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Associations of early life urinary triclosan concentrations with maternal, neonatal, and child thyroid hormone levels

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ABSTRACT

Background: Triclosan, an antimicrobial agent used in some consumer products, reduces endogenous thyroid hormone concentrations in rodents. Despite ubiquitous triclosan exposure and the importance of thyroid hormones for normal fetal development, few human studies have examined the impact of triclosan exposure on maternal, neonatal, or child thyroid hormones.

Methods: In the HOME Study, a prospective cohort from Cincinnati, OH, we measured urinary triclosan concentrations up to three times in pregnant women between 16 weeks and delivery, and up to three times in children between age 1–3 years. We quantified serum concentrations of thyroid stimulating hormone and total and free thyroxine and triiodothyronine in mothers at 16-weeks gestation (n = 202), neonates at delivery (n = 274), and children at age 3 years (n = 153). We estimated covariate-adjusted differences in thyroid hormones with a 10-fold increase in triclosan using linear regression and multiple informants models.

Results: Triclosan was not associated with thyroid hormones during pregnancy. We observed a few associations of triclosan concentrations with thyroid hormone concentrations in neonates at delivery and children at age 3 years. Higher gestational triclosan, particularly around the time of delivery, was associated with lower cord serum total thyroxine (β: 0.3 μg/dL; 95% CI: − 0.6, − 0.0). Childhood triclosan, particularly at age 1 year, was positively associated with total thyroxine at age 3 years (β: 0.7 μg/dL; 95% CI: 0.3, 1.2).

Conclusion: Our findings suggest that triclosan exposure may influence some features of neonatal and early child thyroid function. Given the large number of comparisons we made, these findings should be replicated in other cohorts.

1. Introduction

Triclosan is an antimicrobial agent used in some toothpastes, personal care products, soaps, cleaning supplies, and medical devices (Rodricks et al., 2010). Exposure may occur either through oral ingestion (e.g., toothpaste) or dermal absorption (e.g., soaps or personal care products) (Allmyr et al., 2006; Dann and Hontela, 2011). Triclosan has a biological half-life < 24 h and is predominately excreted in the urine as a glucuronide or sulfate conjugate (Sandborgh-Englund et al., 2006). Triclosan exposure is ubiquitous in many countries with average urinary concentrations ranging from 6 to 30 ng/mL and < 1–32 ng/mL among pregnant women and children, respectively (Casas et al., 2011; Li et al., 2013; Stacy et al., 2017; Wolff et al., 2010; Woodruff et al., 2011).

Triclosan causes reductions in serum thyroxine (T_4) concentrations in rodents by increasing hepatic catabolism of endogenous thyroid hormones (Johnson et al., 2016; Paul et al., 2012; Paul et al., 2010). Decreases in T_4 during fetal neurodevelopment may cause reduced

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cognitive abilities or increased risk of behavior problems in children (Ghassabian et al., 2011; Henrichs et al., 2013). Only a few epidemiological studies examining triclosan exposure and thyroid function in adolescents or adults have been conducted, with inconsistent findings (Cullinan et al., 2012; Geens et al., 2015; Koeppe et al., 2013). In a study of pregnant women, 3rd trimester urinary triclosan concentrations were inversely associated with maternal free T_4 concentrations in the 3rd trimester and cord serum free triiodothyronine (T_3) concentrations (Wang et al., 2017). However, no studies have examined whether urinary triclosan concentrations are associated with thyroid hormones in the first or second trimester of pregnancy, when the fetus is reliant on the mother for T_4 (de Escobar et al., 2004). Moreover, we are not aware of any prospective studies examining the impact of triclosan exposure on thyroid function during early childhood, a critical period of neurodevelopment. Finally, no studies have examined if there are unique windows of heightened susceptibility to triclosan exposure.

To address these important research gaps, we examined the association of repeated gestational and childhood urinary triclosan concentrations with maternal, neonatal, and child serum thyroid hormone concentrations among women and their children in the Health Outcomes and Measures of the Environment (HOME) Study. We also sought to identify whether there were windows of heightened susceptibility to triclosan exposure.

2. Methods

2.1. Study participants

We used data from the HOME Study, a prospective cohort study designed to quantify the health effects of early life exposure to prevalent environmental chemicals. Details regarding eligibility, recruitment, and follow-up have been previously published (Braun et al., 2016). Briefly, we recruited pregnant women from seven prenatal clinics associated with three hospitals in the Cincinnati, Ohio area from March 2003 to January 2006. The eligibility criteria at enrollment were: 1) 16 ± 3 weeks gestation, 2) ≥ 18 years old, 3) living in a home built before 1978, 4) no history of HIV infection, and 5) not taking any medications for seizure or thyroid disorders. After research assistants explained study protocols, all women provided written informed consent for themselves and their children. The institutional review boards of Cincinnati Children's Hospital Medical Center and the cooperating delivery hospitals approved this study.

