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Evaluating the effects of maternal exposure to benzene, toluene, ethyl benzene, and xylene on oral clefts among offspring in Texas: 1999-2008

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Abstract

BACKGROUND—There is evidence from previous studies that maternal occupational exposure to hazardous air pollutants is positively associated with oral clefts, however, studies evaluating the association between residential exposure to these toxicants and oral clefts are lacking. Therefore, our goal was to conduct a case-control study examining the association between estimated maternal residential exposure to benzene, toluene, ethyl benzene, and xylene (BTEX) and the risk of oral clefts among offspring.

METHODS—Data on 6,045 non-syndromic isolated oral cleft cases (3,915 cleft lip with or without cleft palate [CL±P] and 2,130 non-syndromic isolated cleft palate [CP] cases) delivered between 1999 and 2008 were obtained from the Texas Birth Defects Registry. The control group was a sample of unaffected live births, frequency matched to cases on year of birth. Census tract-level estimates of annual average exposures were obtained from the U.S. Environmental Protection Agency 2005 Hazardous Air Pollutant Exposure Model (HAPEM5) for each pollutant and assigned to each subject based on maternal residence during pregnancy. Logistic regression was used to assess the relationship between estimated maternal exposure to each pollutant (benzene, toluene, ethyl benzene, and xylene) separately and the risk of oral clefts in offspring.

RESULTS—High estimated maternal exposure to benzene was not associated with oral clefts, compared with low estimated exposure (CL±P adjusted OR=0.95; 95% CI=0.81-1.12; CP adjusted OR=0.85; 95% CI=0.67-1.09). Similar results were seen for the other pollutants.

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CONCLUSION—In our study, there was no evidence that maternal exposure to environmental levels of BTEX was associated with oral clefts.

Keywords

oral clefts; maternal exposure; hazardous air pollutants; benzene; epidemiology

INTRODUCTION

Oral clefts, complex malformations of the lip or palate that result from improper fusion of tissues during early embryologic development, are one of the most common groups of birth defects (Arosarena 2007). Due to the distinct developmental origins of the lip and primary palate from the secondary palate, oral clefts can be subdivided into cleft lip with or without cleft palate (CL±P) and cleft palate alone (CP). Children with these defects often need lifelong multidisciplinary care and experience significant morbidity compared to their unaffected contemporaries. In spite of the high prevalence of oral clefts relative to other birth defects and the clinical significance of these conditions, the etiology of these defects is not well understood in humans.

A group of suspected risk factors for oral clefts needing additional exploration is environmental pollutants (Leite et al., 2002), including hazardous air pollutants (HAPs). HAPs are a heterogeneous group of 187 environmental toxicants identified in the U.S. Clean Air Act (U.S. EPA 2007). An important subset of HAPs is aromatic organic solvents, including benzene, toluene, ethyl benzene and the combined three isomers (ortho, meta and para) of xylene (BTEX). BTEX can be emitted from on-road and industrial sources and are the most prevalent HAPs in urban areas (Mohamed et al., 2002). The seasonal variability for HAPs, including BTEX, is not consistent and depends on location (Mohamed et al., 2002; Grant et al., 2007). Benzene is of particular interest, as it is a known human carcinogen and has also been associated with other adverse outcomes, including autism and preterm birth (International Agency for Research on Cancer 1987; Bianchi et al., 1997; Reutman et al., 2002; Agency for Toxic Substances and Disease Registry 2004; Windham et al., 2006; Choi et al., 2008; Whitworth et al., 2008). Occupational studies have demonstrated positive associations between maternal exposure to organic solvents and the risk of oral clefts in offspring (Matte et al., 1993; Laumon et al., 1996; Cordier et al., 1997; Garcia et al., 1998; Wennborg et al., 2005). Additionally, cigarette smoking (a source of benzene and other toxicants) is an established risk factor for oral clefts [reviewed in (Little et al., 2004)]. Furthermore, a recent study in Texas suggested maternal exposure to estimated ambient levels of benzene was associated with spina bifida (Lupo et al., 2011), a birth defect that shares some risk factors with oral clefts (Mossey et al., 2009). In spite of these associations, no studies have evaluated the effect of environmental levels of BTEX on oral cleft prevalence. Therefore, the objective of our study was to evaluate the association between estimated maternal exposure to environmental levels of BTEX during pregnancy and the risk of oral clefts among offspring in Texas for the period 1999-2008. Texas serves as an ideal backdrop for this study, as it has variable and high levels of these pollutants. Additionally, Texas has one of the largest population-based birth defects surveillance systems.

