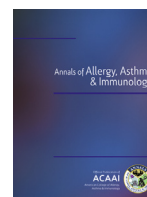




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Letter

Urinary triclosan levels and recent asthma exacerbations

Triclosan is a broad-spectrum antimicrobial chemical with endocrine and immune effects.^{1,2} The primary source of exposure is considered personal care products (eg, toothpaste and hand soap), but multiple potential sources and routes of exposure exist.² Because the airway microbiome may be important in the development or maintenance of asthma,^{3,4} we hypothesized that levels of the antimicrobial chemical triclosan may be associated with asthma prevalence and control.

We previously demonstrated in a cross-sectional study a significantly increased risk of aeroallergen and food sensitization with increasing urinary triclosan levels in US children. Triclosan levels were positively associated with the risk of atopic asthma, although the association did not reach statistical significance.⁵ A cross-sectional Norwegian study also found that triclosan was associated with aeroallergen sensitization and rhinitis but not with asthma.⁶ In a mouse model of asthma, triclosan increased bronchial hyperresponsiveness, total IgE, pulmonary eosinophilia, and interleukin 13.¹ Given these inconsistent findings in humans and the effects of triclosan on respiratory disease in a mouse model, we combined National Health and Nutrition Examination survey (NHANES) data for a 6-year period to increase our power to detect an association between triclosan and asthma prevalence and control.

Data were obtained from the 2005–2006, 2007–2008, and 2009–2010 National Health and Nutrition Examination Survey.⁷ Socio-demographic data, medical condition and smoking questionnaire responses, anthropometry, pulmonary function test results, and urinary triclosan levels were used. Asthma prevalence was determined from the question, “Has a doctor or health professional ever told you that you have asthma?” Participants who answered affirmatively were asked, “Do you still have asthma?” Participants who responded yes to this question were asked, “During the past 12 months have you had an episode of asthma or an asthma attack?” which we used as a measure of asthma control.

In a randomly selected one-third subsample of participants 6 years and older, urinary triclosan was measured by solid-phase extraction coupled online to high-performance liquid chromatography and tandem mass spectrometry (see eMethods and eResults for additional details). All participants underwent spirometry in 2007–2010, unless medically contraindicated. Those 12 years and older answered questions regarding smoking history.

Statistical analyses were performed with Stata statistical software, version 12.0 (StataCorp, College Station, Texas). In all analyses, the primary sampling units, strata, and weights were used to account for the survey design and nonresponse and generate

estimates that are representative of the US noninstitutionalized civilian population. Missing data were considered to be missing at random.

Triclosan had a nonnormal distribution, and triclosan levels were divided into tertiles as performed previously.⁵ The χ^2 test was used to determine whether there were differences in characteristics between participants who varied according to asthma prevalence and control. Linear regression was used to determine whether urinary triclosan levels varied by asthma prevalence and control. Multivariable logistic regression was used to determine the association between urinary triclosan level and asthma prevalence and asthma control. Predicted probabilities for reporting an asthma attack in the last year were derived from a logistic regression model by using log-transformed values of urinary triclosan as a continuous variable.

A total of 31,034 individuals participated in the 3 surveys included in this analysis. A total of 7,303 had complete data for the analysis of urinary triclosan and asthma prevalence, and 639 had complete data for the analysis of urinary triclosan and asthma control. Demographic characteristics of the study participants are given in eTable 1. Log-transformed urinary triclosan levels were higher in individuals with asthma reporting an asthma attack within the last year compared with individuals with asthma not reporting an asthma attack in the last year (1.25 vs 1.05 ng/mL; $P < .03$). After adjusting for age, sex, race, and height, individuals with asthma had significantly lower lung function parameters compared with those who did not (see eMethods and eResults).

In a multivariate model that adjusted for urinary creatinine level, age, race, sex, and poverty-index ratio, urinary triclosan was not associated with asthma prevalence (adjusted odds ratio [OR] for asthma in the third tertile of triclosan compared with the first tertile, 1.14; 95% confidence interval [CI], 0.89–1.46). Among individuals who reported a diagnosis of current asthma, triclosan was positively associated with reporting an asthma attack in the last year (adjusted OR for asthma attack in the third tertile of urinary triclosan, 1.79; 95% CI, 1.01–3.15; and adjusted OR for asthma attack in the second tertile of urinary triclosan, 1.89, 95% CI, 1.15–3.13; P for trend = .05; Fig 1). In a sensitivity analysis of a subset of 372 adults who had additional data, similar point estimates for the association between urinary triclosan and recent asthma attack were identified after adjusting for smoking status and body mass index, as well as covariates mentioned above (see eMethods and eResults for details).

