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Urinary Triclosan Concentrations during Pregnancy and Birth Outcomes

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Abstract

Background—Triclosan is an antimicrobial chemical used in consumer products, and exposure is ubiquitous among pregnant women in the United States. Triclosan may reduce the levels of thyroid hormones that are important for fetal growth and development.

Objective—We investigated the relationship of prenatal triclosan exposure with birth anthropometry and gestational duration.

Methods—We used data from 377 mother-child pairs participating in the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort from Cincinnati, OH. We measured triclosan concentrations in maternal urine samples collected at 16 and 26 weeks of pregnancy. We abstracted information on neonatal anthropometry and gestational duration from medical records. We used multivariable linear regression to estimate the covariate-adjusted association between the average of the two urinary triclosan concentrations and gestational age standardized weight z-score, length, head circumference, and gestational age at birth.

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Results—Median urinary triclosan concentrations were 16 ng/mL (range: <2.4 to 1,501 ng/mL). Each 10-fold increase in triclosan was associated with a predicted 0.15 standard deviation decrease (95% CI: −0.30, 0.00) in birth weight z-score, 0.4-cm decrease (95% CI: −0.8, 0.1) in birth length, 0.3-cm decrease (95% CI: −0.5, 0.0) in head circumference, and 0.3-week decrease (95% CI: −0.6, −0.1) in gestational age. Child sex did not modify the associations between triclosan and birth outcomes.

Conclusions—In this cohort, maternal urinary triclosan concentrations during pregnancy were inversely associated with infants' birth weight, length, head circumference, and gestational age.

Keywords

Birth weight; epidemiology; prenatal; triclosan

Introduction

Triclosan is an antimicrobial chemical that is widely used in some toothpastes, mouthwashes, soaps, cosmetics, lotions, textiles, toys, and kitchenware.[1] Exposure is ubiquitous among pregnant women in the United States.[2–4] The primary routes of exposure are oral and dermal, with the highest exposures hypothesized to be from dermally applied products.[5] Oral care products, including some toothpastes, are another major source of exposure, particularly among children.[5] The U.S. Food and Drug Administration banned over-the-counter consumer wash products that contain triclosan in September of 2016; however other potential sources of triclosan, such as some body lotions and toothpastes, remain in use.[6]

Triclosan may disrupt the actions within the hypothalamic-pituitary-thyroid axis[7], and triclosan exposure reduces thyroxine concentrations in pregnant, fetal, and juvenile rats.[8–10] Of particular concern is the potential for triclosan to disrupt thyroid hormone homeostasis during fetal development because thyroid hormones play a critical role in fetal growth and neurodevelopment; reduced thyroxine levels during gestation can have negative impacts on the developing fetus.[11–13]

Triclosan has been associated with adverse birth outcomes in epidemiological studies. Maternal prenatal urinary triclosan concentrations have been inversely associated with newborn's head circumference, but not with weight or length at birth.[14,15] Another study found that prenatal urinary triclosan concentrations were inversely associated with birth weight and length among newborn boys, but not with head circumference.[3] However, prior studies were limited by having only one measure of prenatal urinary triclosan during pregnancy and this may have resulted in exposure misclassification.

The objective of this study was to investigate the relationship of prenatal urinary triclosan concentrations at 16 and 26 weeks of pregnancy with birth weight, length, head circumference, and gestational duration in a prospective pregnancy and birth cohort. Based on previous animal and epidemiologic studies, we hypothesized that urinary triclosan concentrations would be inversely associated with neonatal anthropometry and gestational duration.

Materials and Methods

Study Participants

We used data collected from women and children enrolled in The Health Outcomes and Measures of the Environment (HOME) Study, an ongoing prospective pregnancy and birth cohort in the greater Cincinnati, Ohio metropolitan area. The HOME Study was designed to investigate the impact of exposure to common environmental contaminants on child health and development. We previously described details of the study.[16] Briefly, from March 2003 to January 2006 we recruited women living in the greater Cincinnati, Ohio metropolitan area who were: 18 years or older and 16±3 weeks of gestation, spoke English, lived in a home built before 1978, and had no history of HIV infection or other medical conditions such as diabetes, bipolar disorder, schizophrenia or cancer that resulted in radiation treatment or chemotherapy. Of the 1,263 eligible women we approached, 468 (37%) agreed to participate in our study. Of these, 67 dropped out before delivery leaving 401 women who delivered 389 singletons, 3 stillbirths, and 9 sets of twins.

The Cincinnati Children's Hospital Medical Center (CCHMC) and participating delivery hospitals' Institutional Review Boards (IRB) approved the HOME Study. After research assistants explained study protocols, all women provided written informed consent for themselves and their children. Brown University relinquished IRB authority to CCHMC through an Interagency Agreement. The Centers for Disease Control and Prevention (CDC) also relied on CCHMC IRB.

