,4-Dichlorophenol	Benzophenone-3	Triclosan	Triclocarban	Methyl paraben	Ethyl paraben	Propyl paraben	Butyl paraben
Pet grooming product	Yes	38	74	**1.0**	48.2	21.0	3.6	65.5	3.0	17.2	0.7
	No	862	1903	**1.2**	41.3	23.1	3.9	79.0	2.8	15.4	0.5
p-Value[d]				**0.04**[*]	0.51	0.33	0.92	0.06[·]	0.68	0.90	0.43

[a] Results shown for associations with p-value ≤ 0.1.
[b] $n = 1003$ total number of participant.
[c] $N = 2166$ total number of total responses.
[d] p-Values from linear mixed effects models accounting for within-person correlations; [·] p from 0.1 to 0.05.
[*] p from 0.05 to 0.01.
[**] $p < 0.01$.

studies where most of them reported corrected concentration of the biomarkers. Similar BPA concentrations have been reported among pregnant women in New York (Perera et al., 2012; Wolff et al., 2008), Ohio (Braun et al., 2011a), Mexico City (Cantonwine et al., 2010), Denmark (Tefre de Renzy-Martin et al., 2014), Germany (Kasper-Sonnenberg et al., 2012), Spain (Casas et al., 2011), France (Philippat et al., 2012; Vernet et al., 2017) and the Netherlands (Ye et al., 2008). Studies of BPF and BPS have been much more limited in number compared with BPA. The first study to report the occurrence of BPF and BPS in pregnant women urine was from the Netherlands, to which the median concentrations of BPF and BPS in our study were comparable (Philips et al., 2018).

Geometric mean concentration of 2,4-Dichlorophenol (1.1 ng/mL) and 2,5-dichlorophenol (13.5 ng/mL) in our study were similar to recent findings in France (1.0 and 9.8 ng/mL, respectively) (Vernet et al., 2017), while the median concentrations of 2,5-dichlorophenol were higher in the Spain and New York (53 ng/mL) studies compared to this study. Median concentrations of triclosan and benzophenone-3 appeared to be higher in this Puerto Rico cohort compared to pregnant women in New York, Spain, and Denmark. Triclocarban concentration was much higher among pregnant women in our study (GM = 3.8 ng/mL) compared to pregnant women in two studies in Denmark (Frederiksen et al., 2014; Tefre de Renzy-Martin et al., 2014), New York (Pycke et al., 2014) and Boston (Ferguson et al., 2018) where the geometric or median concentrations in urine were 0.01, 0.02, 0.17 ng/mL and < LOD, respectively.

Urinary methylparaben concentrations in the present study were similar to pregnant women in France (Vernet et al., 2017) and Greece (Myridakis et al., 2015), but lower than those in Spain (Casas et al., 2011) and Korea (Kang et al., 2013), and higher than in Denmark (Tefre de Renzy-Martin et al., 2014), and Japan (Shirai et al., 2013). Urinary ethylparaben and proplyparaben concentrations in pregnant women in Puerto Rico, were comparable to those in Denmark, France, and Japan, whereas higher concentrations were reported among Korean and Spanish women. In contrast, urinary butylparaben concentrations were lower among women in Puerto Rico compared to those of other studies (Table 5).

Together, these studies demonstrate that exposure to triclocarban, phenols, and parabens vary by location, sex, age, race, and ethnicity. This variability is likely due to differences in the use of chemicals in consumer products in different regions, as well as differences in personal care product use and behaviors among populations and individuals. It is unclear why women in our cohort have such high levels of triclocarban, but frequent use of antimicrobial soap and the availability of brands with high triclocarban content in Puerto Rico probably play a role.

4.2. Between visit difference and ICCs

We found that the geometric mean concentration at first visit for 2,5-dichlorophenol, BPA, and butylparaben was statistically higher than later visits in our study. It is possible that these observations may be due to the physiological changes during pregnancy (Gilbert, 1990). However, if that were the primary explanation then we would expect to see similar trends for all exposure biomarkers measured in the study. This difference may also be attributable to changes in personal care

