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Publication Date

2018-08-01

DOI

10.1016/j.envres.2018.05.005

Peer reviewed



Published in final edited form as:

*Environ Res.* 2018 August ; 165: 379–386. doi:10.1016/j.envres.2018.05.005.

## Associations of maternal exposure to triclosan, parabens, and other phenols with prenatal maternal and neonatal thyroid hormone levels

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### Abstract

Environmental phenols and parabens are commonly used in personal care products and other consumer products and human exposure to these chemicals is widespread. Although human and animal studies suggest an association between exposure to phenols and parabens and thyroid hormone levels, few studies have investigated the association of *in utero* exposure to these chemicals and thyroid hormones in pregnant women and their neonates. We measured four environmental phenols (triclosan, benzophenone-3, and 2,4- and 2,5-dichlorophenol), and three parabens (methyl-, propyl-, and butyl paraben) in urine collected from mothers at two time points during pregnancy as part of the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) study. We measured free thyroxine (T4), total T4, and thyroid-stimulating hormone (TSH) in serum of the pregnant women (N=454) and TSH in their neonates (N=365). We examined potential confounding by a large number of additional chemical exposures and used Bayesian Model Averaging (BMA) to select the most influential chemicals to include in regression models. We observed negative associations of prenatal urinary concentrations of propyl paraben and maternal TSH ( $\beta$  for two-fold increase =  $-3.26\%$ , 95% CI:  $-5.55, -0.90$ ) and negative associations of 2,4-dichlorophenol and maternal free T4 ( $\beta$  for two-fold increase =  $-0.05$ , 95% CI:  $-0.08, -0.02$ ), after controlling for other chemical exposures. We observed negative associations of triclosan with maternal total T4 after controlling for demographic variables, but this association became non-significant after controlling for other chemicals ( $\beta$  for two-fold increase =  $-0.05$ , 95% CI:  $-0.11, 0.00$ ). We found evidence that environmental phenols and parabens are associated with lower TSH and free T4 in pregnant women after controlling for related chemical exposures.

### Keywords

Triclosan; parabens; phenols; thyroid hormone; *in utero* exposure

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Declarations of interest: none

## Introduction

Environmental phenols and parabens, chemicals commonly used in personal care products and other consumer items, have shown endocrine disrupting properties and may impact thyroid hormone regulation and homeostasis (Boberg et al., 2010; Witorsch and Thomas, 2010). Thyroid hormone balance is essential during pregnancy for fetal neurodevelopment (Ghassabian et al., 2014; Haddow et al., 1999; Julvez et al., 2013). Low levels of thyroxine (T4), especially in early pregnancy, can lead to neurological disabilities and underdevelopment of the cortex (De Escobar et al., 2004). Thyroid hormones work in a feedback loop, with low blood levels of triiodothyronine (T3) and T4 leading to increased release of thyroid-stimulating hormone (TSH) (Dietrich et al., 2012).

Particular attention has been paid to the potential thyroid-hormone disrupting properties of triclosan, a chemical used as an antibacterial agent in certain toothpastes, personal care products, and antimicrobial fabrics (Dann and Hontela, 2011). Triclosan was also widely used in antibacterial hand soaps until it was banned by the FDA in 2016 (United States Food and Drug Administration, 2013). Triclosan is structurally similar to T3 and T4 and has been shown to decrease T4 in rodent studies (Crofton et al., 2007; Paul et al., 2012; Paul et al., 2010; Rodriguez and Sanchez, 2010; Zorrilla et al., 2009), although studies in humans have been less consistent (Aker et al., 2018; Aker et al., 2016; Allmyr et al., 2009; Braun et al., 2017; Cullinan et al., 2012; Geens et al., 2015; Koeppe et al., 2013; Ley et al., 2017; Wang et al., 2017)

Benzophenone-3, a chemical that absorbs ultraviolet rays A and B, is used in sunscreens and other products for skin protection, and in cosmetics such as lipsticks, hairsprays, shampoos and skin lotions to prolong the products' durability (Han et al., 2016). Among 106 pregnant Puerto Rican women, urinary benzophenone-3 concentrations were also associated with decreased free T3, but no associations were seen with free T4 and TSH (Aker et al., 2016). However, maternal urinary benzophenone-3 was not associated with maternal serum free or total T3 or T4 in 183 pregnant women in Denmark. (Krause et al., 2018)

Other environmental phenols include 2,4-dichlorophenol, a photo-degradation product of triclosan that is also an intermediate in the manufacturing of the herbicide 2,4-dichlorophenoxyacetic acid (Latch et al., 2005), and 2,5-dichlorophenol, a metabolite of p-dichlorobenzene which is used in moth balls and room and toilet deodorizers (Wei et al., 2014; Ye et al., 2014). A cross-sectional study of 1,889 Flemish adolescents found that 2,5-dichlorophenol was positively associated with TSH and negatively associated with free T4 (Croes et al., 2015). In a study of 618 adolescents in the National Health and Nutrition Examination Survey (NHANES), urinary concentrations of 2,5-dichlorophenol, but not 2,4-dichlorophenol, were associated with increased levels of TSH and thyroglobulin and unchanged levels of free T4 and free T3 (Wei and Zhu, 2016).