Urinary Triclosan Biomarkers

Women provided two urine samples at an average of 16.0 (range: 10.4–22.6) and 26.5 (range: 19.1–34.6) weeks of gestation. We collected urine in polypropylene containers and stored them at −20°C until shipped to the CDC for analysis. We measured total (conjugated + free) urinary triclosan concentrations using online solid phase extraction coupled with high performance liquid chromatography-isotope dilution tandem mass spectrometry as previously described.[17] Concentrations below the limit of detection (LOD) of 2.3 ng/mL were given a value of LOD/√2 for the statistical analysis. Urinary triclosan concentrations were creatinine-standardized (μg/g creatinine) to control for individual variation in urine dilution. Because creatinine-standardized urinary triclosan concentrations were right skewed, we $\log_{10}$-transformed them to reduce the influence of extreme observations before taking the mean of the 16 and 26-week $\log_{10}$-transformed creatinine-standardized urinary triclosan concentrations. Ninety-four percent of women had triclosan measurements at 16 and 26 weeks; for those who had only one measure, we used that in place of the mean.

Birth Outcomes

We extracted birth weight, length, and head circumference, gestational duration, and the method for determining gestational age (last menstrual period, n=368; antenatal ultrasound, n=6; or Ballard Maturational Assessment, n=3) from newborn medical charts. We calculated sex and gestational age standardized birth weight z-scores using United States Natality datasets.[18]

Covariates

We considered adjusting for potential confounders that might be associated with both gestational triclosan concentrations and fetal growth or gestational duration using a directed acyclic graph (DAG) (Supplemental Figure S1). We collected information about sociodemographic factors including maternal race and ethnicity, age, education, marital status, and household income using a computer-assisted questionnaire administered by trained research staff during the second trimester of pregnancy. Depressive symptoms were measured with the Beck Depression Inventory (BDI-II) at 20 weeks of pregnancy [19]. We measured perinatal factors, including delivery method, parity, weight at 16 weeks gestation, and prenatal vitamin use using standardized interviews or medical chart reviews. We assessed tobacco smoke exposure using the average of serum cotinine concentrations taken at 16 and 26 weeks of pregnancy.[20]

Statistical Analysis

Of the 389 women in the HOME Study who gave birth to singletons, we excluded women who had offspring with congenital or chromosomal abnormalities (n=2), were missing the method used to determine gestational age (n=1), or were missing covariate data (n=8). This left 378 mother-neonate pairs for analysis of birth weight z-score and gestational age. Eight children were missing the head circumference measurements and 9 children were missing the birth length measurements, leaving 370 and 369 mother-neonate pairs for the analysis of head circumference and birth length, respectively.

We started our statistical analysis by calculating the geometric mean of the average prenatal triclosan concentrations and the mean birth weight z-score by covariates. Next, we calculated intraclass correlation coefficients (ICCs) between the 16 and 26 week $\log_{10}$-transformed creatinine-standardized urinary triclosan concentrations to estimate the reproducibility of the repeated urinary triclosan concentrations.[21]

We then determined whether there were non-linear relationships between urinary triclosan concentrations and birth outcomes using restricted cubic splines.[22] Because we observed a linear association (non-linearity p-values>0.3), we estimated the unadjusted and adjusted difference in birth weight z-score, gestational age, birth head circumference, and birth length associated with a 10-fold increase in gestational urinary triclosan concentration using multivariable linear regression. To enhance interpretability of the results, we also examined the adjusted mean value in birth outcomes across quartiles of prenatal urinary triclosan concentrations. We examined whether child sex modified the association between triclosan and birth outcomes in our multivariable model by including child sex and a product interaction term between triclosan concentrations and child sex. Finally, we used Poisson regression with robust standard errors to calculate the relative risk of low-birth weight (<2500 grams), preterm birth (<37 weeks gestation), and small for gestational age (SGA, $<10^{th}$ birth weight z-score percentile) for a 10-fold increase in prenatal triclosan concentrations. [23] We used SAS version 9.4 (SAS Institute, Inc. Cary, NC) and R version 3.2 for statistical analysis.

Sensitivity Analysis

We conducted several sensitivity analyses to evaluate the robustness of our results: 1) We adjusted for a reduced set of covariates that were shown to be the most influential confounders; these covariates included maternal age, race, education, marital status, income, and cotinine concentrations; 2) Since gestational diabetes and hypertensive disorders during pregnancy can influence fetal growth (Supplemental Figure S2), we excluded women who had either (n=10 for gestational diabetes and n=30 for hypertension disorders);[24] 3) Due to differences in methods of measuring gestational age, we restricted our analysis to women who had gestational age measured by LMP (n=368); 4) Because exposure to other phenols may impact birth outcomes (Supplemental Figure S2)[3,14], we adjusted for urinary 2,4-dichlorophenol, 2,5-dichlorophenol, bisphenol A, benzophenone-3, methylparaben, propylparaben, and butylparaben concentrations. 5) We excluded women who were missing a urine sample at either 16 or 26 weeks to ensure that these women were not unduly influencing our results; 6) To identify potential periods of heightened vulnerability during gestation, we examined the difference in birth outcomes associated with a 10-fold increase in prenatal urinary triclosan concentration at 16 and 26 weeks separately; 7) To determine if our methods to adjust for urine dilution were sensitive to various assumptions, we conducted additional analyses employing six other urine dilution adjustment methods described by O'Brien et al. (2016). We also excluded women who had extreme creatinine values < 0.3 g/L or > 3.0 g/L (n=7).

