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Association between Exposure to Alkylbenzenes and Cardiovascular Disease among National Health and Nutrition Examination Survey (NHANES) Participants

XIAOHUI XU, NATALIE C. FREEMAN, AMY B. DAILEY, VITO A. ILACQUA, GREG D. KEARNEY, EVELYN O. TALBOTT

Numerous studies have demonstrated that air pollution is associated with an increased risk of mortality and morbidity due to cardiovascular disease (CVD). Alkylbenzenes are ubiquitous in outdoor and indoor air environments. Yet few studies have evaluated the potential links between exposures to alkylbenzenes and CVD independent of tobacco smoking. In this study, we used the 1999-2004 National Health and Nutrition Examination Survey (NHANES) to examine the relationship between alkylbenzenes (toluene, styrene, ethylbenzene, and the xylenes) and CVD prevalence. All five alkylbenzenes suggested linear trends. Subjects in higher exposure categories of blood alkylbenzenes had higher prevalence of CVD, as compared to subjects in the reference group, of below the limit of detection (LOD) and less than the 50th percentile in the case of toluene and styrene. For the remainder of the alkylbenzes, similar statistically significant associations were observed. Further studies are needed to explore associations between these highly prevalent pollutants and CVD. *Key words*: cardiovascular disease, NHANES, alkylbenzenes, volatile organic compounds (VOC)

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INTRODUCTION

Alkylbenzenes are a class of aromatic hydrocarbons with various alkyl groups attached to the benzene ring. Toluene, styrene, ethylbenzene, and the xylenes—all alkylbenzenes—are among the most prevalent contaminants in the environment.[1] These chemicals are used extensively as solvents, thinners, and as raw materials in the synthesis of a variety of other substances such as benzene. Toluene and xylenes are also commonly found in a variety of consumer products, especially paints, automotive-related goods, and adhesives;[2] they are among the most widely used indoor volatile organic compounds (VOC) across a range of climates and building types.[3] Considerable quantities of alkylbenzenes have been released into the environment each year through solvent and fuel evaporation, accidental spills, and misuse.[4] All environmental media have been contaminated with these chemicals through their use as solvents, primarily in industrial applications. However, alkylbenzenes have been recognized primarily as atmospheric pollutants because they can be released into the air as byproducts from a variety of combustion sources, including automobile exhaust, emission from hazardous waste sites, and coal burning.

Epidemiological studies have consistently shown that exposure to air pollution is associated with an increased risk of mortality or morbidity due to cardiovascular diseases (CVD).[5–7] Automobile vehicle emissions are one of major sources of ambient air pollution in the modern world. Traffic-related pollution has also been linked with cardiovascular health effects.[8] Moreover, as vehicle emissions have been found to have high concentrations of alkylbenzenes, they may play an important role in the development of CVD.[9] The possible direct role of exposure to organic solvents (such as alkylbenzenes) in CVD etiology has been identified as an area in need of critical epidemiological research.[10] However, few studies have been able to examine the potential relationships between these chemicals and risk of CVD due to lack of data, high costs associated with personal exposure assessment of the specific chemicals, and the large sample size required to have adequate power to test these associations. Measurements of these chemicals in blood reflects individual-level recent exposure, and perhaps chronic exposure, to these compounds, providing an overall measurement of chemical exposures from all sources and an accurate measurement of internal dose.[11,12] Exposure to alkylbenzenes, including toluene, styrene, ethylbenzene, and the xylenes, was measured using blood samples in a subpopulation of the National Health and

Received from: University of Florida, College of Public Health and Health Professions, Department of Epidemiology and Biostatistics, Gainesville, FL (XX, ABD); University of Florida, College of Public Health and Health Professions, Department of Environmental Health, Gainesville, FL (NCF, VI); Florida Department of Health, Tallahassee, FL (GDK); University of Pittsburgh, Graduate School of Public Health, Department of Epidemiology, Pittsburgh, PA (EOT). Send correspondence to: Dr. Xiaohui Xu, University of Florida, College of Public Health and Health Professions, Department of Epidemiology and Biostatistics, Gainesville, FL 32611; email: <xhxu@phhp.ufl.edu>.

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Nutrition Examination Survey (NHANES). In addition to these alkylbenzene exposure measures, detailed information on blood cotinine levels and CVD risk factors were available, providing for the first time a unique opportunity to examine these associations in a large-scale population-based sample.

