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Prenatal urinary triclosan concentrations and child neurobehavior

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ABSTRACT

Background: Exposure to triclosan, an antimicrobial chemical, is ubiquitous among pregnant women and may reduce thyroid hormone levels that are important for fetal neurodevelopment. Few studies have examined the association between prenatal triclosan exposure and children's neurobehavior.
Objective: We investigated the relationship of prenatal urinary triclosan concentrations with children's behavior and cognitive abilities at age three years in a prospective pregnancy and birth cohort in Canada.
Methods: We measured triclosan in urine samples collected at ~12 weeks of gestation in 794 Canadian women enrolled in a prospective pregnancy and birth cohort study (MIREC) from 2008 to 2011. Around age 3 years, we assessed children's cognitive abilities using the Wechsler Primary and Preschool Scale of Intelligence-III (WPPSI-III), and two scales of the Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P). Parents reported children's problem and reciprocal social behaviors using the Behavior Assessment System for Children-2 (BASC-2) and Social Responsiveness Scale-2 (SRS-2), respectively.
Results: After adjusting for confounders using multivariable linear regression, triclosan was not associated with most of the 30 examined neurobehavioral scales. Each 10-fold increase in triclosan was associated with better WPPSI-III picture completion scores (β: 0.2; 95% CI: 0,0.5) and BASC-2 externalizing (β: −0.5; 95% CI: −1.1, 0) and hyperactivity (β: −0.6; 95% CI: −1.2, −0.1) scores, suggesting less externalizing and hyperactive behaviors. Child sex did not modify these associations.
Conclusions: In this cohort, urinary triclosan concentrations measured once in early pregnancy were not associated with most assessed aspects of neurobehavior and weakly associated with a few others, but not in the hypothesized direction.

1. Introduction

Triclosan is an antimicrobial chemical used in some personal care and consumer products. The U.S. Food and Drug Administration banned triclosan in over-the-counter consumer wash products in 2016 in part because of concerns about its developmental toxicity (Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use, 2016); however, other sources of triclosan exposure remain in commerce, including some toothpastes, body lotions, cosmetics, toys, textiles, and kitchenware (Dann and Hontela, 2011; Rodricks et al., 2010). Triclosan is detected in the urine of > 80% of pregnant women in North America, indicating nearly ubiquitous exposure among this sensitive population (Woodruff et al., 2011; Etzel et al., 2017; Arbuckle et al., 2015a).

Prenatal triclosan exposure may adversely impact fetal neurodevelopment by affecting the hypothalamic-pituitary-thyroid axis during gestation (Brucker-Davis, 1998). Thyroid hormones play a critical role in fetal growth and neurodevelopment (de Escobar et al., 2004;

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Ghassabian et al., 2011; Gilbert et al., 2012; Zoeller and Rovet, 2004; Henrichs et al., 2010; Korevaar et al., 2016; Ghassabian et al., 2012; Andersen et al., 2014; Modesto et al., 2015; Brown et al., 2015; Lyall et al., 2016; Yau et al., 2015) and reduced levels of thyroid hormones during gestation can affect fetal neurodevelopment, which in turn may increase the risk of cognitive and motor deficits, as well as behavioral disorders. Rodent studies show that triclosan exposure can reduce thyroxine concentrations in pregnant, fetal, and juvenile rats (Johnson et al., 2016; Paul et al., 2012; Paul et al., 2010). Two epidemiological studies found an inverse association of prenatal urinary triclosan concentrations with maternal and cord blood thyroxine and triiodothyronine levels (Wang et al., 2017; Braun et al., 2017a). In addition, in vitro studies show that triclosan exposure induces apoptosis in neocortical neurons (Szychowski et al., 2015; Szychowski et al., 2016).

We are not aware of any animal studies examining the neurotoxicity of triclosan exposure; one epidemiological study found no association between prenatal triclosan exposure and children's visual-spatial abilities (Braun et al., 2017b). Given the potential for triclosan to disrupt thyroid hormone homeostasis, we investigated the relationship of prenatal urinary triclosan concentrations with children's behavior and cognitive abilities at age three years in a prospective pregnancy and birth cohort in Canada.

2. Materials and methods

2.1. Study participants

We used data from the Maternal-Infant Research on Environmental Chemicals (MIREC) study, a prospective pregnancy and birth cohort of 2000 pregnant women from ten cities (11 study sites) across Canada. Details about eligibility, recruitment, and follow-up are previously described (Arbuckle et al., 2013). Briefly, we recruited pregnant women during the first trimester of pregnancy from obstetric and prenatal clinics between 2008 and 2011. Women must have planned on delivering at a local hospital, been able to communicate in English or French, been ≥18 years of age, and agreed to participate in the cord blood collection component of the MIREC study. We excluded women if they had a history of major chronic disease, illicit drug use, threatened abortion, or were carrying a fetus with a known malformation or abnormality. Among 8716 women we approached to participate in MIREC, 5108 (58.6%) were eligible, 1983 (38.8%) consented and participated, and 1861 had singleton lives births.