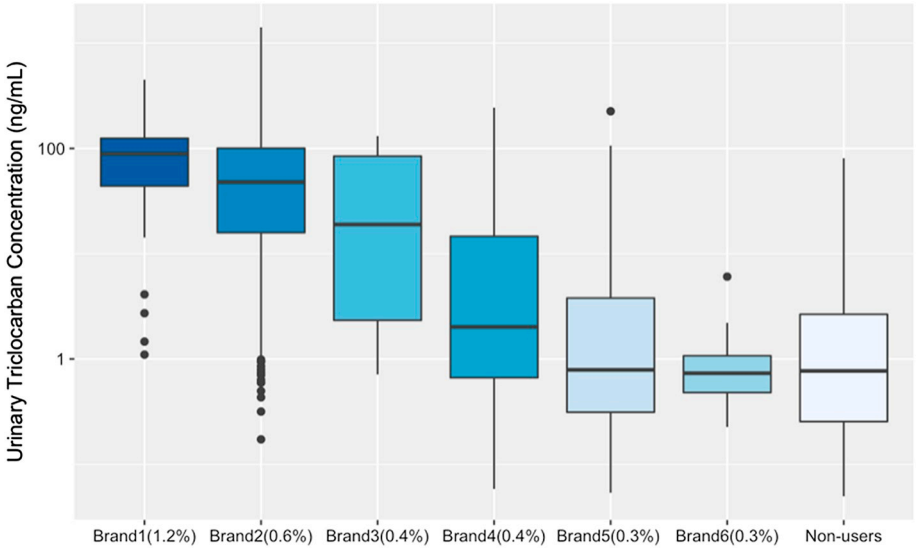

Fig. 2. Distribution of Urinary Triclocarban Concentrations among Different Brands of Bar Soap User and Non-Users Self-reported in the 48-h Recall[a,b].
[a]The percentage number listed in the parenthesis is the active ingredient (triclocarban) content in the corresponding brand product
[b]Number (n) of participants using the particular brands are 60 (brand 1), 12 (brand 2), 401 (brand 3), 163 (brand 4), 185 (brand 5), 15 (brand 6), and 167 (non-users).

Table 5
Urinary triclocarban, phenol and paraben concentrations reported in the present study and previous studies among pregnant women.

Reference	Country/region	n[a]	2,4_Diclorophenol	2,5_Diclorophenol	Benzophenone-3	BPA	BPF	BPS
Present study	**Puerto Rico**	**2166**	**1.1**	**13.5**	**41.6**	**2.1**	**0.3**	**0.5**
Braun et al. (2011a)	Ohio, US	389				1.9		
Wolff et al. (2008)	New York, US	367	2.1	**53.0**	7.5	1.3		
Perera et al. (2012)	New York, US	198				2.0		
Ferguson et al. (2018)	Boston, US	476	0.72	3.22	46.5			< LOD
Cantonwine et al. (2010)	Mexico City	60				1.5		
Kasper-Sonnenberg et al. (2012)	Germany	232				1.8		
Casas et al. (2011)	Spain	120	1.1	16.5	3.4	2.2		
Philippat et al. (2012)	France	191	0.8	6.4	1.3	3.1		
Vernet et al. (2017)	France	587	1.0	9.8	2.1	2.6		
Tefre de Renzy-Martin et al. (2014)	Denmark	200	0.2	0.1	3.0	1.2		
Frederiksen et al. (2014)	Denmark	565	0.2	0.1	4.3	1.2		
Myridakis et al. (2015)	Greece	239				5.6		
Ye et al. (2008)	Netherlands	100				1.7		
Philips et al. (2018)	Netherlands	1396				1.7	0.6	0.4
Pycke et al. (2014)	New York	181						
Kang et al. (2013)	Korea	46						
Shirai et al. (2013)	Japan	111						