METHODS

Study Population

Alkylbenzenes, including toluene, styrene, ethylbenzene, and the xylenes, were measured in a subset of participants of 20–59 years of age in the NHANES data cycles 1999-2000, 2001–2002, and 2003–2004 (n = 3789). For the NHANES 1999–2000 data cycle, 25% of persons aged 20–59 years of age were chosen for a subsample in 1999 and 33% of that subsample was tested for blood alkylbenzenes in 2000 (n = 851). For NHANES 2001–2002, data were available on 33% of participants aged 20–59 years (n = 1449). For NHANES 2003–2004, data were available on 50% of participants aged 20–59 (n = 1489). Each subsample was representative of the total population in each NHANES data cycle and the appropriate weight was calculated for the subsample after considering the additional stage of sampling, the unequal probability of selection, and the non-response rate.[13] After excluding the records of non-respondents (n = 381), the sample size was 3408, a response rate of 89.9%. The final sample size also varied due to the missing values of the dependent variable, exposures, or covariates.

Dependent Variable

The primary dependent variable was a binary self-reported variable: physician-diagnosed CVD (yes/no). The participant was considered as a prevalent CVD case if she/he answered "yes" to any following questions:

- "Has a doctor or other health professional ever told you that you had congestive heart failure?"
- "Has a doctor or other health professional ever told you that you had coronary heart disease?"
- "Has a doctor or other health professional ever told you that you had angina/angina pectoris?"
- "Has a doctor or other health professional ever told you that you had heart attack?"
- "Has a doctor or other health professional ever told you that you had a stroke?"

Alkylbenzene Exposure

Exposure to toluene, styrene, ethylbenzene, and the xylenes was measured by blood sample. All individual chemicals were measured by headspace solid-phase microextraction in conjunction with gas chromatography and benchtop quadrupole mass spectrometer. This method can minimize the interference and chemical noise associated with whole-blood samples; the limit of detection (LOD) is below 50 ppt (pg/ml) for most of tested chemicals.[14] For results below the LOD, the CDC imputed the value for the chemical as the LOD for that specific compound divided by the square root of 2.[15] Quality control procedures follow the standard practices, which was described in the CDC's laboratory procedure manual for VOCs.[15] For each alkylbenzene, participants whose level of blood alkylbenzene was above the LOD were categorized by the cutoff points of 50th and 85th percentiles of detectable values and subjects with the value below the LOD and less than the 50th percentile were regarded as the reference group.

Covariates

Some important covariates related to the development of CVD were selected and controlled for while evaluating the associations between exposure to alkylbenzenes and CVD. Covariates from the household interview included age (20–39/40–59), gender, race/ethnicity (non-Hispanic white, non-Hispanic black, and others), poverty income ratio (< 1.0, 1.0–2.0, or > 2.0), serum cotinine (continuous), alcohol consumption (yes/no), and hypertension status (yes/no). Other covariates from physical examinations or laboratory tests such as body mass index (BMI: < 25.0, 25–29, or ≥ 30), total cholesterol (continuous), and HDL (high-density lipoprotein)-cholesterol (continuous) were also selected.

Statistical Analysis

All statistical analyses were performed using SAS 9.1 software (SAS Institute Inc, Cary, NC) survey procedures, which account for the complex sampling design used in NHANES. The sample weights, stratification, and clustering design variables were incorporated into all SAS survey procedures to ensure the correct estimation of sampling error. A six-year subsample weight was calculated for the combined 1999 to 2004 data by following the NHANES analytic and reporting guidelines: we assigned one-third of the two-year VOC subsample weight (WTSVOC2Y) for 2003 to 2004, if a participant was sampled in 2003 to 2004, and merged it with two-thirds of the 1999 to 2002 four-year VOC subsample weight (WTSVOC4Y) for those sampled in 1999 to 2002.[16] This calculated weight was used to analyze the merged six-year data of NHANES 1999–2004.