Results

Mothers in the cohort were predominately white (62%), college-educated (56%), multiparous (55%), married (65%), and between the ages of 25 and 34 (60%) (Table 1).

Triclosan was detected in 91 and 83% of the 16 and 26 week urine samples, respectively (Supplemental Table S1). Median urinary triclosan concentrations were slightly higher at 16 weeks (17 ng/mL, range: <LOD-1,985 ng/mL) than at 26 weeks (13 ng/mL, range: <LOD-1,657 ng/mL) (Supplemental Figure S3, Supplemental Table S1). The median of the average prenatal urinary triclosan concentration was 16 ng/mL (range: <LOD-1,501 ng/mL). Repeated unstandardized (ICC=0.42, 95% CI: 0.33, 0.50) and creatinine-standardized (ICC=0.53; 95% CI: 0.45, 0.60) urinary triclosan concentrations at 16 and 26 weeks had fair reproducibility. Geometric mean prenatal urinary triclosan concentrations were slightly higher among women who were >25 to 35 years of age, white, had a bachelor's degree or higher, married, had a household income more than $40,000 a year, had minimal depressive symptoms, took prenatal vitamins weekly or daily, and were non-smokers, but not all differences were statistically significant (Table 1).

The mean (±standard deviation [SD]) birth weight, birth weight z-score, birth length, head circumference, and gestational duration were 3,378 grams (±618 grams), 0.06 standard deviation units (±1.0), 51 cm (±3.0), 34 cm (±1.8), and 39 weeks (±1.8 weeks), respectively. At delivery, 33 (8.7%) were low birth weight, 19 infants (5.0%) were preterm, and 31 infants (8.2%) were SGA. Average birth weight z-scores were significantly lower among women who were <25 years of age at delivery, non-Hispanic black, less educated, had a lower household income, unmarried, nulliparous, lower BMI, rarely or never took prenatal

vitamins, exposed to secondhand tobacco smoke or smokers, and not diagnosed with gestational diabetes (Table 1).

In unadjusted models, we observed weak inverse or null associations between prenatal urinary triclosan concentrations and all four outcomes (Table 2). After adjusting for covariates, prenatal urinary triclosan concentrations were inversely associated with the four birth outcomes, although some of the 95% CI's included the null value (Table 2, Supplemental Figure S4). Each 10-fold increase in triclosan was associated with an estimated 0.15 standard deviation decrease (95% CI: −0.30, 0.00) in birth weight z-score, 0.4-cm decrease (95% CI: −0.8, 0.1) in birth length, 0.3-cm decrease (95% CI: −0.5, 0.0) in head circumference, and 0.3-week decrease (95% CI: −0.6, −0.1) in gestational age. There was no evidence of effect modification by child sex; all sex x triclosan effect modification p-values were >0.6 (Table 2).

We observed monotonic decreases in mean birth weight z-score across increasing prenatal urinary triclosan concentration quartiles, whereas mean birth length, head circumference, and gestational duration generally decreased across the first three quartiles and then slightly increased from the third to fourth quartiles (Figure 1, Supplemental Table S2). For example, neonates born to women in the 4^{th} quartile of triclosan concentrations had 0.26 SD units lower birth weight z-score (95% CI: −0.55, −0.02) than neonates born to women in the 1^{st} quartile. Neonates born to women in the 2^{nd}, 3^{rd}, and 4^{th} quartile of triclosan concentrations had a gestational age that was 0.1 weeks (95% CI: −0.6, 0.4), 0.6 weeks (95% CI: −1.1, 0.1), and 0.5 weeks (95% CI: −1.0, 0.1) smaller, respectively, than neonates born to women in the 1^{st} quartile.

Higher prenatal urinary triclosan concentrations were associated with a slight and imprecise increase in risk for low birth weight, preterm birth, and SGA (Table 3). After adjusting for covariates, there was a 30–40% higher risk of low birth weight (RR=1.4, 95% CI: 0.8, 2.4), preterm birth (RR=1.4, 95% CI: 0.9, 2.3), or SGA (RR=1.3, 95% CI: 0.9, 2.1) for every 10-fold increase in prenatal urinary triclosan concentrations.