MATERIALS AND METHODS

Study Population

Data on offspring with oral clefts (CL±P and CP) delivered in Texas between January 1, 1999 and December 31, 2008 were linked to vital records and obtained from the Texas Birth Defects Registry (n=6,045) (Texas Department of State Health Services (TDSHS) 2010). The registry employs statewide active surveillance at hospitals, birthing centers and mid-wife facilities to identify cases with birth defects, including live births, still births and induced pregnancy terminations. We frequency-matched controls (i.e., unaffected live births delivered in Texas between 1 January 1999 and 31 December 2008) on year of birth, using a ratio of five controls to one case. To reduce the potential for heterogeneity among cases, we restricted all CL±P and CP cases to those that were non-syndromic (i.e., cases without possible diagnoses of malformation syndromes or chromosomal abnormalities) and isolated (i.e., non-syndromic cases without additional major structural birth defects, as defined by the National Birth Defects Prevention Study (Rasmussen et al., 2003)). The study protocol was reviewed and approved by the institutional review boards of the Texas Department of State Health Services and The University of Texas Health Science Center at Houston.

Exposure Assessment

Estimates of average annual exposure to environmental concentrations of each BTEX compound for each census-tract in Texas were obtained from the 2005 U.S. EPA National-Scale Air Toxics Assessment Hazardous Air Pollutant Exposure Model, version 5 (HAPEM5) (U.S. EPA 2013). While other years of HAPEM are available (1999 and 2002), HAPEM5 (2005) is the most complete and was used a surrogate for other years as has been done in previous assessments (Windham et al., 2006; Whitworth et al., 2008; Lupo et al., 2011). Furthermore, the U.S. EPA cautions again using multiple years in one analysis as model inputs change over time (U.S. EPA 2006; Ozkaynak et al., 2008). HAPEM5 is an inhalation exposure model appropriate for assessing inhalation exposures of the general population or specific subpopulations, over spatial scales ranging from local (e.g., census tract) to national (Ozkaynak et al., 2008). HAPEM5 uses the general approach of tracking representatives of specified demographic groups as they move among indoor and outdoor microenvironments. Output of HAPEM5 is the weighted-average exposure concentration for a representative individual in a given census tract (Ozkaynak et al., 2008). HAPEM5 uses four primary sources of information: population data from the U.S. Census (U.S.Census Bureau (USCB) 2010), population activity data, modeled ambient air pollution data, and microenvironmental data. Average exposure levels of benzene, toluene, ethyl benzene, xylene, and other HAPs are reported as annual concentrations in micrograms per cubic meter ($\mu g/m^3$) (U.S. EPA 2013). Information from the U.S. EPA National-Scale Air Toxics Assessment is currently the only population-based estimates of exposure to HAPs.

Census tract-level estimates of BTEX exposure were linked to maternal census tract at delivery based on address at delivery as reported on vital records for cases and controls. Addresses were geocoded and mapped to their respective census tracts by the Texas Department of State Health Services. For the main analyses, exposure ($\mu g/m^3$) was categorized as low, medium, medium-high or high, based on the distribution of BTEX levels

in controls (i.e., on cutoffs 25th percentile, >25th percentile and 75th percentile, >75th percentile and 90th percentile and >90th percentile), as used in a previous study (Reynolds et al., 2003).

Potential Covariates

We obtained vital records data for both cases and controls. These data included infant sex, year of birth, maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), maternal birth place (United States, Mexico, or other), maternal age (<20, 20–24, 25–29, 30–34, 35–39, or 40 years), maternal education (less than high school, high school, or more than high school), plurality (1 or 2), maternal smoking (no or yes), and season of conception (spring, summer, fall, or winter).