Spearman rank correlation coefficients between individual chemicals were calculated. Descriptive statistics, including two-sided Student t-tests and Wald chi-square analyses, were also performed where appropriate. Moreover, logistic regression models were used to evaluate the associations between exposure to alkylbenzenes and CVD. Unadjusted associations between

TABLE 1 Distribution of Demographic Factors and Selected Categorical Covariates by Status of Self-reported CVD among US Adults Aged 20–59 Years, 1999–2004 NHANES Survey

	CVD				
	Yes		No		
Characteristics (95% CI)	n	Percent %	n	Percent %	p-value
Age (%)					
20–39 years	19	16.21 (7.24–25.19)	1,847	52.53 (50.12–54.94)	< 0.001
40–59 years	117	83.78 (74.81–92.76)	1,415	47.47 (45.06–49.88)	
Race (%)					
Non-Hispanic White	75	73.28 (63.80–82.76)	1,571	70.52 (67.28–73.77)	0.01
Non-Hispanic Black	35	17.36 (8.44–26.29)	674	11.52 (9.25–13.78)	
Others	26	9.35 (3.92–14.79)	1,020	17.96 (14.87–21.04)	
Gender (%)					
Male	69	58.40 (50.29–66.50)	1,538	48.78 (46.93–50.63)	0.04
Female	67	41.60 (33.49–49.71)	1,727	51.22 (49.36–53.07)	
Poverty income ratio (%)					
< 1.0	36	22.68 (15.74–29.62)	548	12.73 (10.91–14.56)	0.02
1.0–2.0	31	19.10 (11.92–26.28)	741	19.38 (17.32–21.44)	
> 2.0	63	58.22 (47.63–68.81)	1,752	67.89 (64.87–70.91)	
Smoking (%)					
Never	51	35.72 (26.72–44.73)	1,762	51.07 (48.39–53.75)	0.02
Former	37	29.94 (20.37–39.51)	633	21.34 (19.37–23.30)	
Current	48	34.33 (26.67–42.00)	867	27.59 (25.11–30.08)	
Hypertension (%)					
Yes	80	54.22 (43.44–65.01)	601	18.28 (16.75–19.80)	< 0.001
No	56	45.78 (34.99–56.56)	2,617	81.72 (80.19–83.25)	
Body mass index (%)					
< 25.0	22	14.82 (8.46–21.18)	1,163	38.93 (36.83–41.03)	< 0.0001
25–29	43	36.04 (27.48–44.60)	1,067	31.73 (29.92–33.53)	
≥ 30	71	49.14 (39.34–58.94)	1,032	29.34 (27.18–31.50)	
Alcohol consumption (%)					
Yes	87	70.91 (63.15–78.68)	2,169	74.88 (71.55–78.21)	0.28
No	41	29.09 (21.32–36.85)	852	25.12 (21.79–28.45)	

exposure to individual chemicals and CVD were calculated. Furthermore, multivariate logistic regression was used to examine these associations, with adjustment for different combinations of selected and known risk factors. Odds ratios (OR) and 95% confidence intervals (95%CI) were reported.

RESULTS

A total of 3398 participants aged 20–59 years from the NHANES 1999–2004 survey were analyzed in this study. We identified 136 CVD cases and 3262 non-CVD controls. Table 1 shows the distribution of demographic factors and selected categorical covariates by self-reported CVD status. The adults who were diagnosed with CVD were more likely than those without CVD to be in the older age group (83.78% *vs.* 47.47%), male (58.40% *vs.* 48.78%), poor (22.68% *vs.* 12.73%), cigarette smokers (never smoked: 35.72% *vs.* 51.07%), hypertensive (54.22% *vs.* 18.28%), and obese (49.14% *vs.* 29.34%). However, there was no significant difference in alcohol use between participants diagnosed with CVD and those without CVD.

Table 2 shows the comparison of means of log-transformed blood concentrations of alkylbenzenes and selected continuous covariates by CVD status. Adults who reported physician-diagnosed CVD had higher means of log-transformed blood concentrations of alkylbenzenes than adults without a CVD diagnosis (ethylbenzene: 0.05 ng/ml *vs.* 0.037 ng/ml; styrene: 0.055 ng/ml *vs.* 0.04 ng/ml; toluene: 0.248 ng/ml *vs.* 0.152 ng/ml; o-xylene: 0.058 ng/ml *vs.* 0.045 ng/ml; and m-/p-xylene: 0.210 ng/ml *vs.* 0.159 ng/ml). Participants with CVD also had a lower average of blood HDL (44.36 mg/dl *vs.* 50.20 mg/dl) and a higher geometric mean of blood total cholesterol (205.9 mg/dl *vs.* 197.20 mg/dl) and serum cotinine (1.93 ng/ml *vs.* 0.80 ng/ml) compared to those without CVD.