2.2. Urinary triclosan concentration measurements during pregnancy

Women provided up to two urine samples during their prenatal care clinic visits around 16 and 26 weeks of pregnancy and another within 48 h after delivery. Almost all women (97%) provided at least two urine samples. We collected urine samples from children during study visits completed between 2004 and 2009, which included clinic or home visits at ages 1, 2, and 3 years. Eighty-five percent of children provided at least one urine sample; among those 71% provided at least two samples.

Caregivers were asked to wipe their child's genital area with a triclosan-free towelette before urine collection. We collected urine using Kendall abdominal pads placed inside the diaper for non-toilet trained children, a training potty lined with inserts for children who were being toilet trained, or specimen cups for children who were toilet trained. We followed the recommendations of Ye et al. (2013) to minimize the potential for external contamination during urine sample collection, storage, and analysis (Stacy et al., 2017; Ye et al., 2013). Details regarding our quality control procedures are available in the Supplemental Methods and Supplemental Table 1.

All samples were refrigerated until they were processed (≤ 24 h), after which they were stored at or below − 20 °C until shipped on dry ice to Centers for Disease Control and Prevention (CDC) for analysis. Total urine triclosan concentrations (free + conjugated) were measured at the CDC laboratories using previously described analytic chemistry methods and the coefficient of variation (CV) for the assay ranged from 5.2 to 9.3% for low and high concentration quality control samples (Ye et al., 2008). The limit of detection (LOD) for the assay was 2.3 ng/mL and concentrations below the LOD were assigned a value of the LOD/√2. To account for urine dilution, we measured urinary creatinine concentrations using a kinetic Jaffe reaction, and triclosan concentrations were divided by creatinine concentrations and multiplied by 100 to yield units of μg triclosan/g creatinine.

2.3. Maternal, neonatal, and child serum thyroid hormone concentrations

We collected venous blood from mothers at approximately 16 weeks gestation, venous umbilical cord blood from neonates at delivery, and venous blood from children at approximately age 3 years. Blood samples collected during pregnancy and at age 3 years were collected at the same time as the urine samples that we quantified triclosan in. We separated serum from clotted blood and stored it at − 80 °C until analysis. The clinical chemistry laboratory in the Department of Laboratory Medicine at the University of Washington quantified thyroid stimulating hormone (TSH), total and free T_4 (TT_4 and fT_4), total and free T_3 (TT_3 and fT_3), and thyroid antibodies (thyroid peroxidase [TPOAb] and thyroglobulin antibodies [TgAb]) concentrations in maternal and cord sera using an Access2 automated clinical immunoassay analyzer (Beckman Coulter Inc.). Because the volume of serum samples from age 3 years was limited, we prioritized thyroid hormone assays in these samples as follows: TSH > fT_4 > TT_4 > fT_3 > TT_3 > thyroid antibodies. This resulted in varying sample sizes for analyses of thyroid hormones at age 3 years. The coefficient of variation for internal quality control samples ranged from 2.0 to 10%. Masked replicate quality control samples also had low coefficients of variation (≤ 8.5%).

2.4. Covariates

We considered adjusting for potential confounders that might be associated with both urinary triclosan concentrations and maternal, neonatal, or child serum thyroid hormone function. We used a directed acyclic graph (DAG) to select confounders that were not causal intermediates and associated with both urinary triclosan concentrations and thyroid function (Supplemental Figs. 1–3). We used previously published results from this cohort to identify covariates associated with maternal and child triclosan concentrations (Stacy et al., 2017).

Trained research assistants collected covariate information using standardized computer-assisted interviews and medical chart reviews. Sociodemographic covariates included maternal race, age, education, marital status, household income during pregnancy, and child sex and race. We abstracted maternal weight and height at 16 weeks gestation from medical records and measured child weight and height at age 3 years. These were used to calculate maternal and child body mass index (BMI). We measured exposure to tobacco smoke using serum cotinine concentrations, a sensitive and specific biomarker of nicotine (Bernert et al., 2009). Serum cotinine concentrations were measured up to three times during pregnancy and at delivery, as well as up to three times from ages 1–3 years. We calculated the average of available measures for gestational and childhood periods separately. Finally, we assessed urinary iodine concentrations in a subset of women with sufficient urine collected at 16 (3%) or 26 (97%) weeks gestation with an Agilent 7500cx Inductively Coupled Plasma-Mass Spectrometer at the Trace Element Analysis Facility at Dartmouth College (Caldwell et al., 2003). The LOD was 0.5 μg/L, with an average CV% across quality control replicates of 8%.

2.5. Statistical analyses

We began our analyses by describing gestational and childhood