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Relationship between urine dichlorophenol levels and asthma morbidity

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ABSTRACT

Background: Chlorinated phenols are associated with atopic conditions, but it is not known whether they are associated with wheeze or asthma and whether atopy is involved in these associations.

Objectives: To test the association between urine levels of 2 dichlorophenols (2,4- and 2,5-dichlorophenols) and asthma morbidity in atopic and nonatopic wheezers and between total serum immunoglobulin E (IgE) levels.

Methods: Data from a sample of 2,125 participants at least 6 years old from the US National Health and Nutrition Examination Survey 2005 to 2006 were analyzed. Asthma morbidity data were available for those participants who reported wheezing in the past year ("wheezers"; n = 250). This subsample was categorized as atopic or nonatopic.

Results: Atopic wheezers with higher 2,5-dichlorophenol levels were more frequently diagnosed with asthma by a physician (odds ratio [OR] 4.7 for highest vs lowest tertile, $P < .001$), required more prescriptions for asthma medications (OR 2.2, $P = .046$), and reported more exercise-induced wheezing (OR 5.8, $P = .045$) than atopic wheezers with low dichlorophenol levels. Atopic wheezers with higher 2,5- or 2,4-dichlorophenol levels also were more likely to miss work or school because of wheezing (OR 10.0, $P < .001$; OR 11.4, $P < .01$, respectively). In contrast, in nonatopic wheezers, there were no significant associations between dichlorophenol levels and asthma morbidity measurements. The 2 dichlorophenol metabolites were positively associated with increased serum IgE levels in the larger study sample.

Conclusion: These findings indicate that in patients with atopy and a history of wheezing, asthma morbidity is associated with high urinary dichlorophenol levels. Increased urine dichlorophenol levels are associated with higher total serum IgE.

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Introduction

The Westernized lifestyle has been associated with a higher prevalence of allergies and asthma and this is believed to be related at least in part to decreased microbial exposure.^{1,2} This Westernized lifestyle also has been associated with widespread exposure to pesticides. The US Environmental Protection Agency reported finding 800 active pesticide ingredients in approximately 21,000

different consumer products.³ Pesticide exposure has been associated with asthma and rhinitis.^{4–7}

One specific group of organochlorine pesticides, dichlorophenols, are compounds with potent bactericidal effects.⁸ They are typically used as herbicides, fungicides, and disinfectants^{9–11} and can be found in contaminated water, air, and pesticide-treated crops.^{9–12} In addition, chlorine-based cleaning agents can react with wood and paper, leading to the generation of dichlorophenols in packing materials, containers, and storage boxes,¹³ resulting in the contamination of milk, cocoa powder, fruit juices, and dried fruits.^{9,13–15}

Recent studies have indicated that organochlorine compounds might play a role in the increased incidence of atopic diseases because of their immunomodulatory effects.¹⁶ Previous research has shown that exposure to dichlorodiphenyl ethylene is linked to a higher total immunoglobulin E (IgE) level and to an increased risk of asthma in children.^{16,17} Higher dichlorophenol levels in urine have been associated with increased allergic sensitization to foods.¹⁸ In addition, previous reports have suggested that certain

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organochlorines preferentially induce the production in vitro of T-helper type 2 cytokines associated with increased allergic reactivity, such as interleukin-4, and suppress the production of T-helper type 1 cytokines that tend to block allergic reactivity, such as interferon- γ , interleukin-2, and interleukin-10.^{19,20}

In addition to these immunomodulatory effects, dichlorophenols are upper and lower airway irritants.²¹ Dichlorophenols are metabolites of 2,4-dichlorophenoxyacetic acid and 1,4-dichlorobenzene. These latter 2 compounds are used in the production of insecticides and herbicides and exposure to them can occur through contaminated air. Breathing vapors of 1,4-dichlorobenzene has been associated with decreased lung function in adults and higher odds for asthma in children.^{22,23} However, there has been no particular association between atopy and 1,4-dichlorobenzenes in children with asthma.²³ In addition, repeated exposure to chlorine-containing irritant gases has been reported to increase the risk of adult-onset asthma and wheeze regardless of history of hay fever (as a marker of atopy).²⁴

Although these associations among organochlorines, lung function, asthma, and atopy have been shown, less is known about the effect of these compounds on different forms of asthma and wheeze. Because asthma and wheeze have distinct atopic and nonatopic forms,²⁵ this study investigated whether dichlorophenols were associated with wheezing or asthma and, if so, whether atopy played a role in these associations.

Methods

Study Population and Data Collection

The authors analyzed the association among urine levels of 2 dichlorophenols (2,5-dichlorophenol and 2,4-dichlorophenol), self-reported wheezing, self-reported asthma as diagnosed by a physician, asthma morbidity, and total serum IgE level in the sample examined in 2005 to 2006 by the US National Health and Nutrition Examination Survey (NHANES 2005–2006). The NHANES is a database funded by the US Centers for Disease Control and Prevention that is intended to assess the health and nutritional status of adults and children in the United States. All NHANES data are publically available and can be found at <http://www.cdc.gov/nchs/nhanes.htm>. The NHANES has a complex, multistage, clustered, and stratified probability sample design. The sample for the survey was selected to represent the US civilian noninstitutionalized population of all ages. Persons 60 years and older, African Americans, and Hispanics were oversampled to produce reliable statistics.