Relationships between all 15 pairwise combinations of five alkylbenzenes as well as serum cotinine are presented in Table 3 using the Spearman rank correlation test. The results indicated that significant correlations exist between all alkylbenzene pairwise combinations. The Spearman rank correlation coefficients ranged from 0.43 to 0.88. Ethylbenzene was highly correlated with toluene (0.74), o-xylene (0.71), and m-/p-xylene

TABLE 2 Comparison of Means of Log-transformed Blood Alkylbenzenes and Selected Continuous Covariates by Status of CVD

	CVD				
	Cases		Non-cases		
Characteristics (95% CI)	N	Mean (95%CI)	N	Mean (95%CI)	P-value
Ethylbenzene (ng/ml)	94	−3.0 (−3.17, −2.83)	2,461	−3.30(−3.38, −3.22)	0.001
Styrene (ng/ml)	109	−2.90 (−3.10, −2.71)	2,605	−3.22(−3.32, −3.12)	< 0.001
Toluene (ng/ml)	109	−1.39 (−1.62, −1.16)	2,632	−1.88(−2.01, −1.76)	< 0.001
o-Xylene (ng/ml)	112	−2.85 (−2.98, −2.72)	2,674	−3.10(−3.16, −3.04)	< 0.001
m-/p-Xylene (ng/ml)	104	−1.56 (−1.75, −1.37)	2,615	−1.84(−1.95, −1.73)	0.04
Total cholesterol (mg/dl)	127	5.33 (5.28, 5.38)	3,145	5.28(5.28, 5.29)	0.10
HDL (mg/dl)	127	3.79 (3.74, 3.84)	3,145	3.91(3.90, 3.93)	< 0.001
Serum cotinine (ng/ml)	126	0.66 (−0.04, 1.36)	3,129	−0.23(−0.49, 0.033)	0.02

(0.88). M-/p-xylene was also highly correlated with toluene (0.74) and o-xylene (0.72). In addition, serum cotinine is correlated with all alkylbenzenes; the correlation coefficients ranged from 0.21 to 0.43.

Table 4 shows the associations between blood alkylbenzenes and the prevalence of CVD based on both univariate and multivariate logistic regression models. Results from the unadjusted model show significant linear trends for all five alkylbenzenes ($p = < 0.001$). After controlling for other important covariates, including age, gender, race, social economic status, alcohol consumption, history of hypertension, and serum cotinine, there was little change in the estimates of the associations between blood alkylbenzenes and CVD, and the significant linear trend remained for all five alkylbenzenes. Greater exposure to toluene was associated with prevalence of CVD, compared to the reference group (50th–85th percentiles: OR, 2.30; 95%CI, 1.25–4.23; ≥ 85th percentile: OR, 3.49; 95%CI, 1.81–6.73; $p < 0.001$). Greater exposure to styrene was also associated with prevalence of CVD (OR, 2.03; 95%CI, 0.91–4.54 for the category of 50th-85th percentiles; OR, 4.64; 95%CI, 2.49–8.64 for the category of ≥ 85th percentile; $p < 0.001$). For the remainder of the alkylbenzes, similar statistically significant associations were observed. As compared with the reference group, the adjusted ORs are 0.81 (95%CI, 0.43–1.56) for the 50th–85th percentile and 3.10 (95%CI, 1.40–6.86) for the ≥ 85th percentile of ethylbenzene. For m-/p-xylene, the adjusted ORs are 1.12 (95%CI, 0.65–1.93) for the 50th-85th percentile and 2.31 (95%CI, 1.40–3.82) for ≥ 85th percentile compared with the reference group ($p = 0.001$). For o-xylene, the adjusted ORs are 1.49 (95%CI, 0.93–2.38) and 2.68 (95%CI, 1.14–6.25) from the 50th–85th to ≥ 85th percentile of detectable range compared with the reference group ($p = 0.023$), respectively. Additional adjustment for plasma glucose, triglycerides, serum HDL, and total cholesterol did not appreciably change the results.

