Prenatal and early-life triclosan and paraben exposure and allergic outcomes

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Background: In cross-sectional studies triclosan and parabens, ubiquitous ingredients in personal care and other products, are associated with allergic disease.

Objectives: We investigated the association between prenatal and early-life triclosan and paraben exposure and childhood allergic disease in a prospective longitudinal study.

Methods: Subjects were enrollees in the Vitamin D Antenatal Asthma Reduction Trial. Triclosan, methyl paraben, and propyl paraben concentrations were quantified in maternal plasma samples pooled from the first and third trimesters and urine samples from children at age 3 or 4 years. Outcomes were parental report of physician-diagnosed asthma or recurrent wheezing and allergic sensitization to food or environmental antigens based on serum specific IgE levels at age 3 years in high-risk children.

Results: The analysis included 467 mother-child pairs. Overall, there were no statistically significant associations of maternal plasma or child urine triclosan or paraben concentrations with asthma or recurrent wheeze or food or environmental sensitization at age 3 years. A trend toward an inverse association between triclosan and paraben exposure and allergic sensitization was observed. There was evidence of effect measure modification by sex, with higher odds of environmental sensitization associated with increasing paraben concentrations in male compared with female subjects.

Conclusions: We did not identify a consistent association between prenatal and early-life triclosan or paraben concentrations and childhood asthma, recurrent wheeze, or allergic sensitization in the overall study population. The differential effects of triclosan or paraben exposure on allergic sensitization by sex observed in this study warrant further exploration. (J Allergy Clin Immunol 2017;■■■:■■■-■■■.)

Key words: *Triclosan, paraben, prenatal sensitization, asthma*

Triclosan and parabens, including methyl, propyl, ethyl, and butyl parabens, are present in a wide variety of personal care and other products.[1,2] Triclosan and parabens have antibacterial properties[3,4] and endocrine-disrupting characteristics.[2,5-10] Exposure to these chemicals is ubiquitous and occurs through multiple routes, including ingestion and absorption from dermal or mucosal applications.[2,11] In the National Health and Nutrition Examination Survey (NHANES), which was administered in the United States by the Centers for Disease Control and Prevention (CDC), triclosan was detectable in urine in almost 75% of participants,[1] and detection frequencies for the parabens were 99.1%, 92.7%, 47%, and 42.4% for urinary methyl, propyl, butyl, and ethyl parabens, respectively.[12]

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Abbreviations used
CDC: US Centers for Disease Control and Prevention
LOD: Limit of detection
NHANES: National Health and Nutrition Examination Survey
VDAART: Vitamin D Antenatal Asthma Reduction Trial

Cross-sectional evidence suggests that triclosan and paraben exposure can increase the risk of allergic disease. Studies using NHANES data have found a positive association between urinary triclosan concentrations and diagnosis with hay fever[13] and allergic sensitization[14,15] in children aged 6 to 18 years and with recent asthma exacerbations among those with asthma aged 6 years and older.[16] A study of 10-year-old Norwegian children also found an association between urinary triclosan concentrations and allergic sensitization and rhinitis.[17] The evidence with regard to paraben exposure has been less consistent. In NHANES participants aged 6 to 18 years, urinary propyl paraben, butyl paraben, and methyl paraben concentrations were positively associated with aeroallergen sensitization.[14,15] However, methyl paraben concentrations were negatively associated with nonatopic asthma or wheeze, and propyl paraben exposure was not associated with food sensitization or atopic asthma or wheeze.[14]

In this study we aimed to clarify the relationship between prenatal and early-life triclosan and paraben exposure and risk of food sensitization, environmental sensitization, and asthma or recurrent wheeze at age 3 years in a *post hoc* analysis of a relatively large and ethnically diverse clinical trial population with high risk of allergic disease. We hypothesized that higher maternal plasma concentrations of triclosan and parabens during pregnancy or higher child urinary concentrations at age 3 or 4 years are associated with increased risk of allergic disease at age 3 years. To our knowledge, this is the first study using prospective longitudinal data to evaluate an effect of prenatal and early-life triclosan and paraben exposure on the risk of allergic disease.

METHODS

Study design

The Vitamin D Antenatal Asthma Reduction Trial (VDAART) has been described previously (NCT00920621).[18,19] Briefly, VDAART is a randomized, double-blind, placebo-controlled trial of vitamin D supplementation during pregnancy to determine whether higher prenatal maternal vitamin D levels prevent asthma and other allergic disease in childhood. Pregnant women aged 18 to 39 years who presented between the estimated gestational ages of 10 and 18 weeks were recruited from clinical sites in Boston, St Louis, and San Diego between October 2009 and July 2011. All participants had a history of either asthma, eczema, or allergic rhinitis or the biologic father of the child had a history of asthma, eczema, or allergic rhinitis. All participants were nonsmokers. Participants were randomized to 4400 IU/d (treatment arm) or 400 IU/d vitamin D (placebo or usual care arm); a subset of participants in both arms of the trial is included in the current analysis. The study protocol was approved by the institutional review boards at each participating institution and at Brigham and Women's Hospital. All women provided written informed consent.