Parabens, including methyl paraben, propyl paraben, and butyl paraben, are commonly used as preservatives in cosmetics as well as in food, pharmaceuticals, and paper products (Cao et al., 2013; Guo and Kannan, 2013; Liao and Kannan, 2014). A study of 439 pregnant women

in Boston found negative associations of urinary propyl paraben concentrations and maternal free T4 during pregnancy, but found positive associations of methyl paraben and maternal total T4 (Aker et al., 2018). Butyl paraben was positively associated with levels of free T4 among 106 pregnant women in Puerto Rico, and no associations were seen with methyl or propyl paraben or with free T3 or TSH (Aker et al., 2016).

Exposure to environmental phenols and parabens is widespread (CDC, 2018). Although thyroid hormone homeostasis is vital to fetal brain development, few studies have examined the association of environmental phenol and paraben exposure during pregnancy on thyroid hormone levels of pregnant women and their children. We have previously reported an association between bisphenol A (BPA) and lower maternal total T4 and lower male neonatal TSH. (Chevrier J, 2013). In the present study, we examined the association of urinary concentrations of other phenols and parabens in pregnant women with thyroid hormones levels in the women during pregnancy and their neonates at birth.

## Methods

### Participants.

Participants were part of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS), a longitudinal birth cohort study of environmental exposures and health among pregnant women and children living in an agricultural region in Northern California. Pregnant women were recruited from prenatal clinics serving the region's largely Latino farmworker community between October 1999 and October 2000. Women were eligible to participate in this study if they spoke Spanish or English, were 18 years old, were < 20 weeks gestation, qualified for California's low-income health insurance program (MediCal), and planned to deliver at the county hospital. A total of 601 women were enrolled. Losses were due to miscarriages (N=20, 3.3%), stillbirths (N=3, 0.5%), neonatal death (N=2, 0.3%) and loss to follow-up during pregnancy (N=40, 6.9%), leaving 536 women followed through a live delivery. We additionally excluded women taking the medication Levothyroxine that could affect thyroid hormone levels (N=1, 0.2%), women with no urinary biomarker measurements during pregnancy (N=17, 3.2%), and twins (N=5, 1.0%), leaving 513 women and 508 infants. For the analysis of maternal thyroid hormones, we excluded women missing thyroid hormone measurements due to insufficient serum volume (n = 175, 34.1%), leaving a final sample of 338 mothers. For the analyses of neonatal TSH, we excluded neonates with missing TSH measures (n = 144, 28.1%), leaving a total of 364 infants. Written informed consent was obtained from all mothers and all research was approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley prior to the study's conduct. This study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Centers for Disease Control and Prevention (CDC) deferred to the University of California, Berkeley institutional review board (IRB) as the IRB of record.

### Interviews.

We interviewed mothers near the end of the first trimester (mean: 14.1 weeks gestation, range: 5.3 to 28.5) and second trimester (mean: 26.9 weeks gestation, range: 21.1 to 39.5) of

pregnancy using structured questionnaires in English or Spanish to collect demographic information including maternal age, education, country of birth, and family income.

### Measurement of thyroid hormones.

Maternal blood was collected by venipuncture at the time of the second interview and stored at  $-80^{\circ}\text{C}$  until shipment to Quest Diagnostics' Nichols Institute (San Juan Capistrano, CA) for analysis. Free T4 was measured in maternal serum using direct equilibrium dialysis followed by radioimmunoassay (Nelson and Tomei, 1988) which provides accurate measurements despite pregnancy-induced elevations in T4-bound proteins (Nelson et al., 1994). Total T4 and TSH were measured in maternal serum using solid-phase immunochemiluminometric assays (Bayer ADVIA Centaur system; Siemens Healthcare Diagnostics, Deerfield, IL). The limits of detection (LODs) were 0.1 ng/dL (free T4), 0.1  $\mu\text{g/dL}$  (total T4), and 0.01 mIU/L (TSH).

Neonatal TSH was measured by the California Department of Health Services Genetic Diseases Branch (Richmond, CA) as part of the state's routine Newborn Screening Program. Blood spots on filter paper were collected shortly after birth [median = 21 hr; interquartile range (IQR) = 17–26 hr] by heel stick and were analyzed using a solid-phase, time-resolved sandwich fluoroimmunoassay (AutoDELFIA; PerkinElmer, Wellesley, MA). The LOD was 2 mIU/L. Neonatal TSH and age (in hours) at the time of heel stick were abstracted from medical records. Neonatal TSH levels were abstracted from medical records for comparison with maternal prenatal exposures.