Dichlorophenols were measured in urine of a randomly chosen subsample of NHANES 2005–2006 participants at least 6 years of age. Details of the laboratory protocol and measurements can be found on the NHANES Web site.²⁶ Dichlorophenol levels were measured using solid-phase extraction coupled to high-performance liquid chromatography and tandem mass spectrometry.²⁶ The detection level for 2,4- and 2,5-dichlorophenols was 0.14 $\mu\text{g/L}$. Trichlorophenols or *O*-phenylphenol (these chemicals were a part of the pesticide group in NHANES 2005–2006) were not included in these analyses because most observations were below the lower limit of detection for these chemicals.²⁷

The population in whom urinary dichlorophenols were measured was divided into 3 groups: (1) no self-reported wheezing in the past year (nonwheezers), (2) self-reported wheezing in the past year (atopic; atopic wheezers); and (3) self-reported wheezing in the past year (nonatopic; nonatopic wheezers).

Wheezing in the past year was defined by the answer to the following question: In the past 12 months (have you/has study) participant had wheezing or whistling in (your/his/her) chest? Participants who reported wheezing or whistling in the chest in the past 12 months were asked to answer questions about wheezing-related problems during the preceding 12 months. They were

questioned about medication intake for wheezing, missed work or school because of wheezing, and exercise-induced wheezing.^{28,29} A dichotomous variable was created that characterized participants as having no days missed from work or school because of wheezing or at least 1 day missed from work or school because of wheezing.

The exact questions that were used in the NHANES questionnaires and that were included in this study are listed in eTable 1. There were additional questions on asthma and wheezing in the database (eg, regarding asthma attacks in past year, emergency room visits in past year, and still having asthma); however, there were only a limited number (<50%) of responses to these questions in the subsample and therefore a meaningful analysis of those questions was not possible.

The atopic status of participants also was assessed. Participants with atopy were defined as having at least 1 positive allergen-specific IgE level (≥ 0.35 kU/L) to the environmental and/or food allergens measured in the NHANES 2005–2006 (allergen-specific IgE was measured using the ImmunoCAP 1000 System [Pharmacia Diagnostics Kalamazoo, Michigan]: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat, dog, German cockroach, *Alternaria alternata*, short ragweed, ryegrass, Bermuda grass, white oak, birch, *Aspergillus fumigatus*, Russian thistle, mouse, rat, shrimp, egg, milk, or peanut). Participants without atopy had no sensitizations to any of these allergens.

In an exploratory analysis, the present investigation of asthma-related morbidity was performed in participants with self-reported physician-diagnosed asthma defined by the answer to the question: Has a physician or other health professional ever said that (you have/she/he/study participant has) asthma?

Only participants with nonmissing covariables were studied. Those with missing covariable constituted 19.4%.

Statistical Analysis

Associations between dichlorophenols and physician-diagnosed asthma and asthma morbidities, such as prescriptions for medications for wheezing, wheezing during exercise, and days missed from work or school because of wheezing, were analyzed in logistic regression models. The association between urinary dichlorophenols and total IgE was analyzed in adjusted linear regression models (after logarithmic transformation of the 2 continuous variables). All analyses were performed using sample weights to account for the complex survey design (including oversampling), survey nonresponse, and poststratification, thus providing nationally representative estimates. All models were adjusted for urine creatinine and potential confounders: age, sex, race (non-Hispanic white, non-Hispanic black, Hispanic, and other), atopic status of participants, and poverty–income ratio (a ratio <1 defined low socioeconomic status).

Dichlorophenol levels were analyzed as tertiles. Interactions between dichlorophenol levels and age, sex, and atopy were tested by including a multiplicative term in the model. In addition, the correlation between urinary concentration of the 2 dichlorophenols and between dichlorophenols and triclosan, another chlorinated phenol measured in the NHANES, were analyzed because the latter compound has been associated with allergic sensitization and because 2,4-dichlorophenol is a byproduct of triclosan.^{30,31} All statistical analyses were performed with STATA 11.2 (StataCorp, College Station, Texas). *P* values less than .05 were considered significant for all analyses (including interaction effects). The study was classified as exempt by the Albert Einstein College of Medicine institutional review board.