Statistical Analyses

Frequency distributions of maternal demographic and behavioral factors were tabulated for case and control infants. Furthermore, the distributional characteristics of BTEX were determined using the HAPEM5 results. Frequencies of cases and controls were determined for each BTEX exposure category (i.e., those based on the 25th, 75th and 90th percentile cutoffs in controls). In the main analyses, unconditional logistic regression was used to determine the association between each category of maternal exposure to benzene, toluene, ethyl benzene, and xylene and each oral cleft phenotype. Using the category of low exposure as the referent, we estimated the odds ratio (OR) and 95% confidence interval (CI) for each increasing exposure category. The ORs were adjusted for the following *a priori* potential confounders (based on the literature): birth year, infant sex, maternal race/ethnicity, education, age, and smoking (Ritz et al., 2002; Gilboa et al., 2005; Lupo et al., 2011). Finally, we conducted a sensitivity analysis restricting our assessment to urban areas where census tracts would be smaller and therefore the exposure assessment would be more precise. All analyses were carried out using Stata version 12 (Stata Corporation, College Station, TX).

RESULTS

For the period 1999-2008, there were 3,915 and 2,130 cases in Texas with a diagnosis of CL ±P and CP, respectively. Of those, 206 CL±P and 153 CP cases were excluded due to chromosomal abnormalities. Another 115 CL±P and 136 CP cases with known syndromes were also excluded. Further, 831 CL±P and 659 CP cases with additional major structural birth defects were excluded leaving 2,763 CL±P and 1,182 CP non-syndromic isolated cases for analysis. The proportion of subjects missing maternal census tract of residence at delivery, and thus missing BTEX exposure estimates, was similar between isolated CL±P, CP cases and controls (8% [208 of 2,763], 6% [70 of 1,182] and 7% [1,045 of 15,780]).

Selected maternal characteristics summarized by case-control status are presented in Table 1. Briefly, compared to control mothers, mothers of CP offspring were more likely to have female infants, to be non-Hispanic White, to be born in the U.S., to be >40 years of age at conception, and to smoke. Compared to control mothers, mothers of CL±P infants were more likely to have male infants, to be non-Hispanic White, to be born in the U.S., to be >40

years at conception, to have a lower education status, and to smoke. In our data, plurality was not associated with case status.

The distributional characteristics of BTEX in Texas using the 2005 HAPEM5 model are presented in Table 2. The mean levels of the BTEX compounds were 0.85 μg/m^3 (benzene), 1.70 μg/m^3 (toluene), 0.17 μg/m^3 (ethyl benzene), and 0.70 μg/m^3 (xylene).

Results from the final models assessing the associations between BTEX and oral clefts are presented in Table 3. Mothers with high levels of estimated benzene exposure were not more likely to have offspring with CL±P (adjusted OR = 0.95; 95% CI = 0.81-1.12) or CP (adjusted OR = 0.85; 95% CI = 0.67-1.09) compared to mothers with low levels of exposure after adjustment for birth year, infant sex, maternal race/ethnicity, education, age, smoking and season of conception (Table 3). The degree of confounding from all covariates was modest; i.e., adjusted odds ratios differed from crude odds ratios by no more than 10%. Findings were similar for toluene, ethyl benzene, and xylene for both CL±P and CP. Additionally, findings were consistent when restricted to urban census tracts (data not shown).

DISCUSSION

In one of the first studies evaluating the association between estimated exposure to environmental levels of HAPs and oral clefts, we did not find an association between the prevalence of oral clefts in offspring and estimated maternal exposure to environmental levels of benzene, toluene, ethyl benzene, or xylene as estimated from the U.S. EPA HAPEM5 model (U.S. EPA 2013). Our findings are consistent with results from Brender et al., who found women living in close proximity to hazardous waste sites (a source of several HAPs) were not more likely to have offspring affected by oral clefts compared to women who were not in close proximity to such facilities (Brender et al., 2006).

There is some prior evidence that oral clefts may be associated with maternal exposure to criteria air pollutants; however, the evidence is equivocal. Criteria air pollutants are common air pollutants (e.g., ozone) for which the U.S. EPA sets National Air Quality Standards (U.S. EPA 2012). For instance, while one study in Taiwan determined maternal exposure to ozone was associated with oral clefts (Hwang et al., 2008), another study in Australia showed only a weak association between SO$_2$ exposure and oral clefts (Hansen et al., 2009). Also, three U.S. studies (one in Southern California, a second in Texas, and a third in New Jersey) did not report an association between any criteria air pollutants evaluated and oral clefts (Ritz et al., 2002; Gilboa et al., 2005; Marshall et al., 2010). Our results were consistent with these previous results. Analogous to the current study, these studies relied on surveillance data from birth defects registries, birth certificate data matched to the residence at birth, and estimated exposure to air pollutants. However, our analysis is the first of its kind to examine the effects of BTEX, which continues to be a problem in urban areas. Furthermore, these pollutants have been previously associated with adverse health outcomes, including spina bifida (Lupo et al., 2011).