### Measurement of phenols and parabens.

Spot urine samples were collected from participants in sterile, polypropylene urine cups at each of the two pregnancy interviews. Samples were stored at  $-80^{\circ}\text{C}$  until shipment on dry ice to the CDC in Atlanta, GA. Environmental phenols (including BPA which was used as a covariate in this analysis) and parabens were quantified using an on-line solid phase extraction-high performance liquid chromatography-isotope dilution tandem mass spectrometry approach, as previously described (Ye et al., 2006; Ye et al., 2005). The LODs were 2.3 ng/mL (triclosan), 0.4 ng/mL (benzophenone-3), 0.2 ng/mL (2,4-dichlorophenol, 2,5-dichlorophenol, propyl paraben, butyl paraben), and 1.0 ng/mL (methyl paraben). For concentrations below the LOD, we used instrument-generated values when available; if no signal was detected, we substituted a random value  $<\text{LOD}$  based on a log-normal probability distribution whose parameters were determined by maximum likelihood estimation (Lubin et al. 2004). Several samples had biomarkers with concentrations above the highest calibration standard (methyl paraben: 39 measurements [23 at baseline, 16 at 26 weeks]; propyl paraben: 41 measurements [5 at baseline, 36 at 26 weeks]; triclosan: 18 measurements [14 at baseline, 4 at 26 weeks]; 2,4-dichlorophenol: 34 measurements [14 at baseline, 20 at 26 weeks]; 2,5-dichlorophenol: 111 measurements [55 at baseline, 56 at 26 weeks]; benzophenone-3: 66 measurements [34 at baseline, 32 at 26 weeks]); these concentrations were not reported as a numeric value when the urine was analyzed in 2010 (at the time, the main focus of the project was BPA). For the current data analysis, we replaced the non-numeric concentrations with the highest calibrator concentration used (100 ng/mL for 2,4-dichlorophenol, 1000 ng/mL for all other parabens and phenols). We determined urinary

specific gravity using a hand-held refractometer (National Instrument Company, Baltimore, MD) and measured creatinine concentrations in urine samples using a commercial diagnostic assay (Vitros CREA slides; Ortho Clinical Diagnostics, Raritan, NJ).

### Measurement of other environmental chemicals.

Concentrations of several other chemicals during pregnancy have already been quantified in this cohort, including phthalate metabolites (Harley et al., 2017) and the sum of dialkyl phosphate metabolites of organophosphate pesticides (Bradman et al., 2005) in urine; and the sum of polybrominated diphenyl ether (PBDE) flame retardants (Eskenazi et al., 2011), the sum of polychlorinated biphenyls (PCB) (Chevrier et al., 2007) and the organochlorine pesticide and hexachlorobenzene (HCB) (Bradman et al., 2007) in serum. We have previously reported associations of PBDEs, PCBs, HCB, and BPA with maternal or neonatal thyroid hormone in this population (Chevrier et al., 2013; Chevrier et al., 2010). Thus, these chemicals were tested as covariates in the current analyses, as described below.

### Statistical analysis.

We expressed pregnancy exposure to phenols and parabens as the average of the two pregnancy measurements of their corresponding urinary biomarkers. Biomarker concentrations were heavily right-skewed and were thus log<sub>2</sub>-transformed for statistical analysis. To account for urinary dilution, biomarker concentrations were corrected for specific-gravity using the formulas suggested by Cone et al (Cone et al., 2009). Although urinary creatinine concentrations are often used to correct for urinary dilution, creatinine concentrations are not reliable during pregnancy because of the rapid change in renal creatinine clearance during this time (Edwards and Whyte, 1959; Miller et al., 2004). Thus, we chose to use specific gravity which is not dependent on these changing factors (Boeniger et al., 1993; Suwazono et al., 2005). Missing specific gravity values were imputed for 78 participants by regressing specific gravity on creatinine and multiplying the coefficient by existing creatinine values to generate missing specific gravity values, and sensitivity analyses were run excluding the women with imputed specific gravity.

To compare CHAMACOS data with national data, we calculated geometric means and percentiles for environmental phenols and parabens for women of reproductive age (18–40) from the 2005–2006 NHANES (CDC, 2005–2006), the closest year to CHAMACOS urine collection when NHANES measured all parabens and phenols analyzed in this study, correcting for sampling weights.

We performed separate multiple linear regression models for each target biomarker with maternal and neonatal thyroid hormone levels as continuous outcome variables. Free and total T4 were normally distributed and expressed on the arithmetic scale but we log<sub>10</sub>-transformed both maternal and neonatal TSH to normalize residuals. Regression coefficients thus represent mean (for free and total T4) or percent (for TSH) change in outcomes for each doubling of urinary biomarker concentration.