DISCUSSION

There are few population-based epidemiological studies available to assess the potential associations between exposure to alkylbenzenes, such as toluene, styrene, ethylbenzene, m-/p-xylene and o-xylene, and CVD. This cross-sectional study suggested that exposure to alkylbenzenes was positively associated with the prevalence of CVD in the US general population aged 20–59 years. Moreover, this study also suggested linear trends

TABLE 3 Spearman Correlations Matrix between Blood Alkylbenzenes as well as Continine (ng/ml) among the Subsample of NHANES 1999–2004 Participants Aged 20–59 Years

Chemicals	Ethylbenzene	Styrene	Toluene	o-Xylene	m-/p-Xylene	Cotinine
Ethylbenzene	1.0 (N=2,560)	0.56* (N=2,494)	0.74* (N=2,512)	0.71* (N=2,555)	0.88* (N=2,511)	0.42* (N=2,548)
Styrene	—	1.0 (N=2,718)	0.64* (N=2,639)	0.43* (N=2,684)	0.60* (N=2,620)	0.43* (N=2,701)
Toluene	—	—	1.0 (N=2,747)	0.52* (N=2,736)	0.74* (N=2,697)	0.49* (N=2,730)
o-Xylene	—	—	—	1.0 (N=2,792)	0.72* (N=2,712)	0.21* (N=2,775)
m-/p-Xylene	—	—	—	—	1.0 (N=2,725)	0.32* (N=2,709)
Cotinine	—	—	—	—	—	1.0 (N=3,546)

*$p < 0.001$

TABLE 4 Concentration (ng/ml), Number of Cases/Total Number, and Crude (COR) and Adjusted ORs (AOR)* for Prevalence of Self-reported Cardiovascular Diseases by Categories of Five Alkylbenzenes

Chemicals		Detection Rate (%)	Exposure Categories			P-value
			< 50th*	50th to < 85th	≥ 85%	
Toluene (ng/ml)		94.4				
	Concentration(ng/ml)		0.064	0.0237	0.751	
	Cases/n		39/1435	40/917	30/389	
	COR		1.0	1.94 (1.10–3.44)	3.46 (2.01–5.96)	< 0.001
	AOR		1.0	2.30 (1.25–4.23)	3.49 (1.81–6.73)	< 0.001
Styrene (ng/ml)		52.1				
	Concentration		0.021	0.084	0.180	
	Cases/n		62/1994	25/502	22/218	
	COR		1.0	1.75 (0.84–3.63)	3.58 (2.31–5.57)	< 0.001
	AOR		1.0	2.03 (0.91–4.54)	4.64 (2.49–8.64)	< 0.001
Ethylbenzene (ng/ml)		68.1				
	Concentration		0.024	0.058	0.135	
	Cases/n		54/1682	17/594	23/239	
	COR		1.0	0.82 (0.44–1.54)	2.96 (1.76–5.00)	< 0.001
	AOR		1.0	0.81 (0.43–1.56)	3.10 (1.40–6.86)	0.005
m-/p-Xylene (ng/ml)		97.5				
	Concentration		0.095	0.200	0.478	
	Cases/n		45/1381	30/941	29/397	
	COR		1.0	1.12 (0.65–1.93)	2.31 (1.40–3.82)	0.001
	AOR		1.0	1.27 (0.7–2.32)	2.36 (1.19–4.67)	0.014
o-Xylene (ng/ml)		42.5				
	Concentration		0.035	0.077	0.143	
	Cases/n		73/2192	23/411	16/183	
	COR		1.0	1.85 (1.21–2.84)	3.14 (1.61–6.14)	0.001
	A OR		1.0	1.49 (0.93–2.18)	2.68 (1.14–6.25)	0.023

*OR adjusted for age, gender, race, social economic status, alcohol consumption, BMI, hypertension, and serum cotinine.

for all five alkylbenzenes studied. Alkylbenzenes could come from tobacco smoking and other sources, including traffic emissions. The moderate correlations between serum cotinine, a biological marker of both passive and active smoking, and the alkylbenzenes suggest that tobacco smoking is not the sole source of alkylbenzenes in the US general population. Moreover, the high correlations between the different alkylbenzenes may indicate a potential common source of alkylbenzenes, such as traffic pollution. After controlling for the effects of serum cotinine, the observed independent associations between alkylbenzenes and the prevalence of CVD suggest that alkylbenzenes may play a significant role in the development of CVD. These findings are in general agreement with the limited epidemiological evidence from previous occupational cohort studies. Some occupational epidemiological studies have suggested that exposure to alkylbenzenes, such as styrene, were likely associated with an increased risk of CVD.[17,18] Matanoski et al. have also reported an increase in CVD among styrene-exposed workers in a case-cohort study.[19,20]