Sensitivity Analyses

In trying to identify which individual covariates were responsible for the observed negative confounding, we found an inverse relation between prenatal urinary triclosan concentrations and birth outcomes when individually adjusting for maternal age, race, education, marital status, household income, and serum cotinine concentrations during pregnancy (Supplemental Figure S5); the results of models only adjusting for these covariates was not appreciably different than the model that included our full set of covariates (Supplemental Table S3). Adjusting for gestational duration attenuated the association of prenatal urinary triclosan concentrations with birth length and head circumference (Supplemental Table S3). Excluding women with gestational diabetes or hypertension disorders, restricting the analysis to women with only LMP gestational duration measurements, excluding women who only had one prenatal urine sample, and adjusting for other phenols did not appreciably change the association between prenatal urinary triclosan concentrations and birth outcomes (Supplemental Table S3).

The associations between prenatal triclosan concentrations taken during the second and third trimester and birth outcomes were slightly attenuated and had greater precision than the association between average prenatal triclosan concentration and birth outcomes (Supplemental Table S4). For example, each 10-fold increase in 16 and 26-week triclosan concentrations was associated with a 0.12 (95% CI: −0.27, 0.03) and 0.12 (95% CI: −0.26, 0.02) SD-unit decrease in birth weight z-score, respectively.

The associations between prenatal urinary triclosan concentrations and birth outcomes were similar when we used different methods to adjust for urine dilution or excluded women with extreme creatinine values (Supplemental Table S5).

Discussion

Among 378 mother-infant pairs in the HOME Study, we found that higher urinary triclosan concentrations measured during pregnancy were associated with modest reductions in birth weight, length, head circumference, and gestational duration. In addition, higher gestational urinary triclosan concentrations were associated with a modestly elevated risk of low birth weight, preterm birth, and SGA. We found an attenuation of birth length and head circumference estimates when adjusting for gestational duration. However, gestational age is a strong predictor of fetal growth and our gestational age-adjusted estimates would be attenuated because we were adjusting for a causal intermediate.

Some of our results are consistent with previous epidemiological studies observing inverse associations between prenatal urinary triclosan concentrations and birth outcomes.[3,14,15] Similar to Wolff et al. (2008), we found an inverse association between prenatal urinary triclosan concentrations and birth length and weight. However, Wolff et al. (2008) only found this association among boys. In contrast, Lassen et al. (2016) and Philippat et al. (2014) did not find any association between prenatal urinary triclosan concentrations and birth weight and length. Consistent with our findings, Philippat et al. (2014) and Lassen et al. (2016) observed an inverse association between prenatal triclosan concentrations and head circumference at birth, but this was not observed by Wolff et al. (2008). Wolff et al. (2008) did not observe an association between prenatal triclosan concentrations and gestational age; Lassen et al. (2016) and Philippat et al. (2014) did not examine gestational age as one of their outcomes.

Differences in the results of this and previous studies could be explained by the number and timing of urine sample collections. We had two measures of urinary triclosan concentrations during the 2nd and 3rd trimesters of pregnancy. In contrast, all three previous studies only had one measure taken during either the 2nd or 3rd trimester. Two measurements may enhance the accuracy of gestational triclosan exposure assessment. Others have concluded that a single measure of urinary triclosan concentrations could result in non-differential exposure misclassification and this could explain the lack of associations in some previous studies.[25]

It does not appear that discrepancies in study results are related to differences in the central tendency of triclosan concentrations. For instance, Lassen at al. (2016) observed an inverse

association between prenatal triclosan concentrations and birth weight, despite having the lowest median urinary triclosan concentrations (1.0 ng/mL) compared to the HOME Study (median=16 ng/mL) and Philippat et al. (2014) study (median=30 ng/mL). Inconsistencies could also be due to differences in the attributes of the study participant characteristics. For instance, Philippat et al. (2014) studied a cohort of women who had male infants.

Previous research suggests that prenatal triclosan exposure could affect several biological mechanisms involved in fetal growth. Triclosan may disrupt the homeostasis of thyroid hormones by reducing the availability of thyroxine through increased hepatic metabolism.[7,8,26] Several studies have shown that triclosan exposure reduces thyroxine concentrations in pregnant and fetal rats.[7,10,26,27] A decrease in thyroxine availability during pregnancy could be detrimental for the growth and development of the fetus since the fetal thyroid does not become functional until the 12th week of gestation, making the fetus exclusively dependent on maternal thyroxine during the first trimester.[11] Because thyroid hormones play a critical role in brain development during fetal development, triclosan exposure may adversely affect brain development and growth.[12,13,28]

This study has some potential limitations that should be considered. First, triclosan exposure may be misclassified due to the moderate within-person variability of urinary triclosan concentrations. Triclosan has a half-life <24 hours [29] and exposures are likely be episodic in nature. Thus, accurate exposure assessment can be challenging. However, a strength of our study is that we had two triclosan measurements during the second and third trimesters of pregnancy and >94% of women had a measure in both trimesters. Assuming non-differential exposure misclassification of our urinary triclosan biomarker, it is likely that our reported results would be attenuated towards the null.[30]