We included covariates in final models based on directed acyclic graphs (Supplemental Figure S1). We conducted two sets of adjusted models; Model 1 adjusted only for demographic factors, while Model 2 adjusted for both demographic factors and other

chemical exposures. Model 1 for maternal and neonatal outcomes adjusted for: maternal age, maternal education, maternal country of birth, and household income (as a proportion of the federal poverty threshold).

Model 2 for maternal and neonatal outcomes additionally adjusted for other chemical exposures. Because many of the phenol and paraben concentrations were moderately correlated with each other, we were interested in controlling for multiple phenols and parabens rather than simply analyzing one compound at a time. Additionally, we wanted to assess the influence of other chemicals, including phthalates, BPA, PBDEs, PCBs, and organophosphate and organochlorine pesticides, on the association of these phenols and parabens with thyroid hormone levels. Because the large number of potentially confounding chemicals precluded including them all in multivariable models, we determined which of these additional chemicals to include in Model 2 using Bayesian Model Averaging (BMA). BMA conducts variable selection by determining Posterior Inclusion Probabilities (PIPs), which are measurements of each variable's influence on the outcome relative to other variables in the BMA model (Madigan et al., 1996). We conducted BMA using all of the environmental phenols and parabens as well as the other chemicals of interest and obtained PIPs for each of our three maternal and one neonatal thyroid hormone outcomes. We constructed versions of Model 2 including either the three, five, or seven most influential additional chemicals for each outcome. We present models including the three most influential chemicals, because results were similar to those including five and seven chemicals but power was increased. In cases where the main chemical of interest matched one of the three chosen influential variables, Model 2 only controlled for the other two chemicals from the BMA analysis. Because some participants were missing some of the additional chemical covariates, in sensitivity analyses we compared Model 2 to versions of Model 1 conducted only for participants with complete data on the other chemicals.

## Results

As shown in Table 1, most study participants were under age 30 (79%), of low education (80% had not completed high school), born in Mexico (85%), and had household incomes below the federal poverty level (61%). Approximately half of the infants were boys and half girls, and most of the infants (76%) had their TSH measured within 48 hours of birth.

All paraben and phenol biomarkers were detected in at least 70% of samples, with most detected in at least 95%. Percentiles and geometric means are shown in Table 2. CHAMACOS creatinine-corrected geometric means were within the interquartile range of NHANES concentrations, with the exception of 2,4-dichlorophenol and 2,5-dichlorophenol, which were on average higher in CHAMACOS participants (Supplemental Table S1). The mean (SD) maternal free and total T4 serum levels were 0.82 (0.24) ng/dL and 10.60 (1.53) µg/dL respectively. The geometric mean (GSD) of maternal and child TSH serum levels were 1.15 (1.73) and 5.61 (1.81) mIU/L respectively.

Table 3 shows that, in models adjusting for demographic variables (Models 1), maternal urinary triclosan concentrations were inversely associated with maternal total T4 ( $\beta = -0.060$ , 95% CI:  $-0.116, -0.004$ ) and 2, 4-dichlorophenol concentrations were inversely

associated with maternal free T4 ( $\beta = -0.017$ , 95% CI:  $-0.031, -0.004$ ). Methyl paraben and propyl paraben were inversely associated with maternal TSH in models that adjusted for demographic variables ( $\beta = -3.99\%$ , 95% CI:  $-7.50, -0.33$  for methyl paraben;  $\beta = -2.73\%$ , 95% CI:  $-4.76, -0.66$  for propyl paraben). However, after additionally controlling for other influential chemicals in Models 2, the association of methyl paraben with maternal TSH was no longer statistically significant. The associations of 2,4-dichlorophenol with maternal free T4 ( $\beta = -0.019$ , 95% CI:  $-0.033, -0.005$ ) and of propyl paraben with maternal TSH ( $\beta = -3.32\%$ , 95% CI:  $-5.61, -0.97$ ) became stronger after controlling for other biomarker concentrations. R-squared values ranged from 0.0000 to 0.0199 for crude models, 0.0601 to 0.0948 for models controlling for demographic variables, and 0.0974 to 0.1675 for models controlling for other chemicals. PIPs from the BMA analysis to identify other influential chemicals can be found in Supplemental Table S2.

We did not detect any statistically significant associations of maternal urinary concentrations of any of the target biomarkers with neonatal TSH levels in models that adjusted for demographic factors (Model 1) or additionally adjusted for other biomarkers (Model 2), as shown in Table 4. R-squared values ranged from 0.0000 to 0.0117 for crude models, 0.0709 to 0.0791 for models controlling for demographic variables, and 0.1222 to 0.1276 for models controlling for other chemicals.