Results

Demographic Characteristics of Study Population

Of the NHANES participants at least 6 years of age 2,125 had data on dichlorophenol levels and all relevant covariables of interest to

Table 1
Characteristics of study participants^a by presence of wheezing

Characteristic	Nonwheezers (n = 1,852)	Atopic ^b wheezers (n = 156)	Nonatopic ^b wheezers (n = 94)	P value
Age (y), mean (SE)	38.9 (1.1)	37.1 (2.4)	39.9 (1.3)	<.001
Male sex, % (SE)	44.9 (0.04)	55.7 (0.07)	48.9 (0.04)	.3
Race/ethnicity, % (SE)				.01
Non-Hispanic white	70.3 (0.03)	72.1 (0.05)	80.4 (0.04)	
Non-Hispanic black	11.9 (0.2)	13.8 (0.03)	4.9 (0.02)	
Mexican American	9.7 (0.01)	5.1 (0.01)	3.3 (0.01)	
Other	8.2 (0.01)	9.0 (0.03)	11.4 (0.02)	
Low SES ^c , % (SE)	12.6 (0.01)	15.6 (0.04)	10.9 (0.03)	.6
Asthma ^d , % (SE)	7.5 (0.01)	48.7 (0.08)	36.2 (0.05)	<.001
Atopy ^b , % (SE)	43.2 (0.01)	100 (0)	—	<.001
2,5-Dichlorophenol concentration in urine (μg/L), geometric mean (95% CI)	33.1 (27.4–39.9)	30.0 (19.2–46.8)	25.6 (16.0–41.1)	<.001
Lower tertile	1.9 (1.6–2.3)	2.4 (1.8–3.2)	1.3 (0.7–2.4)	.1
Middle tertile	12.9 (12.2–13.7)	14.0 (11.6–16.9)	11.5 (9.2–14.5)	<.001
Upper tertile	142.6 (112.1–181.4)	134.0 (74.6–240.4)	115.8 (76.6–175.0)	<.001
2,4-Dichlorophenol concentration in urine (μg/L), geometric mean (95% CI)	2.4 (2.1–2.8)	2.4 (1.7–3.4)	2.2 (1.5–3.1)	<.01
Lower tertile	0.30 (0.28–0.34)	0.35 (0.28–0.45)	0.27 (0.22–0.34)	<.001
Middle tertile	1.18 (1.1–1.2)	1.22 (1.1–1.4)	1.20 (1.1–1.3)	<.01
Upper tertile	6.0 (4.8–7.6)	5.1 (3.3–8.1)	6.1 (5.3–7.0)	<.001
Medications for wheezing ^e , % (SE)	—	52.4 (0.07)	56.0 (0.05)	.7
Wheezing during exercise ^f , % (SE)	—	48.5 (0.05)	52.4 (0.06)	.7
Missing work or school because of wheezing ^g , % (SE)	—	26.8 (0.04)	16.8 (0.05)	.2

Abbreviations: CI, confidence interval; SES, socioeconomic class.

^aAll estimates are weighted to the sampling weights.

^bAtopy was defined as the presence of an allergen-specific IgE level of at least 0.35 kU/L to at least 1 environmental and/or food allergen.

^cPercentage of participants with a poverty–income ratio lower than 1.0.

^dAsthma was defined by the answer to the question: Has a physician or other health professional ever told that (you have/she/he/survey participant has) asthma?

^eIn the past 12 months, (have you/has study participant) taken medication, prescribed by a physician, for wheezing or whistling?

^fIn the past 12 months has (your/study participant's) chest sounded wheezy during or after exercise or physical activity?

^gDuring the past 12 months, did (you/study participant) miss any days of work or school because of wheezing or whistling?

the authors. Of these 2,125 participants, 1,852 (87.2%) reported no wheezing in the past year. Two hundred seventy-three participants (12.8%) reported wheezing in the preceding 12 months and were offered questionnaires to fill out on wheezing-related problems. Two hundred fifty participants completed the questionnaires, of which 120 (48%) had been given a diagnosis of asthma by a

physician. The 2,5-dichlorophenol was detected in the urine of 2,098 participants (98.7%) and 2,4-dichlorophenol was detected in the urine of 1,941 participants (91.3%). Participants' characteristics are presented in Table 1.

Atopic wheezers were significantly younger than nonwheezers and nonatopic wheezers ($P < .001$) and there were fewer Mexican

Table 2
Odds ratio^a for 2,5-dichlorophenol levels and asthma morbidity in wheezers stratified by atopic status

Outcome	Atopic ^b wheezers (n = 156)		Nonatopic ^b wheezers (n = 94)	
	OR (95% CI)	P for trend	OR (95% CI)	P for trend
Asthma, diagnosed by a physician ^c		<.001 ^g		.9
Lower tertile	1.0		1.0	
Middle tertile	2.9 (1.2–7.2) ^g		1.0 (0.3–4.1)	
Upper tertile	4.7 (1.8–12.1) ^g		1.0 (0.1–9.8)	
Medications for wheezing ^d		.046 ^g		.3
Lower tertile	1.0		1.0	
Middle tertile	1.5 (0.8–3.0)		0.7 (0.2–2.8)	
Upper tertile	2.2 (0.9–5.1)		2.9 (0.7–12.4)	
Missing work or school because of wheezing ^e		<.001 ^g		.9
Lower tertile	1.0		1.0	
Middle tertile	2.0 (0.6–6.5)		0.7 (0.2–2.6)	
Upper tertile	10.0 (4.6–21.6) ^g		1.4 (0.3–5.8)	
Wheezing during exercise ^f		.045 ^g		.9
Lower tertile	1.0		1.0	
Middle tertile	6.1 (2.1–18.0) ^g		1.1 (0.3–4.0)	
Upper tertile	5.8 (0.97–34.6)		0.8 (0.2–3.4)	

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAll estimates are weighted to the sampling weights. Results were adjusted for sample weights, urine creatinine, age, sex, race, and poverty–income ratio.