In this large, nationally representative sample, we found that the likelihood of reporting an asthma attack increased with increasing urinary triclosan levels among individuals reporting current asthma. To our knowledge, this is the first epidemiologic report of an association between urinary triclosan levels and asthma control. This finding was consistent with the findings of Anderson et al,¹ which demonstrated that triclosan can augment

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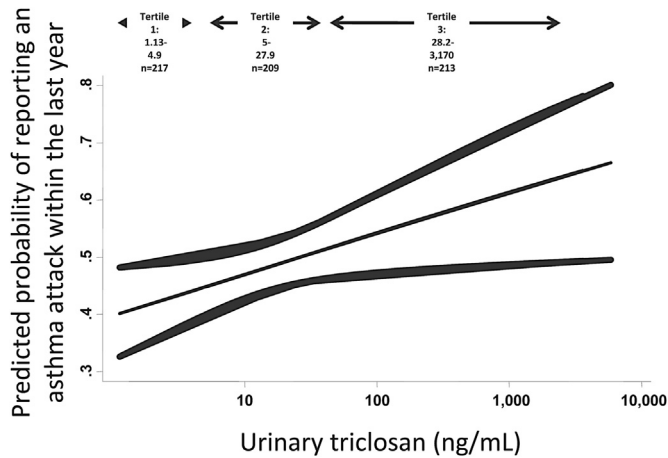


Figure 1. Predicted probability of reporting an asthma attack within the last year (with 95% confidence intervals) by urinary triclosan level. Horizontal bar inset indicates triclosan levels within each tertile of urinary triclosan.

bronchial hyperresponsiveness in a mouse model of asthma. We had previously hypothesized that triclosan was associated with allergic disease because of its antimicrobial effects, potentially altering the human microbiome and subsequent immune development and function. Triclosan may modify the airway microbiome, rendering the airway epithelium more susceptible to pathogens or other environmental perturbations. This should be evaluated in future studies.

Because of the cross-sectional design of our study, several limitations exist. Triclosan has a short half-life (<24 hours), and measured values are thought to reflect recent use.⁸ Thus, there is a potential for misclassification of study participants by triclosan levels. However, triclosan measured in the urine has good correlation among samples collected weeks to months apart (intraclass correlation coefficient, >0.4), suggesting frequent exposures despite a short half-life.⁹ Further, we expect this potential bias to be nondifferential with respect to the outcome and therefore would attenuate, not magnify, associations. In addition, patients with poorly controlled asthma may be more likely to use triclosan-containing hand soap or wash their hands more frequently than those with more controlled asthma, and we were unable to control for this with our observational study design. Confounding caused by topical use of triclosan-containing products is unlikely to solely underlie our findings, however, because only a small amount of triclosan is absorbed cutaneously (5%–6%) compared with orally (>80%; eg, from toothpaste).^{8,10} Overall, our findings are intriguing because there are consistent murine observations and they suggest a potential role for commonly used antimicrobial chemicals in asthma control.

We did not identify an association between triclosan and asthma prevalence in the general population. This may have been limited by our ability to stratify results by atopic disease status because specific IgE data are not available in all NHANES survey years studied. In our previous study, which was limited to the 2005–2006 NHANES survey, which included specific IgE

measurements, there was a positive but nonsignificant association between triclosan levels and atopic asthma defined by a history of physician-diagnosed asthma and detectible aeroallergen specific IgE.⁵

In summary, in this large, nationally representative sample of more than 600 asthmatic patients, we found that triclosan exposure was associated with a more than 70% increased risk of reporting an asthma exacerbation in the last year. Exposure to triclosan may directly lead to asthma exacerbations, or elevated triclosan levels may be a marker for poor asthma control. Future prospective studies are needed to determine whether triclosan exposure has a role in the development and maintenance of allergy and allergic respiratory disease.

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eMethods

Triclosan Assay

The detection limit in 100 μL of urine was 2.3 ng/mL.¹ For values less than the limit of detection, a value of the detection limit divided by the square root of 2 was used.

Pulmonary Function Testing

Spirometry was performed in the 2007–2008 and 2009–2010 National Health and Nutrition Examination Survey.¹ Individuals 6 to 79 years old were eligible for the spirometry portion of the examination. Individuals were excluded if they reported current chest pain or a physical problem with forceful expiration; taking supplemental oxygen, recent surgery of the eye, chest, or the abdomen; or a recent myocardial infarction, stroke, tuberculosis exposure, or coughing up blood. Adults with a personal history of detached retina or a collapsed lung and children with painful ear infections were also excluded.