Another limitation of the present study is that a majority of women had gestational age measured by LMP instead of an ultrasound, which is a more accurate method of pregnancy dating. However, previous research has shown that LMP reasonably approximates gestational age obtained from an ultrasound in the first trimester.[31] Generalizability is a third potential limitation of this study because our cohort is predominantly white and college educated (Table 1). However, the average triclosan concentration is consistent with the nationally representative National Health and Nutrition Examination Survey (NHANES) triclosan concentrations (17 ng/mL) and we have no evidence to suggest that women in the HOME Study are more susceptible to the effects of triclosan.[4,32] Fourth, different methods of adjusting for urine dilution could also result in exposure misclassification. Previous research based on simulations has shown that not adjusting for urine dilution introduces more bias compared to other statistical methods of urine dilution adjustment.[33] However, we used several different methods to adjust for urine dilution and our results did not vary by the method of adjustment

Finally, while we adjusted for many potential confounders, there is the possibility of residual confounding from other factors associated with both triclosan exposure and fetal growth or gestational duration. We observed that the relationship between urinary triclosan concentrations and neonatal size or gestational duration was negatively confounded by sociodemographic factors.[34] Women who were white, older, more educated, married, and

had a higher household income had higher urinary triclosan concentrations, and their infants had better birth outcomes compared to other women. This finding, in particular the association between household income and triclosan concentrations, is consistent with results from NHANES.[32] Given the observed negative confounding by sociodemographic factors in these data, the presence of any residual negative confounding from other unmeasured sociodemographic factors suggests that the results presented here would be biased towards the null. However, there is still a possibility of positive confounding from factors that are associated with poor birth outcomes and higher triclosan exposure. It is also important to consider other chemical exposures correlated with triclosan and birth outcomes as potential confounders. Reassuringly, our results did not change when we adjusted for several other urinary phenol biomarkers.

In this cohort, maternal urinary triclosan concentrations during pregnancy were associated with a decrease in birth weight, length, head circumference, and gestational duration. These findings suggest that triclosan exposure during pregnancy may be associated with adverse birth outcomes. While we did not find evidence that the association between triclosan and birth outcomes depended on the timing of exposure in the latter-two thirds of pregnancy, future research could attempt to identify windows of heightened vulnerability to triclosan using repeated assessments of exposure and statistically appropriate methods.[35] Finally, more research is needed to understand the relation between early life triclosan exposure and other infant and child health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Dann AB, Hontela A. Triclosan: environmental exposure, toxicity and mechanisms of action. J Appl Toxicol. 2011; 31(4):285–311. [PubMed: 21462230]
2. Philippat C, Wolff MS, Calafat AM, et al. Prenatal exposure to environmental phenols: concentrations in amniotic fluid and variability in urinary concentrations during pregnancy. Environ Health Perspect. 2013; 121(10):1225–1231. [PubMed: 23942273]
3. Wolff MS, Engel SM, Berkowitz GS, et al. Prenatal phenol and phthalate exposures and birth outcomes. Environ Health Perspect. 2008; 116(8):1092–1097. [PubMed: 18709157]
4. Woodruff TJ, Zota AR, Schwartz JM. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ Health Perspect. 2011; 119(6):878–885. [PubMed: 21233055]
5. Rodricks JV, Swenberg JA, Borzelleca JF, Maronpot RR, Shipp AM. Triclosan: a critical review of the experimental data and development of margins of safety for consumer products. Crit Rev Toxicol. 2010; 40(5):422–484. [PubMed: 20377306]

6. Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use, 81 FR 61106(2016).
7. Brucker-Davis F. Effects of environmental synthetic chemicals on thyroid function. Thyroid. 1998; 8(9):827–856. [PubMed: 9777756]
8. Paul KB, Hedge JM, Bansal R, et al. Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: a dynamic and kinetic evaluation of a putative mode-of-action. Toxicology. 2012; 300(1–2):31–45. [PubMed: 22659317]
9. Paul KB, Hedge JM, Devito MJ, Crofton KM. Developmental triclosan exposure decreases maternal and neonatal thyroxine in rats. Environ Toxicol Chem. 2010; 29(12):2840–2844. [PubMed: 20954233]
10. Johnson PI, Koustas E, Vesterinen HM, et al. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. Environ Int. 2016
11. de Escobar GM, Obregon MJ, del Rey FE. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Pract Res Clin Endocrinol Metab. 2004; 18(2):225–248. [PubMed: 15157838]
12. Gilbert ME, Rovet J, Chen Z, Koibuchi N. Developmental thyroid hormone disruption: prevalence, environmental contaminants and neurodevelopmental consequences. Neurotoxicology. 2012; 33(4):842–852. [PubMed: 22138353]
13. Ghassabian A, Bongers-Schokking JJ, Henrichs J, et al. Maternal thyroid function during pregnancy and behavioral problems in the offspring: the generation R study. Pediatr Res. 2011; 69(5 Pt 1):454–459. [PubMed: 21471776]
14. Philippat C, Botton J, Calafat AM, Ye X, Charles MA, Slama R. Prenatal exposure to phenols and growth in boys. Epidemiology. 2014; 25(5):625–635. [PubMed: 25061923]
15. Lassen TH, Frederiksen H, Kyhl HB, et al. Prenatal Triclosan Exposure and Anthropometric Measures including Anogenital Distance in Danish Infants. Environ Health Perspect. 2016
16. Braun JM, Kalloo G, Chen A, et al. Cohort Profile: The Health Outcomes and Measures of the Environment (HOME) study. Int J Epidemiol. 2016
17. Ye X, Kuklenyik Z, Needham LL, Calafat AM. Automated on-line column-switching HPLC-MS/MS method with peak focusing for the determination of nine environmental phenols in urine. Anal Chem. 2005; 77(16):5407–5413. [PubMed: 16097788]
18. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr. 2003; 3:6. [PubMed: 12848901]
19. Beck, ATST., Brewn, GK. Beck Depression Inventory. 2. San Antonio, TX: Psychological Corporation; 1996. (BDI-II)
20. Benowitz NL, Bernert JT, Caraballo RS, Holiday DB, Wang J. Optimal serum cotinine levels for distinguishing cigarette smokers and nonsmokers within different racial/ethnic groups in the United States between 1999 and 2004. Am J Epidemiol. 2009; 169(2):236–248. [PubMed: 19019851]
21. Rosner B. On the estimation and testing of interclass correlations: the general case of multiple replicates for each variable. Am J Epidemiol. 1982; 116(4):722–730. [PubMed: 7137158]
22. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Stat Med. 2010; 29(9):1037–1057. [PubMed: 20087875]
23. Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004; 159(7):702–706. [PubMed: 15033648]
24. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab. 2015; 66(Suppl 2):14–20.
25. Bertelsen RJ, Engel SM, Jusko TA, et al. Reliability of triclosan measures in repeated urine samples from Norwegian pregnant women. J Expo Sci Environ Epidemiol. 2014; 24(5):517–521. [PubMed: 24472755]
26. Erika S, Koeppe KKF, Colacino Justin A, Meeker John D. Relationship between urinary triclosan and paraben concentrations and serum thyroid measures in NHANES 2007–2008. Science of the Total Environment. 2013; 445–446:299–205.

27. Paul, Katie B., JMH, Devrro, Michael J., Crofton, Kevin M. Developmental triclosan exposure decreases maternal and neonatal thyroxine in rats. Environmental Toxicology and Chemistry. 2010; 29(12):2840–2844. [PubMed: 20954233]

28. Sui L, Gilbert ME. Pre- and postnatal propylthiouracil-induced hypothyroidism impairs synaptic transmission and plasticity in area CA1 of the neonatal rat hippocampus. Endocrinology. 2003; 144(9):4195–4203. [PubMed: 12933695]

29. Sandborgh-Englund G, Adolfsson-Erici M, Odham G, Ekstrand J. Pharmacokinetics of triclosan following oral ingestion in humans. J Toxicol Environ Health A. 2006; 69(20):1861–1873. [PubMed: 16952905]

30. Perrier F, Giorgis-Allemand L, Slama R, Philippat C. Within-subject Pooling of Biological Samples to Reduce Exposure Misclassification in Biomarker-based Studies. Epidemiology. 2016; 27(3):378–388. [PubMed: 27035688]

31. Hoffman CS, Messer LC, Mendola P, Savitz DA, Herring AH, Hartmann KE. Comparison of gestational age at birth based on last menstrual period and ultrasound during the first trimester. Paediatr Perinat Epidemiol. 2008; 22(6):587–596. [PubMed: 19000297]

32. Calafat AM, Ye X, Wong LY, Reidy JA, Needham LL. Urinary concentrations of triclosan in the U.S. population: 2003–2004. Environ Health Perspect. 2008; 116(3):303–307. [PubMed: 18335095]

33. O'Brien KM, Upson K, Cook NR, Weinberg CR. Environmental Chemicals in Urine and Blood: Improving Methods for Creatinine and Lipid Adjustment. Environ Health Perspect. 2016; 124(2): 220–227. [PubMed: 26219104]

34. Mehio-Sibai A, Feinleib M, Sibai TA, Armenian HK. A positive or a negative confounding variable? A simple teaching aid for clinicians and students. Ann Epidemiol. 2005; 15(6):421–423. [PubMed: 15967387]

35. Sanchez BN, Hu H, Litman HJ, Tellez-Rojo MM. Statistical methods to study timing of vulnerability with sparsely sampled data on environmental toxicants. Environ Health Perspect. 2011; 119(3):409–415. [PubMed: 21362588]

Highlights

- Triclosan exposure was associated with reduced birth weight.
- Triclosan exposure was also associated with a reduction in gestational age.
- These associations were not different in boys and girls.