^bAtopy was defined as the presence of an allergen-specific IgE level of at least 0.35 kU/L to at least 1 environmental and/or food allergen.

^cAsthma was defined by the answer to the question: Has a physician or other health professional ever told that (you have/she/he/survey participant has) asthma?

^dIn the past 12 months, (have you/has study participant) taken medication, prescribed by a physician, for wheezing or whistling?

^eDuring the past 12 months, did (you/study participant) miss any days of work or school because of wheezing or whistling?

^fIn the past 12 months has (your/study participant's) chest sounded wheezy during or after exercise or physical activity?

^gValues are statistically significant.

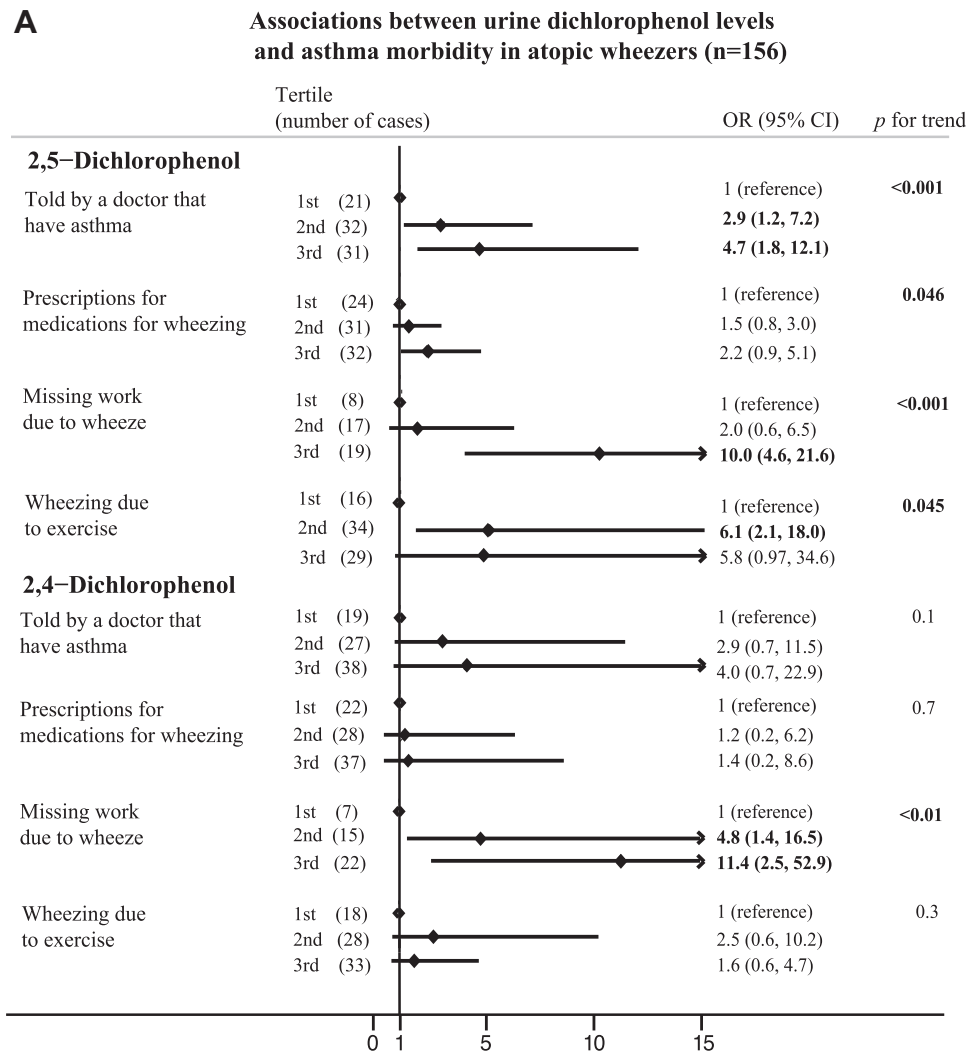


Figure 1. Relation between asthma morbidity and urine 2,5- and 2,4-dichlorophenol levels in (A) atopic and (B) nonatopic wheezers. Adjusted for sample weights, urine creatinine, age, sex, race, and poverty–income ratio. CI, confidence interval; OR, odds ratio.

Americans among the wheezers ($P < .01$). Mean dichlorophenol levels were lower in the group of nonatopic wheezers ($P < .001$ for 2,5-dichlorophenol level, $P < .01$ for 2,4-dichlorophenol level).

Of the 2,125 participants, 280 (13.2%) reported having asthma diagnosed by a physician. One hundred thirty of them reported wheezing in the preceding 12 months and 120 filled out questionnaires on wheezing-related problems.