In sensitivity analyses, results of Models 2 using the top five or top seven biomarker covariates produced by BMA were very similar to the main Models 2, using the top three biomarker covariates, reported in Tables 3 and 4 (data not shown). Including the additional biomarker covariates reduced the sample sizes in Models 2 compared to Models 1 because of women missing data on some of the additional biomarker covariates. Thus, in sensitivity analyses, we reanalyzed Models 1 including only participants with no missing values for the additional biomarkers, so that the sample size for Models 1 and 2 were the same (Supplemental Table S3). Results were generally similar for Models 1 using either the original or reduced sample size, suggesting that the changes in effects seen with Models 2 were due to confounding by other biomarkers. In further sensitivity analyses restricting the sample to women who did not have imputed specific gravity, the associations between 2,4-dichlorophenol and lower free T4, and propyl paraben and lower TSH persisted, and the associations between triclosan and lower total T4, 2,5-dichlorophenol and higher free T4, and benzophenone-3 and lower neonatal TSH gained significance in Model 2 (Supplemental Table S4).

## Discussion

We report significant associations between maternal urinary concentrations of certain phenols and parabens during pregnancy and maternal thyroid hormone serum levels, after adjusting for demographic covariates and additional chemical exposures. Specifically, we observed two associations with phenols in the direction of lower thyroid hormone levels: an inverse association of maternal 2,4-dichlorophenol concentrations with maternal free T4 and an inverse association of maternal triclosan concentrations with maternal total T4. Because 2,4-dichlorophenol is a breakdown product of triclosan, we cannot rule out that the association with 2,4-dichlorophenol could reflect, at least in part, triclosan exposure,



although 2,4-dichlorophenol also derives from pesticide exposure. We also observed an association with parabens in the opposite direction: propyl paraben concentrations were inversely associated with TSH, although we observed no corresponding increases in T4. We did not observe associations of maternal urinary biomarkers with neonatal TSH.

Few other studies have examined the association of phenol and paraben exposure with thyroid hormone levels during pregnancy. Wang et al found that urinary concentration of triclosan in Chinese pregnant mothers (N=398) was inversely associated with free T4 in mothers and with free T3 in their newborns (Wang et al., 2017). Aker et al, in a study of 439 pregnant women in Boston, found triclosan was positively associated with TSH in mothers, which does not match our findings but is consistent with our inverse association between triclosan and total T4 (Aker et al., 2018). However, unlike our study, the PROTECT Study in Puerto Rico did not find associations of triclosan with thyroid hormone (Aker et al., 2016), nor did a randomized intervention assigning products containing or not containing triclosan to 154 pregnant women for use during their pregnancy found no difference in maternal T3, T4, or TSH levels at delivery (Ley et al., 2017). Additionally, Braun et al reported urinary triclosan concentrations during pregnancy were unassociated with maternal thyroid hormone in pregnancy, but were inversely associated with total T4 in newborns in a cohort study of 202 mothers and children in Cincinnati (Braun et al., 2017). We did not find any associations of triclosan and neonatal thyroid hormones but, unlike other studies, we only measured neonatal TSH and not T3 and T4.

Only a few other studies have examined parabens and thyroid hormone, with conflicting results. The PROTECT Study in Puerto Rico found that butyl paraben was positively associated with free T4 in mothers (Aker et al., 2016). The Aker et al study of pregnant women in Boston found methyl paraben was associated with higher maternal total T4 and propyl paraben was associated with lower maternal free T4 (Aker et al., 2018). Additionally, in a cross-sectional study of non-pregnant NHANES adult women, several parabens, including propyl-, butyl- and ethyl paraben, were inversely associated with levels of T3 and T4 (Koeppel et al., 2013). None of these studies is particularly consistent with our finding of an inverse association of propyl paraben with TSH.

Consistent with our findings, a study of 183 Danish pregnant women found maternal urinary concentrations of benzophenone-3 were not associated with maternal serum concentrations of free or total T3 and T4. (Krause et al., 2018) Two other human studies in non-pregnant populations found 2,5-dichlorophenol to be positively associated with TSH (Croes et al., 2015; Wei and Zhu, 2016), unlike our study, but no other studies have found associations with 2,4-dichlorophenol.

Our results of negative associations of prenatal urinary triclosan concentrations with maternal total T4 but not maternal TSH is consistent with animal studies showing that prenatal exposure to triclosan, at doses ranging from 10 mg/kg/day (Rodriguez and Sanchez, 2010) to 300 mg/kg/day (Paul et al., 2012; Paul et al., 2010), was inversely associated with total T4 levels in dams, and no change in TSH. Additionally, rats fed 62.5, 250 and 1000 mg/kg of parabens for 20 days had increased levels of T4 when exposed to methyl- and propyl paraben, but not butyl paraben (Vo et al., 2010). Although we did not observe

changes in T4 with paraben concentrations, we did observe decreases in TSH with both methyl- and propyl paraben concentrations in models controlling for demographic factors, and propyl paraben in models additionally controlling for other chemical exposures, which is consistent with increases in T3 and T4.