Testing procedures followed guidelines of the American Thoracic Society (ATS).² Spirometers were Ohio 822/827 dry-rolling seal volume spirometers, reconditioned for use in the current survey. The overall goal was for the participant to achieve 3 acceptable exhalation maneuvers by ATS criteria in which the 2 highest values for the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV₁) (each taken from an acceptable forced expiratory maneuver) revealed minimal variability (ie, the 2 largest FVC values taken from 2 acceptable curves should agree within 150 mL and similarly for the 2 largest values for the FEV₁).

Smoking History

Participants 12 years and older provided a smoking history. Participants were categorized as never, former, and current smokers. Former smokers reported smoking more than 100 cigarettes in their lifetime but no current use, whereas current smokers reported current use. Never smokers denied smoking more than 100 cigarettes in their lifetime.

Body Measurements

Height and weight were obtained on all study participants by trained health technicians. Body mass index (BMI) was

calculated as weight in kilograms divided by the square of height in meters.

Statistical Analysis

Linear regression was used to compare lung function parameters (FEV₁, FVC, and FEV₁/FVC ratio) between participants who did and did not report a history of asthma and between participants with asthma who did and did not report a history of an asthma attack in the last year. Covariates included in the model were race, age, height squared, and sex.

In a sensitivity analysis, logistic regression was used to determine the association between urinary triclosan levels and recent asthma attacks, adjusting for age, race, sex, urinary creatinine, poverty index ratio, BMI, and smoking status. Fewer participants had complete data for this analysis in part because smoking status was only collected in those 12 years and older and in part because of missing smoking data even for those older than 12 years. Because of the small sample size, this analysis was performed without using survey weights, strata, and sampling units.

eResults

Pulmonary Function of the Study Participants

Compared with participants not reporting a history of asthma, those reporting a history of asthma had a significantly lower FEV₁ (–132 mL; 95% confidence interval [CI], –183 to –80 mL), FVC (–74 mL; 95% CI, –136 to –11 mL), and FEV₁/FVC ratio (–0.024; 95% CI, –0.029 to –0.019) in models adjusted for age, height squared, sex, and race (n = 4,503). Compared with participants reporting a history of asthma and no exacerbation within the last year, those with asthma reporting a recent exacerbation had similar FEV₁ (mean difference, 99 mL; 95% CI, –47 to 246 mL), FVC (mean difference, 97 mL; 95% CI, –73 to 268 mL), and FEV₁/FVC ratio (mean difference, 0.006; 95% CI, –0.11 to 0.23) in adjusted models (n = 467).

Sensitivity Analysis of Triclosan Levels and Recent Asthma Attacks

After adjusting for age, race, sex, poverty index ratio, urinary creatinine, smoking status, and BMI, among participants reporting

eTable 1

Sociodemographic characteristics of NHANES participants with urinary triclosan levels and information on asthma history^a

Characteristic	Physician-diagnosed asthma (n = 7,303) ^b			Asthma attack in last year (n = 639) ^c		
	No (n = 6,236)	Yes (n = 1,067)	P value	No (n = 327)	Yes (n = 312)	P value
Sex			.10			.56
Male	50	46		41	38	
Female	50	54		59	62	
Age, y			.003			.08
6–18	19	24		23	31	
≥19	81	76		77	69	
Ethnicity			.001			.47
White	69	67		68	67	
African American	11	16		17	18	
Hispanic	14	11		12	10	
Other	6	6		3	5	
Poverty Index Ratio			.002			.06
<1	15	19		19	25	
≥1	85	81		81	75	
Detectable urinary triclosan	80	81	.52	76	83	.07
Log urinary triclosan level, mean (95% CI), ng/mL	1.17 (1.14–1.21)	1.19 (1.11–1.27)	.55	1.05 (0.92–1.17)	1.25 (1.10–1.39)	<.03

Abbreviations: CI, confidence interval; NHANES, National Health and Nutrition Examination Survey.

^aData are presented as percentage of study participants unless otherwise indicated.

^bAsked of all participants.

^cAsked of participants reporting current asthma.

a diagnosis of current asthma, triclosan was positively associated with reporting an asthma attack in the last year (adjusted odds ratio for asthma attack in third tertile of urinary triclosan, 2.14; 95% CI, 1.23–3.71; and adjusted OR for asthma attack in second tertile of urinary triclosan, 1.88; 95% CI, 1.09–3.21; *P* for trend <.01; *n* = 372).

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