Reference	Triclosan	Triclocarban	Methylparaben	Ethylparaben	Propylparaben	Butylparaben	Correction[b]	GM[c]/median	Units
Present study	**22.7**	**3.8**	**78.2**	**2.8**	**15.4**	**0.5**	**SG**	**GM**	**ng/mL**
Braun et al. (2011a)							Cr	GM	ug/g
Wolff et al. (2008)	11.0						–	Median	ng/mL
Perera et al. (2012)							SG	GM	ng/mL
Ferguson et al. (2018)	13.5	< LOD	186	2.6	43.3	1.3	SG	Median	ng/mL
Cantonwine et al. (2010)							SG	GM	ng/mL
Kasper-Sonnenberg et al. (2012)							Cr	GM	ug/g
Casas et al. (2011)	6.1		191.0	8.8	29.8	2.4	–	Median	ng/mL
Philippat et al. (2012)	17.5		104.3	1.5	10.4	2.2	–	Median	ng/mL
Vernet et al. (2017)	29.3		118.0	4.5	16.1	1.9	–	Median	ng/mL
Tefre de Renzy-Martin et al. (2014)	0.6	0.0	20.5	0.9			Cr	Median	ug/g
Frederiksen et al. (2014)	1.2	0.0	11.0	1.0	2.2	0.2	–	GM	ng/mL
Myridakis et al. (2015)			121.9	2.9			Cr	Median	ug/g
Ye et al. (2008)							Cr	GM	ug/g
Philips et al. (2018)							–	Median	ng/mL
Pycke et al. (2014)	7.2	0.2					Cr	Median	ug/g
Kang et al. (2013)			169.9	44.6	8.6	< LOD	SG	Median	ng/mL
Shirai et al. (2013)			83.6	9.2	7.3	0.8	SG	GM	ng/mL

[a] Sample Size.
[b] No correction applied, **SG** corrected for specific gravity **Cr** corrected for creatinine.
[c] GM geometric mean.

product use. We conducted a trend test to determine whether self-reported product use changed over the three visits and did not observe a statistically significant declining trend in the use of any personal care product reported. Interestingly, there was an increasing trend in use of lotion and liquid soap during pregnancy among women in our cohort.

The knowledge about the degree to which biomarker concentrations from a single urine sample reflects an individual's long-term exposure to these chemicals (or their precursors) is essential for conducting and interpreting epidemiologic studies of associations. The reproducibility of a single sample is determined by the within-person variability of concentration over time. Increased measurement error of a single measurement can result from large within-person variability which can consequently lead to the attenuation of observed associations. When designing a new study (e.g., calculating effective sample size needed to be able to capture a certain difference and/or determining the measurement method), one should take into account within-person variability of concentrations of the biomarker of interest to avoid issues discussed above.

The half-lives of the biomarkers we measured are relatively short (e.g., cleared from the body within 24–48 h). However, the ICCs for SG corrected biomarker concentrations in our study, based on three urine samples collected over several months, range from weak to good reproducibility, with the lowest ICC found for BPS (0.02) and the highest for triclocarban (0.69). Among studies that have reported individual variability in repeated measurements of urinary phenols concentrations, BPA has been investigated the most in different populations. Considering pregnant women may have different patterns of exposure and metabolism from those of non-pregnant adults or children, we only compared our findings to ICCs reported in studies of pregnant women.

The observed ICC for BPA measurements in our study (0.09) is in agreement with studies among pregnant women whose spot urine samples were collected on three pregnancy visits in New York (n = 71), Ohio (n = 389) and Norway (n = 45), which reported similarly low ICCs of 0.04–0.11 (Braun et al., 2011a; Guidry et al., 2015; Philippat et al., 2013). In these studies, lower ICCs were reported for creatinine corrected values, where higher ICCs were observed with shorter durations between repeated samples. Findings from these studies suggest that multiple measurements are needed to reflect long-term exposure to BPA rather than a single measurement. Only one study assessed between-week ICC for BPS measurements among 24 pregnant women from three visits in France (ICC = 0.33) which was higher than the estimate from our study (ICC = 0.02) (Vernet et al., 2018). However, caution is required when comparing these two studies given the small sample size and large confidence intervals (0.00, 0.80) in the France study. To our knowledge, this is the first study to quantify the reliability of BPF and triclocarban in urine samples from pregnant women.

Our estimates of temporal variability in 2,4-dichlorophenol (ICC = 0.25) and 2,5-dichlorophenol (ICC = 0.29) among pregnant women is lower than reported in the New York study where they found high reproducibility for 2,4-dichlorophenol (ICC = 0.6) and 2,5-dichlorophenol (ICC = 0.61) (Philippat et al., 2013). We reported moderate reproducibility for benzophenone-3 (ICC = 0.54), similar to studies among pregnant women in New York and Norway (Guidry et al., 2015; Philippat et al., 2013),

The ICC of 0.59 for triclosan indicated moderate reproducibility among urine samples collected across pregnancy. This result was comparable to that of recent studies among pregnant women in Canada, which collected spot urine samples from 80 participants at five prenatal and post-partum visits (Weiss et al., 2015), Norway (Bertelsen et al., 2014), and New York (Philippat et al., 2013), who reported corrected ICCs for triclosan of 0.50, 0.49, and 0.58 respectively. For parabens, low to moderate reproducibility over time was found in our study. Our results were comparable to previous estimates for ethylparaben, but lower than prior reports methylparaben and propylparaben, and higher than prior reports for butylparaben when compared to studies conducted on pregnant women in Boston, New York and Norway (Guidry et al., 2015; Philippat et al., 2013; Smith et al., 2012).