Our study differed from previous studies in that we controlled for other potentially confounding chemicals in our analysis. Several of the phenols (or their precursors) and parabens measured in this study are jointly used in consumer products and exposures are correlated. Additionally, exposure to other endocrine disruptors, including phthalates, flame retardants, and pesticides, is common. A strength of this study is that we used BMA to identify other endocrine disrupting chemicals that were most strongly associated with thyroid hormone from an extensive list of chemicals already measured in this cohort and included them in our fully adjusted models. Some associations observed in the models that only controlled for demographic factors were no longer present after controlling for other chemical exposures. For example, a strong association of methyl paraben with decreased maternal TSH was no longer present after controlling for propyl paraben and other chemicals. Other studies only controlled for demographic factors and not other chemical exposures (similar to our Models 1), which may explain some differences in findings between our study and previous publications.

We assessed exposure to phenols and parabens using two measurements of urinary concentrations during pregnancy. Many of these chemicals are non-persistent with short half-lives in the body. For example, the terminal plasma half-life of triclosan is ~21 hours, with maximum concentrations occurring 1–3 hours after ingestion (Sandborgh-Englund et al., 2006). However, because use of personal care products tends to be fairly consistent from day to day, biomarkers concentrations from spot urine samples have been shown to be reasonably representative of on-going exposure during a period of several months (Meeker et al., 2013; Teitelbaum et al., 2008). In our study, intraclass correlation coefficients across the two measurements in pregnancy range from 0.41 – 0.46 for parabens, and are 0.46 for triclosan and 2,4-dichlorophenol, 0.55 for 2,5-dichlorophenol, and 0.56 for benzophenone-3.

Our study examined associations between seven biomarkers and four measures of thyroid hormone, and results should be interpreted with consideration of these multiple comparisons. However, all of our main findings were consistent across crude and adjusted models, suggesting they are not spurious findings.

This is one of the first studies to examine the association between phenol and paraben exposure during pregnancy and maternal or neonatal thyroid hormones, a critical time period due to the importance of thyroid hormone homeostasis on fetal and infant brain development. Altered maternal T4 levels, even within the normal clinical range, have been associated with poorer neurodevelopment in children (Li et al., 2010; Man et al., 1991; Pop et al., 1999). Thus, environmental exposures that may affect maternal thyroid hormone levels during pregnancy could have long-term health consequences on children.

Our study suggests that in this group of pregnant women, exposure to some phenols and parabens or their precursors, chemicals commonly found in consumer products, may

influence thyroid hormone levels during pregnancy. This finding is consistent with animal literature but would benefit from replication in other human studies. Additional research on the potential effects of these chemicals on thyroid hormone should include controls for other, related chemical exposures.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

We acknowledge Xiaoliu Zhou and Tao Jia for their technical assistance measuring the urinary biomarkers.

Funding sources: This work was supported by the National Institute of Environmental Health Sciences (NIEHS) [grant numbers P01 ES009605, R01 ES021369, 1RC2 ES018792, and R01 ES017054]; and the US Environmental Protection Agency (EPA) [grant numbers R82670901, RD83171001, and RD83451301]. Funding sources had no involvement in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication

Written informed consent was obtained from all mothers and all research was approved by the Committee for the Protection of Human Subjects at the University of California, Berkeley.

Disclaimer

The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC). Use of trade names is for identification only and does not imply endorsement by the CDC, the Public Health Service, or the US Department of Health and Human Services.

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**Table 1.**

## Maternal and neonatal characteristics of CHAMACOS participants

Maternal characteristics	<i>n</i> (%)
Age (years)	
18–24	224 (49)
25–29	136 (30)
30–34	63 (14)
35–45	31 (7)
Education	
<= 6th grade	194 (43)
7–12th grade	166 (37)
>= High school	94 (21)
Country of birth	
United States	59 (13)
Mexico	384 (85)
Other	11 (2)
Household income	
<100% poverty	276 (61)
100–200% poverty	162 (36)
>200% poverty	16 (4)
Neonatal characteristics	
Sex	
Female	224 (50)
Male	227 (50)
Age at TSH measurement (hours)	
Within 24 hours	252 (69)
25 to 48 hours	92 (25)
After 48 hours	110 (24)

**Table 2.**

Uncorrected (plain text) and specific gravity-corrected (*italics*) urinary concentrations of environmental phenols in CHAMACOS mothers (N=452)