The ethics review boards or committees from Québec and Sainte-Justine research centers, Health Canada, and participating recruitment sites approved this research. We provided potential participants with information about the student design and objectives before asking them to sign informed consent forms for the prenatal and child follow-up part of the study.

2.2. Prenatal triclosan exposure assessment

At an average of 12.1 weeks gestation (range: 5.1–15.0) we collected a single urine sample from women. Samples were aliquoted and frozen at −20 °C within 2 h of collection, and later shipped on dry ice to the MIREC coordinating center in Montréal where they were stored at −30 °C. For triclosan analysis, urine samples were shipped to the Centre de toxicologie du Québec, Institut National de Santé Publique du Québec. We quantified total (conjugated + free) triclosan concentrations using gas chromatography coupled with tandem mass spectrometry (GC–MS/MS) (Arbuckle et al., 2015b). Field blanks were used to assess for potential exogenous contamination from the materials used for urine specimen collection and storage, and from the environment of the collection sites. All field blanks were free of triclosan contamination. Several quality control samples, reagents blanks, and urine blanks were incorporated into each batch of samples (Arbuckle et al., 2015b). The intraday precision ranged from 2.5% to 7.7%, and the interday precision ranged from 4.3% to 13%.

We measured urine specific gravity (SG) with a refractometer and used SG to account for individual variation in urine dilution by SG-standardizing urinary triclosan concentrations with the following formula (Duty et al., 2005):

$$P_s = P_i\left(\frac{SG_m - 1}{SG_i - 1}\right)$$

where P_s is the SG-standardized triclosan concentration, P_i is the observed triclosan concentration for the i-th woman, SG_m is the median SG (1.013), and SG_i is the observed SG for the i-th woman. We $\log_{10}$-transformed SG-standardized urinary triclosan concentrations to reduce the influence of extreme observations.

2.3. Child follow-up and neurobehavior assessments

We conducted follow-up on 896 (46.9%) singleton children from all MIREC study sites when they were approximately 3 years old (mean: 3.4 years; range: 2.8–4.2). Among these, 794 had urinary triclosan concentrations measured at about 12 weeks, complete covariate data, and internet questionnaire-based assessments of neurobehavior (Supplemental Table 1; Supplemental Fig. 1). We conducted additional in-person neurobehavioral assessments of 531 (27.8%) children with complete data from the 7 most populous MIREC study sites (Supplemental Table 1; Supplemental Fig. 1). At this visit, trained research personnel measured child anthropometry, collected children's blood and urine, and administered questionnaires to the parents and neurobehavioral assessments to the child. Minor variations in the sample size arose from invalid administration of in-person tests (e.g., inadequate test environment) or incomplete questionnaires (e.g., parent did not complete surveys). Because of limited resources, we were unable to conduct follow-up on all MIREC study participants and only conducted follow-up on children who were in our target age range (~3–4 years) during the follow-up phase of this study. Thus, our follow-up rates reflect this, as well as loss to follow-up.

We assessed child neurobehavior with standardized and age-appropriate tests described below because previous studies report that the traits they measure are associated with prenatal environmental chemical exposures, including chemicals that may disrupt thyroid function (Dietrich et al., 2005; Chen et al., 2014; Vuong et al., 2015). These tests are routinely used in studies of developmental neurotoxicants (Dietrich et al., 2005). Additionally, performance on or behaviors measured by some of these tests have been associated with alterations in maternal thyroid function during pregnancy (Ghassabian et al., 2011; Korevaar et al., 2015). Finally, these tests provide a broad assessment of child neurobehavior, including omnibus features like child cognitive abilities (i.e., IQ), as well as specific features of clinical disorders like attention-deficit/hyperactivity disorder (ADHD) (e.g., externalizing behaviors) and autism spectrum disorder (ASD) (e.g., affect recognition).

Caregivers completed the Behavioral Assessment System for Children-2 (BASC-2) and two subscales from the Behavior Rating Inventory of Executive Function-Preschool (BRIEF-P) using paper-and pencil versions or an internet-based platform. The BASC-2 is a reliable and valid 134-item assessment of children's problem behaviors in home and community settings (Reynolds and Kamphaus, 2002). The BASC-2 include three composite scores that measure children's total (Behavioral Symptom Index [BSI]), internalizing, and externalizing behavior problems, as well as eight clinical subscales (attention, atypicality, aggression, anxiety, depression, hyperactivity, somatization, and withdrawal). Children's executive function were assessed by caregiver report using 27 items from the working memory and plan/organize subscales of the BRIEF-P (Gioia et al., 2003).

During the in-person assessment, children who were between the ages of 36 and 47 months completed the Receptive Vocabulary, Information, Block Design, Object Assembly, and Picture Naming