4.3. Temporal trend in biomarker concentrations

We explored temporal patterns of biomarkers of exposure to triclocarban, phenols, and parabens in the study population from 2011 to 2016. Concerning the adverse health effects associated with these chemicals, monitoring long-term trends could be a valuable approach for identifying factors associated with human exposure, identifying susceptible populations, and directing future research and/or legislative actions. A decreasing temporal trend was statistically significant for urine concentrations of BPA during the study period, while the BPA substitute BPS showed an increasing temporal trend. A similar declining trend for BPA has also been seen in the U.S. NHANES between 2003 and 2012 (LaKind and Naiman, 2015) and among mothers in Sweden between 2009 and 2014 (Gyllenhammar et al., 2017). No statistically significant trends were seen for BPF, however, 59% of the samples had concentrations below LOD and the estimation of the temporal trend is therefore highly uncertain. Industries have begun to remove BPA from commercial products as a result of consumer concern, and since then chemicals such as BPS and BPF have been used as substitutes (Rochester and Bolden, 2015). Our results showed that efforts to phase out production of BPA and the use of substitute chemicals may have resulted in a decreased exposure to BPA among our study population but increased the exposure to BPS at the same time. Studies have indicated that BPS and BPF have hormonal activity (Molina-Molina et al., 2013; Owens and Ashby, 2002; Stroheker et al., 2003; Vinas and Watson, 2013) and endocrine-disrupting effects (Ji et al., 2013; Naderi et al., 2014) similar to BPA, therefore, they could potentially pose similar health hazards as BPA.

Decreasing temporal trends were observed for both dichlorophenols, all parabens, and triclosan. A similar trend for triclosan was observed in the general U.S. population from 2003 to 2012 (Han et al., 2016) and in pregnant women from 2005 to 2010 (Mortensen et al., 2014). The declining trend is probably because of decreasing use of products containing triclosan due to increasing public awareness concerning the possible health impacts prior to recent FDA action on use of triclosan.

4.4. Product use

Our findings on the associations between urinary biomarker concentration and demographics variables were similar to and discussed in our precious study (Meeker et al., 2013). The positive associations between urinary biomarker concentrations and self-reported product use were overall consistent with the findings from previous studies. Use of sunscreen, hand/body lotion and cosmetics were associated with higher benzophenone-3 concentrations. Benzophenone-3 is a UV filter found mainly in sunscreens and cosmetics offering sun protection (Dodson et al., 2012; Gonzalez et al., 2006), which is consistent with our finding that self-reported sunscreen use was associated with the greatest increase for benzophenone-3 biomarker concentration in our study (difference = 148 ng/mL). Many cosmetics and lotions may contain benzophenone-3 as they often claim to have sun protecting properties. Parabens are commonly used preservatives and antibacterial agents in cosmetics and other personal care products (Guo and Kannan, 2013; Shen et al., 2007; Soni et al., 2005). Higher paraben concentrations were found among women who reported using cosmetics and lotion which is in line with other recent studies (Braun et al., 2014; Fisher et al., 2017; Nassan et al., 2017; Philippat et al., 2015). Consistent with our findings, parabens were detected in a study that measured parabens in cosmetics and other personal care products (Dodson et al., 2012; Guo and Kannan, 2013). We also found higher urinary concentrations of butylparaben in relation to self-reported perfume and nail polish use.

Braun et al. reported similar findings among pregnant women from a fertility clinic. However, studies that quantified chemicals in various personal care products reported that parabens are seldom found in perfume and nail polish (Dodson et al., 2012; Guo and Kannan, 2013). It is possible that these associations were due to confounding in that people who use perfume and nail polish may be more likely to use other products that do contain parabens.