Biomarker	LOD (ng/mL)	Early	Late	Average of 2 Pregnancy Measurements (ng/mL)				
		Pregnancy	Pregnancy	Geometric Mean	Percentiles			
		% >LOD	% >LOD		25%	50%	75%	95%
Triclosan	2.3	70.6	75.1	17.5	4.3	16.5	84.4	502.8
				<i>22.1</i>	<i>6.0</i>	<i>20.3</i>	<i>106.1</i>	<i>648.0</i>
Benzophenone-3	0.4	99.6	98.6	21.0	3.9	13.7	120.6	693.0
				<i>27.0</i>	<i>4.8</i>	<i>16.6</i>	<i>155.7</i>	<i>1005.8</i>
2,4-Dichlorophenol	0.2	100.0	99.8	4.9	1.7	3.3	12.9	53.8
				<i>6.3</i>	<i>2.3</i>	<i>4.1</i>	<i>16.4</i>	<i>69.3</i>
2,5-Dichlorophenol	0.2	99.8	99.8	63.7	13.1	59.5	428.0	964.0
				<i>80.5</i>	<i>16.3</i>	<i>81.6</i>	<i>482.5</i>	<i>1132.6</i>
Methyl paraben	1.0	100.0	99.8	126.5	56.8	148.2	335.6	712.0
				<i>159.0</i>	<i>75.1</i>	<i>183.2</i>	<i>391.7</i>	<i>772.8</i>
Propyl paraben	0.2	96.6	97.8	30.9	8.6	37.3	132.0	535.2
				<i>38.5</i>	<i>10.3</i>	<i>48.5</i>	<i>163.6</i>	<i>631.4</i>
Butyl paraben	0.2	43.9	44.9	0.4	0.1	0.2	1.4	23.0
				<i>0.5</i>	<i>0.1</i>	<i>0.3</i>	<i>1.7</i>	<i>27.2</i>

Abbreviations: LOD=Limit of detection



**Table 3.**

Associations of each two-fold increase in average urinary biomarker concentrations during pregnancy (specific gravity corrected) with maternal thyroid hormone levels

	Maternal Free T4				Maternal Total T4							
	Crude Model	Model 1 <sup>2</sup>	Model 2 <sup>3</sup>	Crude Model	Model 1 <sup>2</sup>	Model 2 <sup>3</sup>	Model 2 <sup>4</sup>					
	N=314-316 β (95% CI)	R-squared β (95% CI)	R-squared β (95% CI)	N=317-319 β (95% CI)	R-squared β (95% CI)	R-squared β (95% CI)	N=317-319 β (95% CI)					
Triclosan	-0.004 (-0.013, 0.005)	0.0027	-0.005 (-0.014, 0.004)	0.0783	-0.004 (-0.013, 0.005)	0.1675	-0.054 (-0.111, 0.003)	0.0107	-0.060 (-0.116, -0.004)	0.0948	-0.055 (-0.111, 0.002)	0.1067
BP-3	-0.006 (-0.014, 0.003)	0.0056	-0.004 (-0.013, 0.004)	0.0775	-0.003 (-0.012, 0.005)	0.1670	-0.060 (-0.114, -0.005)	0.0142	-0.043 (-0.097, 0.011)	0.0890	-0.038 (-0.094, 0.018)	0.1067
2,4-DCP	-0.016 (-0.029, -0.002)	0.0156	-0.017 (-0.031, -0.004)	0.0933	-0.049 (-0.082, -0.016)	0.1651	-0.048 (-0.136, 0.041)	0.0035	-0.043 (-0.130, 0.043)	0.0847	-0.030 (-0.118, 0.058)	0.1067
2,5-DCP	-0.007 (-0.016, 0.003)	0.0059	-0.008 (-0.017, 0.002)	0.0850	0.022 (-0.001, 0.046)	0.1651	-0.022 (-0.084, 0.040)	0.0016	-0.020 (-0.081, 0.041)	0.0858	0.019 (-0.125, 0.163)	0.1100
Methyl Paraben	0.007 (-0.010, 0.023)	0.0022	0.006 (-0.011, 0.022)	0.0762	0.000 (-0.017, 0.017)	0.1651	0.016 (-0.090, 0.121)	0.0003	-0.012 (-0.116, 0.091)	0.0820	0.100 (-0.038, 0.237)	0.1127
Propyl Paraben	0.002 (-0.007, 0.011)	0.0006	0.000 (-0.009, 0.010)	0.0749	-0.002 (-0.011, 0.008)	0.1655	-0.031 (-0.091, 0.029)	0.0033	-0.046 (-0.105, 0.012)	0.0889	-0.031 (-0.091, 0.030)	0.1067
Butyl Paraben	-0.003 (-0.012, 0.006)	0.0015	-0.001 (-0.010, 0.008)	0.0751	0.000 (-0.009, 0.009)	0.1651	0.001 (-0.057, 0.059)	0.0000	-0.006 (-0.064, 0.051)	0.0819	0.019 (-0.043, 0.080)	0.1078