Association between Urine Dichlorophenol Levels and Asthma Morbidity in Wheezers

On multivariable analysis, higher urinary 2,5-dichlorophenol levels in the atopic wheezers were strongly associated with more asthma morbidity. These participants were more likely to have physician-diagnosed asthma (odds ratio [OR] 4.7 for highest vs lowest tertile of 2,5-dichlorophenol, P for trend $< .001$), more likely to require prescriptions for medications for wheezing (OR 2.2 for highest vs lowest tertile, P for trend = .046), more likely to miss work or school because of wheezing (OR 10.0 for highest vs lowest tertile, P for trend $< .001$), and more likely to wheeze with exercise (OR 5.8 for highest vs lowest tertile, P for trend = .045; Table 2, Fig 1A). In the atopic group, 2,4-dichlorophenol also was associated with missing work or school because of wheezing (OR 11.4 for highest vs lowest tertile, P for trend $< .01$; Table 3, Fig 1A).

There was a significant interaction between atopy and the presence of 2,5-dichlorophenols in urine ($P < .02$ for interaction term), with atopic wheezers being more likely to take days off work or school because of wheezing.

In contrast, in nonatopic wheezers, there were no significant associations with any of the asthma morbidity outcomes (P for trend $> .05$ for all comparisons; Tables 2 and 3, Fig 1B).

The predicted probability of asthma and wheezing-related problems for participants with atopy and those without atopy based on 2,5-dichlorophenol or 2,4-dichlorophenol levels is shown in Figure 2.

Exploratory Analysis of Association between Urine Dichlorophenol Levels and Asthma Morbidity in Participants with Asthma

On multivariable analysis, participants with atopy and asthma were more likely to miss work or school because of wheezing (OR 92.0 for highest vs lowest tertile, 95% confidence interval 13.6–619.0, P for trend $< .01$), whereas there was no significant association with missing work or school in those without atopy and with asthma ($P = .8$; data not shown). There were no significant associations with medication use or wheezing during exercise in participants with asthma and atopy vs without atopy (data not shown). However, because of the small number of participants with

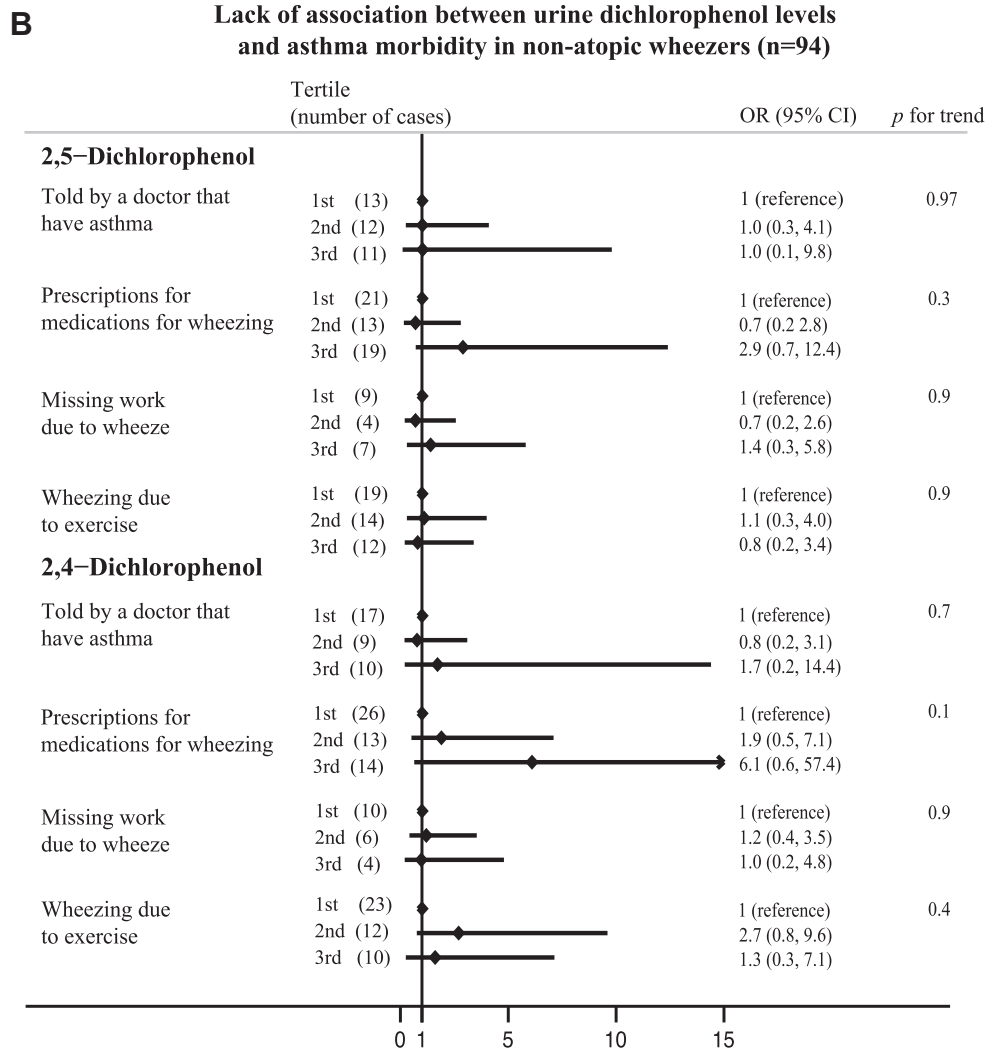


Figure 1. (continued).

asthma who responded to the questions on medication use and wheezing during exercise, a meaningful analysis of associations with these outcomes was not possible because the models became “unstable” and several covariables were omitted from the models.