4.5. Triclosan and triclocarban

Higher triclosan and triclocarban concentrations were found among women who reported using liquid soap and bar soap use in the 48 h preceding urine sample collection, respectively. This was hypothesized because triclosan and triclocarban have been used as active ingredients in many antibacterial liquid hand/dish soap and bar hand soap, respectively, and have been also detected in conventional soap at slightly lower concentrations (Dodson et al., 2012; Perencevich et al., 2001). Women reporting the use of lotion also had higher concentrations of triclosan than among women who did not, and lotion is one of the primary exposure sources of triclosan along with soaps, toothpaste, and mouthwashes (Bhargava and Leonard, 1996; Moss et al., 2000). One previous study in Sweden also showed that the triclosan concentrations in both plasma and milk were significantly higher in pregnant women who used triclosan-containing personal care products (Allmyr et al., 2006).

Dermal exposure from personal care products is believed to be the main route of human exposure to triclosan and triclocarban (Bhargava and Leonard, 1996; Moss et al., 2000; Ye et al., 2011), which suggests that the presence of triclosan and triclocarban in soap can lead to exposure in humans. According to U.S. Food and Drug Administration (FDA), there is no evidence that the use of triclosan and triclocarban in antibacterial soaps improves consumer or patient health or prevents disease (Food and Drug Administration, 2016). The FDA issued a final rule in September 2016 which regulates the use of both chemicals in consumer antiseptic wash products due to insufficient data regarding their safety and effectiveness, and the potential for bacterial resistance or hormonal effects (Food and Drug Administration, 2016). The FDA first proposed the rule back in 2013, and since then manufacturers have started phasing out the use of triclosan and triclocarban in antibacterial washes. Based on our observation of significant relationships between soap use and biomarker concentrations of these chemicals, this suggests that the policies to remove these chemicals from soap could effectively reduce human exposure moving forward.

Considering the timeline of our study (2010–2016), it is possible that at least some of the soap products used by women in Puerto Rico contained triclosan and triclocarban to some degree. Urinary concentrations of triclosan and triclocarban among pregnant women in our study were much higher than women enrolled in NHANES. Triclocarban median concentrations among PROTECT participants in 2011 and 2016 were 130- and 51-fold greater compared to NHANES cycles 2011–2012 and 2013–2014, respectively. We also found that there was an increasing trend of urinary triclocarban concentrations with increased concentrations of triclocarban listed as the active ingredient in the brands of bar soap products that were reported being used by study participants. In addition, participants who reported using products containing triclosan had higher levels of urinary triclosan levels than non-users. These findings further reinforce that the use of products containing triclosan and triclocarban likely contributed to human exposure, and suggest that increased public awareness regarding the use of products containing chemicals like triclosan and triclocarban may be effective in reducing the magnitude of these exposures.

4.6. Strengths and limitations

Utilizing a longitudinal repeated measures design, we described a detailed human study investigating exposures to environmental triclocarban, phenols and parabens, and trends and predictors of these exposures among pregnant women. A major advantage of this analysis is that the large sample size provided robust statistical power to assess the association between urinary biomarker concentrations and produce use in our cohort. Collection of multiple biomarker measurements in pregnant women also allowed women to in part serve as their own comparison for time-varying predictors of exposure biomarker concentrations. This study also had several limitations. We did not collect detailed information regarding the frequency of personal product use, amount of product used, and triclocarban, phenols, and parabens content from the specific products themselves. However, we analyzed the influence of variable levels of triclosan and triclocarban in products using publicly available brand information on the urinary biomarker concentrations. The lack of information on frequency and amount of product use may have attenuated our results toward the null due to non-differential measurement error. Lastly, our findings may not be generalizable to other populations, especially men or children since their personal care product use may be quite different compared to pregnant women.

5. Conclusion

Concentrations of triclocarban, phenols, and parabens among pregnant women living in Puerto Rico tended to be higher than or similar to those in women of reproductive age from the general U.S. population. This study also suggests that the pregnant women's exposures to select chemicals or their precursors are decreasing with time, while the substitute chemical BPS showed an increasing trend. Our results suggest potential exposure sources in this population and may help inform targeted approaches to reduce exposure to these chemicals. We found that there was an increasing trend of urinary triclocarban/triclosan concentrations with increased concentrations of triclocarban/triclosan listed as the active ingredient in the bar soap/liquid soap products that were reported being used by study participants. Our findings support that the use of products containing triclosan and triclocarban during pregnancy can significantly elevate exposure to these chemicals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.08.020.

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