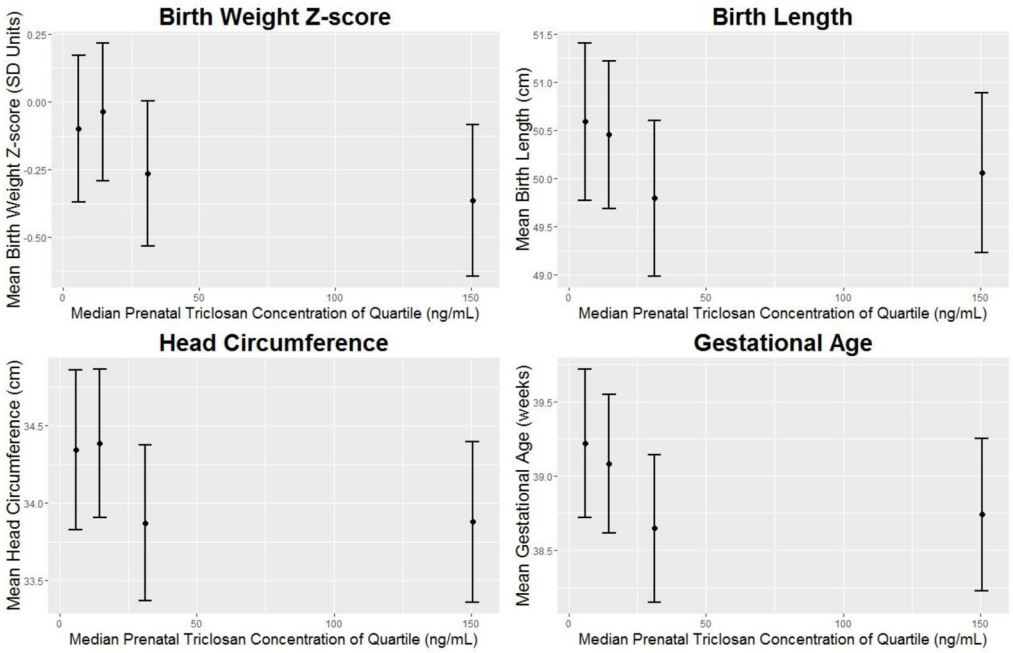

Figure 1.

Adjusted mean birth weight z-score, birth length, head circumference, and gestational age by maternal urinary triclosan quartiles in the HOME Study (2003–2006). *Adjusted for maternal race, education, marital status, age at delivery, income, prenatal vitamin use, delivery method, BDI score, and maternal serum cotinine concentrations during pregnancy. Head circumference is also adjusted for delivery method. Mean birth outcomes are presented at the median triclosan concentration within each quartile.

Table 1

Urinary triclosan concentrations during pregnancy and birth weight z-scores by covariates among women and their infants in the HOME study (2003–2006).

	N (%)	Triclosan Geometric Mean, ng/mL (GSD)[a]	Mean Birth weight z-score (SD)
All Maternal Age (years)	378	19 (4.1)	0.06 (1.03)
18–25	90 (24)	16 (3.6)	−0.43 (0.86)
>25–35	227 (60)	20 (4.4)	0.23 (0.98)
>35	61 (16)	19 (3.5)	0.17 (1.22)
p-value		0.17	<0.01
Maternal Race			
White	235 (62)	20 (4.3)	0.28 (1.05)
Black	117 (31)	17 (3.8)	−0.32 (0.89)
Other	26 (7)	17 (3.9)	−0.20 (0.87)
p-value		0.57	<0.01
Maternal Education			
Bachelor's/Grad/Prof	191 (51)	21 (4.4)	0.27 (1.06)
Tech school/Some College	94 (25)	19 (4.2)	−0.02 (0.93)
High School	52 (14)	17 (3.6)	−0.19 (1.08)
<High School	41 (11)	14 (2.9)	−0.42 (0.79)
p-value		0.31	<0.01
Marital Status			
Married	245 (65)	21 (4.5)	0.25 (1.04)
Not married (Living Alone)	55 (15)	16 (3.7)	−0.21 (0.83)
Not married (Living w/Someone)	78 (21)	15 (2.9)	−0.34 (0.96)
p-value		0.08	<0.01
Household Income			
>$80K	103 (27)	21 (3.9)	0.16 (0.97)
$40–80K	128 (34)	22 (4.9)	0.37 (1.09)
$20–40K	63 (17)	15 (3.9)	−0.07 (1.00)
<$20K	84 (22)	16 (3.1)	−0.44 (0.80)
p-value		0.17	<0.01
Parity			
Nulliparous	169 (45)	19 (4.2)	−0.11 (1.04)
1 to 2	117 (31)	18 (4.1)	0.19 (0.98)
3+	90 (24)	20 (3.9)	0.21 (1.04)
p-value		0.94	0.01
Delivery Method			
Vaginal	269 (71)	18 (3.9)	0.00 (0.99)
Cesarean	109 (29)	20 (4.4)	0.20 (1.12)
p-value		0.62	0.09
Depressive Symptoms			
Minimal	294 (78)	20 (4.4)	0.10 (1.03)