Association between Dichlorophenol Levels and Total Serum IgE

Because asthma morbidity was positively associated with the presence of dichlorophenols only in atopic wheezers and the presence of asthma has been linked to total serum IgE levels,³² the association between dichlorophenol levels and total serum IgE was examined. In multivariable linear regression analyses conducted on the entire sample ($n = 2,125$), a positive association was found between total serum IgE with 2,5- and 2,4-dichlorophenol levels (β coefficients for association were 0.047 and 0.055, respectively; $P = .03$ for either association; Fig 3).

Correlation between 2,5- and 2,4-Dichlorophenol Levels and Triclosan

Concentrations between urine levels of 2,5- and 2,4-dichlorophenols in the entire study population ($n = 2,125$) were highly correlated (Pearson correlation coefficient [R] = 0.87, $P < .001$; data not shown). Because 2,4-dichlorophenol is a byproduct of triclosan (another chlorophenol-based chemical with antibacterial properties), the correlation between dichlorophenol levels

and triclosan was analyzed. The correlation between 2,5- and 2,4-dichlorophenol levels and triclosan was poor ($R = 0.06$, $P < .01$; $R = 0.28$, $P < .001$, respectively; data not shown).

Discussion

The present results indicate that atopic wheezers with urinary dichlorophenol levels in the upper tertile are more likely to have physician-diagnosed asthma, to miss days from work or school because of wheezing, to require medications for wheezing, or to have wheezing with exercise. There were no significant associations with these outcomes in nonatopic wheezers. In addition, a positive direct association was found between 2,4- and 2,5-dichlorophenol and total serum IgE levels. Participants with atopy, asthma, and urinary dichlorophenol levels in the upper tertile also were more likely to miss work or school because of wheezing.

These findings are consistent with several previous reports on atopic disorders and pesticides. Exposure to several insecticides and herbicides has been associated with the presence of allergic rhinitis and atopic asthma,^{4,5,7} and dichlorophenols have been associated with increased allergic sensitization to foods.¹⁸

The mechanisms by which dichlorophenols might increase atopy and asthma are not well understood. Previous reports have suggested that organochlorine compounds have direct immunomodulatory effects and are associated with decreased

Table 3Odds ratio^a for 2,4-dichlorophenol levels and asthma morbidity in wheezers stratified by atopic status