  

	Maternal TSH <sup>1</sup>					
	Crude Model	Model 1 <sup>2</sup>	Model 2 <sup>3</sup>	R-squared		
	N=317-319 β (95% CI)	R-squared β (95% CI)	R-squared β (95% CI)	R-squared		
Triclosan	-0.81 (-2.83, 1.25)	0.0019	-1.23 (-3.21, 0.80)	0.0638	-0.12 (-2.33, 2.15)	0.0997
BP-3	-0.76 (-2.70, 1.23)	0.0018	-1.19 (-3.12, 0.77)	0.0639	0.13 (-2.17, 2.49)	0.0997
2,4-DCP	-2.74 (-5.77, 0.38)	0.0094	-2.47 (-5.49, 0.64)	0.0669	-2.08 (-5.39, 1.36)	0.0997
2,5-DCP	-1.79 (-3.93, 0.41)	0.0081	-1.49 (-3.64, 0.71)	0.0651	-1.24 (-3.66, 1.23)	0.0974
Methyl Paraben	-4.71 (-8.21, -1.08)	0.0199	-3.99 (-7.50, -0.33)	0.0733	2.38 (-3.28, 8.38)	0.1036
Propyl Paraben	-2.67 (-4.72, -0.57)	0.0192	-2.73 (-4.76, -0.66)	0.0794	-3.32 (-5.61, -0.97)	0.0997
Butyl Paraben	-0.46 (-2.52, 1.64)	0.0006	-0.46 (-2.52, 1.63)	0.0601	0.48 (-1.90, 2.93)	0.1009

<sup>1</sup>TSH shown as percent change, as given by  $(10^{\beta}-1)*100$

<sup>2</sup>Adjusted for maternal age, maternal education, maternal country of birth, poverty index at baseline

<sup>3</sup>Adjusted for maternal age, maternal education, maternal country of birth, poverty index at baseline, 2,4-dichlorophenol, the sum of di(2-ethylhexyl) phthalate metabolites, monobenzyl phthalate, mono(3-carboxypropyl) phthalate, and 2,5-dichlorophenol

<sup>4</sup>Adjusted for maternal age, maternal education, maternal country of birth, poverty index at baseline, benzophenone-3, triclosan, the sum of dialkyl phosphate metabolites, propyl paraben, and 2,4-dichlorophenol

5 Adjusted for maternal age, maternal education, maternal country of birth, poverty index at baseline, propyl paraben, the sum of polybrominated diphenyl ether congeners, monocarboxyisononyl phthalate, mono(3-carboxypropyl) phthalate, and 2,4-dichlorophenol

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**Table 4.**

Associations of each two-fold increase in average urinary biomarker concentrations during pregnancy (specific gravity corrected) and neonatal TSH levels

	Neonatal TSH <sup>1</sup>					
	Crude Model		Model 1 <sup>2</sup>		Model 2 <sup>3</sup>	
	$\beta$ (95% CI)	R-squared	$\beta$ (95% CI)	R-squared	$\beta$ (95% CI)	R-squared
Triclosan	0.52 (-1.64, 2.72)	0.0006	0.53 (-1.64, 2.76)	0.0709	1.51 (-0.88, 3.97)	0.1222
BP-3	-2.13 (-4.12, -0.10)	0.0117	-2.02 (-4.04, 0.04)	0.0791	-1.82 (-4.06, 0.48)	0.1273
2,4-DCP	-2.96 (-6.13, 0.31)	0.0087	-2.62 (-5.83, 0.71)	0.0744	-2.65 (-6.20, 1.02)	0.1250
2,5-DCP	-2.06 (-4.22, 0.15)	0.0093	-1.83 (-4.03, 0.42)	0.0739	-1.82 (-4.21, 0.64)	0.1245
Methyl Paraben	1.32 (-2.25, 5.02)	0.0014	1.41 (-2.19, 5.14)	0.0728	2.12 (-1.91, 6.32)	0.1257
Propyl Paraben	0.00 (-2.27, 2.31)	0.0000	-0.05 (-2.33, 2.29)	0.0710	1.47 (-1.09, 4.09)	0.1276
Butyl Paraben	0.16 (-2.03, 2.40)	0.0001	0.15 (-2.08, 2.42)	0.0716	0.10 (-2.26, 2.51)	0.1231

<sup>1</sup> TSH shown as percent change, as given by  $(10^{\beta}-1)*100$

<sup>2</sup> Adjusted for maternal age, maternal education, maternal country of birth, poverty index at baseline

<sup>3</sup> Adjusted for maternal age, maternal education, maternal country of birth, poverty index at baseline, monocarboxyisononyl phthalate, the sum of di(2-ethylhexyl) phthalate metabolites, mono(3-carboxypropyl) phthalate, monocarboxyisooctyl phthalate, and triclosan