	N (%)	Triclosan Geometric Mean, ng/mL (GSD)[a]	Mean Birth weight z-score (SD)
Mild	53 (14)	15 (3.2)	−0.09 (1.08)
Moderate/Severe	31 (8)	17 (2.9)	−0.04 (0.92)
p-value		0.30	0.39
Maternal BMI * (kg/m²)			
<25	161 (43)	18 (3.9)	−0.12 (0.98)
25–30	124 (33)	21 (4.4)	0.14 (1.01)
>30	93 (25)	17 (4.0)	0.27 (1.08)
p-value		0.44	0.01
Prenatal Vitamin			
Rarely/Never	56 (15)	14 (3.3)	−0.23 (0.91)
Weekly/Daily	322 (85)	20 (4.2)	0.11 (1.04)
p-value		0.09	0.02
Child Sex			
Female	204 (54)	18 (4.0)	−0.02 (0.96)
Male	174 (46)	20 (4.2)	0.15 (1.10)
p-value		0.43	0.1
Tobacco Smoke Exposure[b]			
Unexposed	140 (37)	23 (4.5)	0.26 (1.08)
Secondhand Smoke	197 (52)	17 (4.0)	−0.03 (0.98)
Active	41 (11)	15 (3.0)	−0.17 (0.99)
p-value		0.12	0.01
Gestational Diabetes			
Yes	10 (3)	15 (3.2)	0.79 (1.55)
No	319 (97)	19 (4.2)	0.05 (1.03)
p-value		0.62	0.03
Hypertension Disorders			
Yes	30 (8)	21 (5.3)	−0.19 (1.06)
No	346 (92)	19 (4.0)	0.08 (1.03)
p-value		0.62	0.16

[a] Triclosan concentrations are from the mean of the 16-week and 26-week urinary concentrations. These values are not adjusted for urine dilution.

[b] Smoking status is based on prenatal serum cotinine concentrations; < 0.015ng/mL was classified as unexposed, 0.014 to ≤ 3.0 ng/mL was classified as secondhand smoke, and >3.0 ng/mL was considered active smoking exposure.

* BMI: Body Mass Index

* p-values reflect the difference in the urinary triclosan geometric mean among the different categories.

Table 2

Difference in birth outcomes with 10-fold increase in prenatal urinary triclosan concentrations in the HOME Study (2003–2006)[a]

Birth Outcome	n	Unadjusted All Children (95% CI)	Adjusted All Children (95% CI)	n	Boys (95% CI)	n	Girls (95% CI)	Sex x Triclosan EMM p-value
Birth Weight Z- Score (SD Units)	378	0.02 (−0.18, 0.13)	−0.15 (−0.3, 0.0)	174	−0.10 (−0.32, 0.12)	204	−0.18 (−0.38, 0.02)	0.60
Birth Length (cm)	369	0.1 (−0.4, 0.6)	−0.4 (−0.8, 0.1)	167	−0.4 (−1.1, 0.3)	202	−0.3 (−0.9, 0.3)	0.88
Head Circumference (cm)	370	0.0 (−0.3, 0.3)	−0.3 (−0.5, 0.0)	168	−0.3 (−0.7, 0.2)	202	−0.3 (−0.6, 0.1)	0.95
Gestational Age (weeks)	378	−0.1 (−0.4, 0.1)	−0.3 (−0.6, − 0.1)	174	−0.3 (−0.7, 0.1)	204	−0.3 (−0.7, 0.0)	0.99

[*] Estimates are adjusted for maternal race, education, marital status, age at delivery, income, prenatal vitamin use, BDI score, and maternal BMI, and maternal serum cotinine concentrations during pregnancy. Head circumference is also adjusted for delivery method.

Table 3

Unadjusted and adjusted relative risk for low birth weight, preterm birth, and SGA per 10-fold increase in prenatal urinary triclosan concentrations among women in the HOME study (2003–2006).

Outcome	Number with outcome (%)	Crude RR (95% CI)	Adjusted RR (95% CI)[1]
Low birth weight (<2500 g)	33 (8.7)	1.1 (0.7, 1.9)	1.4 (0.8, 2.4)
Preterm Birth (<37 weeks)	19 (5.0)	1.2 (0.8, 1.9)	1.4 (0.9, 2.3)
SGA (<10th Percentile)	31 (8.2)	1.2 (0.8, 1.8)	1.3 (0.9, 2.1)

[1] Adjusted for mother's race, household income, age at delivery, education, marital status, BDI score, mother's BMI, prenatal vitamin use, and maternal serum cotinine concentrations during pregnancy.