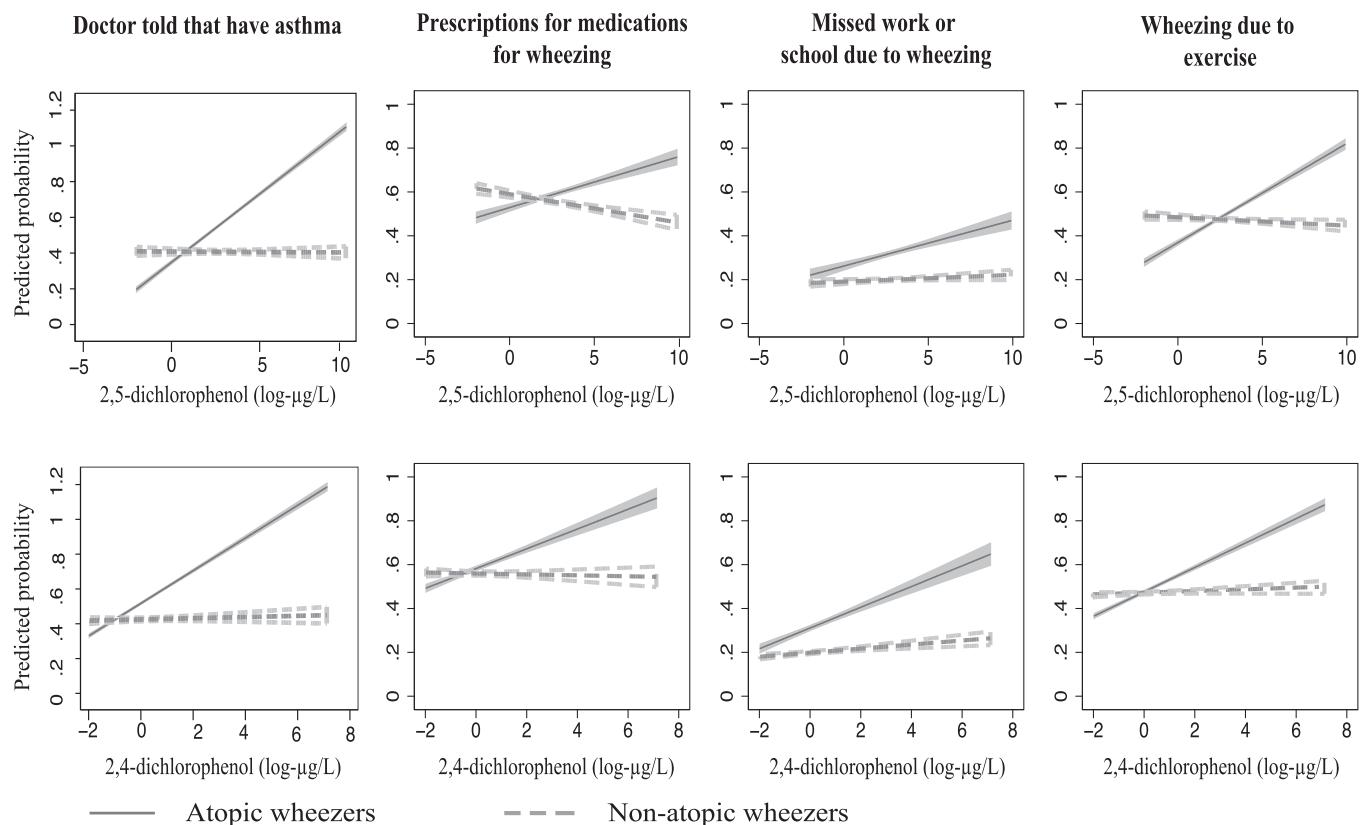
Outcome	Atopic ^b wheezers (n = 156)		Nonatopic ^b wheezers (n = 94)	
	OR (95% CI)	P for trend	OR (95% CI)	P for trend
Asthma, diagnosed by a physician ^c		.1		.7
Lower tertile	1.0		1.0	
Middle tertile	2.9 (0.7–11.4)		0.8 (0.2–3.1)	
Upper tertile	4.0 (0.7–22.9)		1.7 (0.2–14.4)	
Medications for wheezing ^d		.7		.1
Lower tertile	1.0		1.0	
Middle tertile	1.2 (0.2–6.2)		1.9 (0.5–7.1)	
Upper tertile	1.4 (0.2–8.6)		6.1 (0.6–57.4)	
Missing work or school because of wheezing ^e		<.01 ^g		.9
Lower tertile	1.0		1.0	
Middle tertile	4.8 (1.4–16.5) ^g		1.2 (0.4–3.5)	
Upper tertile	11.4 (2.5–52.9) ^g		1.0 (0.2–4.8)	
Wheezing during exercise ^f		.3		.4
Lower tertile	1.0		1.0	
Middle tertile	2.5 (0.6–10.2)		2.7 (0.8–9.6)	
Upper tertile	1.7 (0.6–4.6)		1.3 (0.2–7.1)	

Abbreviations: CI, confidence interval; OR, odds ratio.

^aAll estimates are weighted to the sampling weights. Results were adjusted for sample weights, urine creatinine, age, sex, race, and poverty–income ratio.^bAtopy was defined as the presence of an allergen-specific IgE level of at least 0.35 kU/L to at least 1 environmental and/or food allergen.^cAsthma was defined by the answer to the question: Has a physician or other health professional ever told that (you have/she/he/survey participant has) asthma?^dIn the past 12 months, (have you/has study participant) taken medication, prescribed by a physician, for wheezing or whistling?^eDuring the past 12 months, did (you/study participant) miss any days of work or school because of wheezing or whistling?^fIn the past 12 months has (your/study participant's) chest sounded wheezy during or after exercise or physical activity?^gValues are statistically significant.

interferon- γ production, increased levels of interleukin-4, and higher serum IgE levels, possibly leading to the increased incidence of atopic diseases in children and in adults.^{16,17,19,20,33} The present finding of a positive association between urine dichlorophenol levels and total serum IgE levels supports this hypothesis. In

addition, dichlorophenols might be associated with atopy indirectly because of their antimicrobial properties⁸ and possibly through a change in microbiome. By analogy, a chlorine-containing bactericidal agent has been shown to suppress the diversity of intestinal flora in animals.³⁴

**Figure 2.** Predicted probabilities of asthma morbidity by urinary dichlorophenol levels (logarithmically transformed) with 95% confidence intervals.

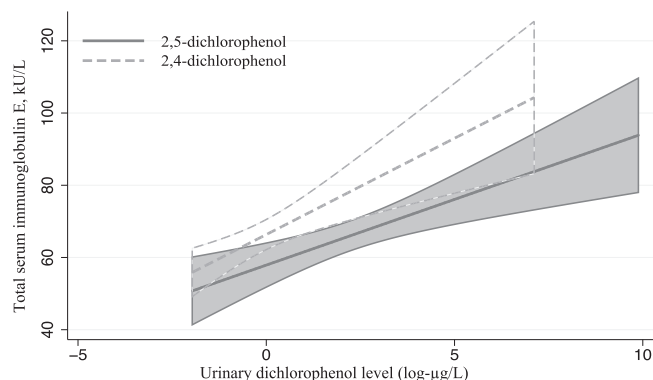


Figure 3. Positive associations between urine dichlorophenol levels and total serum IgE in study population ($n = 2,125$) with 95% confidence intervals ($P = .03$ for either association). Adjusted for sample weights, urine creatinine, age, sex, race, and poverty–income ratio.