Our study must be considered in the light of certain limitations. First, the use of modeled predictions of exposure to BTEX (as opposed to measured levels) may have resulted in exposure misclassification. However, there are currently no other population-based estimates of exposure to HAPs, and this data source (i.e., the U.S. EPA National-Scale Air Toxics Assessment) has been commonly used in other assessments evaluating the association between HAPs and adverse health outcomes, including birth defects (Reynolds et al., 2003; Windham et al., 2006; Whitworth et al., 2008; Lupo et al., 2011). Another potential limitation is that HAPEM5 data was not available for the entire study period, however this may be a suitable surrogate for other years as the sources of HAPs (e.g., emissions from roadways and industrial facilities) were unlikely to change during the study period (Sexton et al., 2007). While our exposure assessment enabled us to capture spatial variability in BTEX concentrations, we were not able to account for temporal variability due to the use of an annual estimate of exposure, which could result in exposure misclassification. The reliability of maternal smoking on birth certificates, an important potential confounder for the present analysis, is also questionable. Finally, exposure misclassification due to use of maternal address at time of delivery is also a potential source of bias in this study. As oral clefts occur around the time of conception, address at delivery may not be as be as relevant as address at conception when estimating exposure (Selevan et al., 2000). However, our own analyses, using a smaller set of cases and controls from Texas included in the National Birth Defects Prevention Study with complete residential information during pregnancy, suggest there was no significant change in benzene exposure assignment when using address at delivery versus address at conception (Lupo et al., 2010).

Our study also has several important strengths, including the use of one of the world's largest active population-based birth defects surveillance systems with detailed information on cases. The study population included non-live births, which reduced the potential for selection bias. We had a large sample with sufficient power to evaluate modest associations. An additional strength was the application of relatively local (census-tract level estimates) measures of exposure. Reports indicate that the use of larger geographical units (e.g., counties) may not capture the spatial variation of benzene (Pratt et al., 2004). Moreover, we examined associations separately for CL±P and CP, as well as among nonsyndromic and isolated cases in order to reduce phenotypic heterogeneity.

In conclusion, this study provides the first assessment of the relationship between maternal exposure to estimated census-tract levels of BTEX and the prevalence of oral clefts in offspring. Our analyses suggest that maternal exposure to estimated exposure to environmental levels of BTEX is not associated with the prevalence of oral clefts among offspring. We recommend future investigations of air pollutants and oral clefts that include novel measures of exposure, as well as the inclusion of genotypes responsible for the metabolism of these toxicants.

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Table 1

Characteristics of controls and oral cleft cases (CL±P[a] and CP[b]) in Texas, 1999-2008