However, the biological mechanisms underlying the associations between exposure to alkylbenzenes and CVD remain unclear. Studies have suggested that the carcinogenicity of polycyclic aromatic hydrocarbons (PAH) is relevant to the mechanisms involved in the pathogenesis of atherosclerotic lesions[21] and the development of atherosclerotic plaques.[22] Studies have also demonstrated the carcinogenic effects of alkylbenzenes.[23–26] It was hypothesized that alkylbenzenes could play a similar role as PAHs in development of atherosclerotic lesions and atherosclerotic plaques. In addition, oxidative stress has been suggested as one of the mechanisms in development of CVD. Oxidative stress could cause inflammation, alter the vascular system, and lead to DNA damage.[27] Studies have found that exposure to alkylbenzenes can reduce the level of glutathione, decrease activity of antioxidant enzymes, and cause oxidative damage of biological macromolecules.[28–31] Moreover, alkylbenzenes could also potentially play an important role in acute changes in cardiovascular systems, such as changes in plasma viscosity, increasing heart rates, and alterations of heart rate variability, which have been reported to be associated with air pollution.[32–35] Further studies are required to examine these potential underlying biological mechanisms.

The potential links between exposure to akylbenzenes and CVD have not been well studied, likely due to the expense and resources needed to collect, store, and analyze biological samples. The NHANES survey data provided a rare and unique opportunity to assess the relationships between blood concentrations of alkylbenzenes and CVD in a large population-based random

sample of US adults. In addition to the availability of these biological samples, NHANES data also allowed for adjustment for a wide range of potential confounders, such as demographic characteristics; lifestyle factors such as smoking and alcohol consumption; and physical, medical, and laboratory factors including BMI, status hypertension, blood cholesterol, and HDL. The ability to control for these covariates makes the results from the present study more convincing.

The present study also has several limitations. First, this is a cross-sectional study, and the information on the dependent variable of CVD and other variables was collected based on interview questionnaires. The cross-sectional study design could limit the value of the study in casual inference due to the temporal sequence of exposure and outcome, and the possibility that the presence of the disease may alter the exposure. Second, an additional limitation lies in the measurement of chemical exposures using a blood sample. We are unable to determine if the blood levels are indicators of chronic exposure or if there are great differences between current exposure sources and past exposure sources for each subject. Furthermore, misclassification of exposure could result from the heterogeneity of measurement error and categorization of continuous exposure variables in the study sample.[36,37] However, these misclassifications of exposure biases are likely to be non-differential errors, making them unlikely to explain the observed positive association. While we were able to compare estimates from different statistical models that adjusted for many potential confounders, it is possible that additional unmeasured variables, such as diet and physical activity, could have confounded our results. Although we were able to control for smoking-related alkylbenzene exposure via serum cotinine levels, there may be additional sources of alkylbenzenes, such as occupational exposures, that we were unable to identify with this dataset. Therefore, we cannot rule out the possibility that other sources of alkylbenzenes, besides traffic emission-related sources, are responsible for the associations we found. While we hypothesize that traffic emissions are a likely contributor to these associations, future studies will need to clarify alkylbenzene sources. Finally, a relatively small of number of CVD cases (n = 137) were observed in the 1999–2004 NHANES population samples. At this time, the relevant data from NHANES 2005–2008 have not been released to the public, but it will be important to update this analysis when these data become available.

Despite these limitations, our study suggested that exposure to environmental alkylbenzenes may have adverse cardiovascular effects on the general population. As both CVD and alkylbenzenes are highly prevalent in the US population, the public health significance of a potential causal relationship between alkylbenzenes exposure and CVD should be noted. If the findings of this study are confirmed by additional analytical epidemiological studies, we can begin using this information in interventions designed to target reductions in alkylbenzene exposures, which can lead to lessening the health burden due to CVD.

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CORRECTION

An error appeared in the abstract, as well as on page 717, of the article "Mesothelioma Mortality in Brazil, 1980–2003" in the July–September issue (Int J Occup Environ Health. 2008;14(1): 18-24). This information should have appeared as follows: "Mesothelioma mortality rates increased over the period studied, from 0.56 to 1.01 deaths per 1,000,000 habitants."