Previous reports have associated exposure to triclosan, a chlorophenol-based chemical with antibacterial properties used in toothpaste and hand sanitizers, with allergic sensitization and hay fever but not with atopic asthma or atopic wheeze.^{30,31} Interestingly, 2,4-dichlorophenol is a byproduct of triclosan in chlorinated water and the 2 compounds seem to coexist in urine.^{35,36} The authors found a high correlation between the 2 dichlorophenol metabolites, suggesting they might share a common source of exposure and/or the same metabolic path. However, there was a low correlation between triclosan and dichlorophenols, implying that triclosan is probably not the main source of exposure to dichlorophenols in the study population. This presumption is supported by a recent study on dichlorophenols in the US population.³⁷ In addition, dichlorophenols seem to be different from triclosan in its effect on IgE levels. Although triclosan has been reported to be not significantly associated with total serum IgE levels,³⁰ the authors found that dichlorophenols were positively associated with total serum IgE levels in the entire study sample. Atopy has been independently associated with asthma and wheezing, and the prevalence of asthma has been found to increase with total serum IgE levels in patients with atopy.³⁸ Therefore, dichlorophenols might be associated with asthma and asthma morbidity in atopic wheezers through their association with total serum IgE levels. The reasons for the difference in relations among triclosan, dichlorophenols, and total serum IgE are not known, but this difference is interesting and certainly merits further exploration.

Dichlorophenols have a relatively short half-life in the human body and exposure to them varies over time.³⁹ Thus, an estimation of long-term exposure to dichlorophenols based on a 1-time urine sample is limited. However, most of the present study outcomes were symptoms reported within past 12 months and they are likely less affected by the daily fluctuations in exposure to dichlorophenols. In addition, exposure to 2,5-dichlorophenol has been reported to have less temporal variability and to be more consistent over time than other phenols.⁴⁰ It is reasonable to question whether serum IgE level is affected over time. Little is known about how environmental exposures can affect its variability. A de novo formation of food-specific IgE in adults has been reported after only 3 months of exposure to antacid treatments, such as H₂ receptor blockers or proton-pump inhibitors. In addition, total serum IgE levels nearly tripled after this treatment.⁴¹ These findings persisted at least several months after the treatment with antacid agents was stopped. Thus, it is plausible that other environmental exposures could affect serum IgE in a similar fashion.

Dichlorophenols have other associations with human health. For example, 2,4- and 2,5-dichlorophenol levels in urine have been found to be higher in obese adults than in nonobese adults.⁴²

The present study has several limitations: its cross-sectional design, exclusion of children younger than 6 years in whom dichlorophenols were not measured in the NHANES 2005–2006 dataset, and the relatively small sample in this analysis (resulting in wide confidence intervals). Because asthma in school-age children and adolescents commonly starts during the preschool years, not having dichlorophenols measured in children younger than 6 years is a major limitation to the present analysis. All data on wheezing-related problems were self-reported and thus possibly affected by recall bias. Owing to the small number of participants with asthma who responded to the questionnaires in this sample, only a limited exploratory analysis of the associations with asthma morbidity was possible. Such analysis could be a potential future research topic. Because this study is based on a cross-sectional analysis, there is also a possible reverse causality in the relation between atopy and dichlorophenols. Dichlorophenols are found in toilet deodorizers, moth balls, insecticides, and herbicides and are used in daily life.^{10,11} Individuals with atopy might be more likely to be exposed to dichlorophenols because of their increased use of chlorine-containing pesticides and cleaning products in an attempt to maintain a less allergenic environment.

Despite these limitations, the findings from this study highlight the unique association between urine dichlorophenol levels and wheezing in a nationally representative sample of participants.

In summary, these findings suggest that higher levels of dichlorophenols in urine contribute to greater asthma morbidity in atopic wheezers and atopic asthmatics. Prospective studies are necessary to determine the cause-and-effect relation underlying these associations in wheezers and those with asthma.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2014.03.011>.

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eTable 1

Questions regarding asthma and wheezing-related problems used for study, National Health and Nutrition Examination Survey 2005 to 2006

Has a physician or other health professional ever said that (you have/she/he/SP has) asthma?
In the past 12 mo (have you/has SP) had wheezing or whistling in (your/his/her) chest?
In the past 12 mo, (have you/has SP) taken medication, prescribed by a physician, for wheezing or whistling?
In the past 12 mo has (your/SP's) chest sounded wheezy during or after exercise or physical activity?
During the past 12 mo, how many days of work or school did (you/SP) miss because of wheezing or whistling?

Abbreviation: SP, survey participant.