Characteristic	Controls (n=15,780) N, (%)	CL±P (n=2,763) N, (%)	CP (n=1,182) N, (%)
Infant sex			
Female	7,770 (49.2)	985 (35.6)	696 (58.9)
Male	8,010 (50.8)	1,778 (64.4)	486 (41.1)
Maternal race/ethnicity			
Non-Hispanic white	5,694 (36.1)	1,110 (40.3)	529 (44.8)
Non-Hispanic black	1,778 (11.3)	175 (6.3)	105 (8.9)
Hispanic	7,671 (48.7)	1,354 (49.1)	493 (41.7)
Other	617 (3.9)	118 (4.3)	55 (4.6)
Maternal birthplace			
United States	12,354 (78.2)	2,163 (78.2)	962 (81.4)
Mexico	3,342 (21.2)	589 (21.4)	218 (18.4)
Other	84 (0.6)	11 (0.4)	2 (0.2)
Maternal age (years)			
<20	2,236 (14.1)	413 (14.9)	155 (13.1)
20-24	4,500 (28.6)	826 (30.0)	319 (27.0)
25-29	4,273 (27.0)	709 (25.6)	302 (25.5)
30-34	3,092 (19.7)	516 (18.8)	257 (21.8)
35-39	1,396 (8.8)	239 (8.6)	113 (9.6)
40	280 (1.8)	59 (2.1)	36 (3.0)
Maternal education			
<High school	4,875 (31.2)	913 (33.5)	358 (30.5)
High school	4,591 (29.4)	845 (31.0)	371 (31.5)
>High school	6,142 (39.4)	968 (35.5)	447 (38.0)
Plurality			
1	15,312 (97.0)	2,688 (97.3)	1,146 (97.0)
2	467 (3.0)	74 (2.7)	36 (3.0)
Maternal Smoking			
No	14,740 (94.0)	2,545 (92.7)	1,072 (90.9)
Yes	950 (6.0)	200 (7.3)	108 (9.1)
Season of conception			
Summer	3,888 (24.7)	627 (22.8)	279 (23.8)
Fall	4,065 (25.8)	726 (26.4)	283 (24.0)
Winter	3,984 (25.4)	696 (25.4)	298 (25.4)
Spring	3,792 (24.1)	696 (25.4)	315 (26.8)

[a] Cleft lip with or without cleft palate

[b] Isolated cleft palate

Table 2

Distribution of BTEX ($\mu g/m^3$) in Texas using the 2005 HAPEM5 Model (n=18,402)[a]

Pollutant	Mean	SD	10th percentile	50th percentile	90th percentile
Benzene	0.85	0.46	0.41	0.78	1.37
Toluene	1.70	0.97	0.65	1.57	2.89
Ethyl benzene	0.17	0.14	0.03	0.14	0.33
Xylene	0.70	0.57	0.14	0.61	1.38

SD, Standard deviation

[a]Number of census tracts

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Table 3

Adjusted odds ratios and 95% confidence intervals for the association between HAPEM5 modeled estimates of BTEX and oral clefts in Texas, 1999–2008_

Pollutant	Pollutant levels (µg/m³)	CL±P Cases/Controls, N	Adjusted OR[a] (95% CI)	CP Cases/Controls, N	Adjusted OR[a] (95% CI)
Benzene					
Low (Reference)	0.58	673/3687	1.00 (ref)	309/3687	1.00 (ref)
Medium	0.58–1.01	1273/7365	0.96 (0.87–1.07)	552/7365	0.94 (0.81–1.09)
Medium-high	1.01–1.38	356/2208	0.88 (0.77–1.02)	155/2208	0.89 (0.73–1.10)
High	1.38	253/1475	0.95 (0.81–1.12)	96/1475	0.85 (0.67–1.09)
Toluene					
Low (Reference)	1.10	658/3684	1.00 (ref)	285/3684	1.00 (ref)
Medium	1.10–2.08	1248/7364	0.96 (0.86–1.07)	578/7364	1.04 (0.89–1.20)
Medium-high	2.08–2.89	390/2213	1.01 (0.88–1.16)	152/2213	0.96 (0.78–1.18)
High	2.89	259/1474	1.01 (0.86–1.19)	97/1474	0.91 (0.72–1.17)
Ethyl benzene					
Low (Reference)	0.077	682/3682	1.00 (ref)	302/3682	1.00 (ref)
Medium	0.077–0.21	1234/7365	0.91 (0.82–1.01)	548/7365	0.93 (0.80–1.08)
Medium-high	0.21–0.33	382/2216	0.95 (0.83–1.10)	176/2216	1.04 (0.86–1.27)
High	0.66	257/1472	0.95 (0.81–1.12)	86/1472	0.78 (0.60–1.01)
Xylene					
Low (Reference)	0.33	678/3682	1.00 (ref)	303/3682	1.00 (ref)
Medium	0.33–0.92	1255/7371	0.93 (0.84–1.03)	563/7371	0.96 (0.83–1.11)
Medium-high	0.92–1.28	372/2210	0.92 (0.80–1.06)	152/2210	0.90 (0.73–1.10)
High	1.28	250/1472	0.93 (0.80–1.10)	94/1472	0.85 (0.66–1.08)

[a] Adjusted for birth year, infant sex, maternal race/ethnicity, education, age, and smoking.