Participating mothers provided blood samples at enrollment during the first trimester (10-18 weeks' gestation) and again in the third trimester (32-38 weeks' gestation). After delivery, children were monitored by telephone every 3 months and in person annually for 3 years and provided a blood sample at age 3 years for measurement of total and serum specific IgE concentrations.

Allergic outcome ascertainment

The outcome of asthma or recurrent wheeze was based on parental report of a physician's diagnosis of asthma or occurrence of recurrent wheeze in the child's first 3 years of life, as previously reported.[19] Serum total and specific IgE levels were measured from plasma collected at the 3-year visit in a subset of VDAART study participants by the Thermo Fisher PIRL Laboratory (Phadia Immunology Reference Laboratory, Portage, Mich). Of all participants in the current analysis (ie, who had available triclosan and parabens concentrations), a subset also had available serum specific IgE concentrations measured, and this subset included both children with and without asthma or recurrent wheeze. Food allergens tested were as follows: egg white, walnut, milk, peanut, soybean, and wheat. Environmental allergens tested were as follows: *Alternaria alternata*, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, German cockroach, cat dander, dog dander, grass pollen mix, and tree pollen mix. Food or environmental sensitization was determined to be present if specific IgE levels to at least 1 of the tested foods or environmental allergens, respectively, was 0.35 kU/L or greater. Food or environmental sensitization was considered missing if specific IgE levels were not available to all food or environmental allergens, respectively.

Evaluation of biomarker concentrations

Triclosan and paraben concentrations were measured in a subset of the VDAART study population. Urine collection from children at age 3 years was initiated after approximately one third of participants had already completed their year 3 visits, and therefore urine samples were not obtained for the entire cohort; in many children urine collection was deferred until age 4 years, when they no longer required diapers. Urine collection kits were provided to participants for home collection to be followed by storage in a refrigerator for less than 24 hours before delivery to the study site.

Maternal plasma samples were collected in EDTA tubes, and children's urinary samples were collected in Starplex Scientific LeakBuster 3 specimen containers (Starplex Scientific, Etobicoke, Ontario, Canada). At study sites, specimens were frozen until shipment to the Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, Massachusetts. There, samples were divided into aliquots and frozen at −80°C until shipped overnight to the CDC. Plasma samples from the first- and third-trimester visits were pooled for each participating mother. All samples were analyzed at the National Center for Environmental Health of the CDC for triclosan, methyl paraben, propyl paraben, butyl paraben, and ethyl paraben by using online, solid-phase extraction, HPLC isotope dilution tandem (mass spectrometry); limits of detection (LODs) were 0.1 ng/mL for propyl paraben and butyl paraben and 1 ng/mL for ethyl paraben, methyl paraben, and triclosan.[20-22] A subset of plasma samples was analyzed for free (eg, unconjugated) concentrations of the biomarkers. The major species of triclosan and parabens were conjugates (data not shown), suggesting that plasma concentrations of these biomarkers reflect true exposures and are not the result of external contamination.[23-25]

Four children had 2 aliquots from the same urinary collection date; triclosan and paraben concentrations were similar and were in the same tertile of chemical concentration for each subject with the exception of 1 subject who had discrepant triclosan concentrations: one in the second tertile (1.8 ng/mL) and another in the third tertile (10.6 ng/mL). For these 4 children, the average of the 2 concentrations for each chemical was used in analysis. One mother had biomarker concentrations available from 2 aliquots, and the average of the 2 concentrations for each biomarker was used in analysis. For analyte concentrations of less than the LOD, a value equal to the LOD divided by the square root of 2 was used for analysis, as previously described.[26] Involvement of the CDC laboratory did not constitute engagement in human subjects research.

Urine specific gravity was determined by using a digital handheld refractometer (Model PAL-10S; Atago, Tokyo, Japan). For analyses using specific gravity-corrected chemical concentrations, the following formula was used:

$$P_c = P[(1.021-1)/(SG-1)],$$

where P_c is the specific gravity-adjusted urinary concentration (in nanograms per milliliter), P is the measured urinary concentration, and SG is the specific gravity of the urine sample. A specific gravity of 1.021 was the median specific