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The Association between Benzene and Congenital Anomalies in Oklahoma, 1997-2009

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Abstract

Objectives: Although the most common cause of death in infants, little is known about the etiology of congenital anomalies. Recent studies have increasingly focused on environmental exposures, including benzene. While benzene is known to affect the central nervous system, the effects on the developing fetus are unclear.

Methods: We conducted a retrospective cohort study to evaluate the association between ambient benzene exposure and the prevalence of congenital anomalies among 628,121 singleton births in Oklahoma from 1997–2009. We obtained benzene from the Environmental Protection Agency's 2005 National-Scale Air Toxics Assessment for the census tract of the birth residence. We used modified Poisson regression with robust standard errors to calculate prevalence proportion ratios (PPR) and 95% confidence intervals (CI) between quartiles of benzene exposure and critical congenital heart defects (CCHDs), neural tube defects (NTDs), and oral clefts adjusted for maternal education and tobacco use.

Results: Median benzene exposure concentration in Oklahoma was 0.57 $\mu\text{g}/\text{m}^3$. We observed no association between benzene exposure and oral clefts, CCHDs or NTDs. When specific anomalies were examined, we observed an increased prevalence of cleft lip among those exposed to the second quartile of benzene compared to the first (PPR: 1.50, 95% CI: 1.05, 2.13), though no association with higher levels of exposure.

Conclusions: Our findings do not provide support for an increased prevalence of anomalies in areas more highly exposed to benzene. Future studies would benefit from pooling data from multiple states to increase statistical power and precision in studies of air pollutants and specific anomalies.

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Contributors

AEJ was primarily responsible for designing the study, analyzing the data, and wrote the manuscript. HDD programmed and contributed to data analysis, interpretation, and review of the manuscript. JEC contributed to the study design and data access and provided critical review of the manuscript. JAS contributed to the statistical analysis and critical review of the manuscript. JDP contributed to the design and analysis of the study and critical review of the manuscript.

Competing Interests

None declared.

Keywords

Congenital abnormalities; benzene; air pollution

INTRODUCTION

Congenital anomalies are the top cause of infant death in the US and Oklahoma has the second highest rate of infant deaths due to anomalies of any US state from 2007–2014 (1.77 deaths per 1,000 live births).¹ Congenital anomalies are a heterogeneous group of conditions affecting many body systems and have differing etiologic factors.² While causal factors for some anomalies have been identified, such as lack of prenatal folic acid, certain medications, and genetic factors, the etiology of the majority of anomalies remains unknown.³ Recent studies have increasingly focused on environmental exposures, including benzene, as potential risk factors for congenital anomalies. The United States Environmental Protection Agency (EPA) established the minimal risk level for ambient benzene as 28.71 $\mu\text{g}/\text{m}^3$ for acute exposures (<15 days) and 9.57 $\mu\text{g}/\text{m}^3$ for chronic exposures (>365 days).⁴ Sources of ambient benzene include motor vehicle exhaust, oil refineries, gasoline stations, auto repair stations, and oil and gas development.^{4–6}

Although the biologic mechanism for benzene to be a cause of congenital anomalies is unknown, benzene crosses the placenta and levels in the fetus can be higher than those in the mother.⁴ In addition, benzene is known to affect the central nervous system (CNS) and genetic toxicity due to benzene can potentially lead to neural tube defects (NTD) if exposure occurs during a critical window of development, though the mechanism is unclear for congenital heart defects (CHD) and orofacial anomalies.^{4,7}

Several recent studies have reported a positive association between benzene and NTDs, including both residential and occupational exposure to benzene. Two recent studies of residential benzene exposure and spina bifida in Texas using the same data observed approximately two times higher odds of spina bifida among those highly exposed to benzene compared to lower exposure.^{7,8} In a small occupational case-control study of Mexican-American women residing in Texas-Mexico border counties, Brender et al.⁹ observed a relationship between maternal occupational exposure to cleaning agents and NTDs (OR: 9.5, 95% CI: 1.1, 82.2, n=6 cases, n=1 control) adjusted for maternal age, education, and body mass index.

A few studies have evaluated the association between benzene and both CHD and oral clefts. In a retrospective cohort study, Tanner et al.¹⁰ observed a protective association between benzene and non-isolated pulmonary atresia (n=25 with pulmonary atresia, 973,797 without anomalies). For oral clefts, results were mixed with one study observing a 30–50% elevated odds of any oral cleft or cleft palate, respectively among those exposed to the highest quartile of benzene exposure compared to the lowest,¹⁰ with another study observing no association with any oral cleft.¹¹ In addition, in a small occupational study, Wennborg et al.¹² observed a five times higher odds of neural crest malformations, which included cleft lip/palate, ear anomalies, thymus aplasia, double-outlet ventricle, tetralogy of Fallot, and

ventricular septal defects, among those occupationally exposed to benzene in biomedical laboratories.

Because of the limited literature on benzene exposure and congenital anomalies, we aimed to further evaluate the relationship between ambient benzene exposure during pregnancy and critical congenital heart defects (CCHD), NTD, and oral clefts. We also aimed to evaluate exposure misclassification due to residential mobility during pregnancy.

METHODS

We conducted a retrospective cohort study of all singleton children born in Oklahoma who geocoded to the ZIP code level or better (n=628,121) using data collected by the Oklahoma Birth Defects Registry (OBDR) and vital statistics as part of their legislatively-mandated public health surveillance activities for birth years 1997–2009. These birth years were the most recent OBDR data available for analysis. The OBDR is an active surveillance system that identifies congenital anomalies from births occurring at hospitals in Oklahoma and is a member of the National Birth Defects Prevention Network (NBDPN).¹³ Registered nurses visit all birthing hospitals in Oklahoma to identify children with congenital anomalies, identify potential cases based on reportable International Classification of Diseases, 10th revision codes, review the medical record, and determine if the child meets eligibility criteria for inclusion in OBDR following NBDPN guidelines. Diagnoses included in the registry were then converted to Centers for Disease Control and Prevention British Pediatric Association (CDC BPA) codes, which are more specific to the site of the anomaly. Children must be diagnosed with or have signs/symptoms of an eligible anomaly prior to their second birthday. An additional level of review is conducted by an assigned editor at OBDR to ensure the record is complete.¹⁴ Institutional Review Board approval was obtained from the University of Oklahoma Health Sciences Center and the Oklahoma State Department of Health.

We linked birth certificates and OBDR datasets using last name, first name, and date of birth with Registry Plus™ Link Plus software v. 2.0 (CDC, Atlanta, GA), with 95% of records in OBDR linking to a birth certificate. We obtained data related to the type of anomaly from the OBDR. Covariates for births obtained from the birth certificate included characteristics of both the child and mother at delivery. We geocoded maternal residence at delivery from the birth certificate masked to congenital anomaly status using Texas A&M Geocoding Service¹⁵ and in ArcGIS v. 10.4 using 2014 TIGER/Line files.¹⁶ We used a Chi-Square test to determine if geocoding differed by congenital anomaly status.

To determine exposure to benzene, we obtained data from the EPA's 2005 National Scale Air Toxics Assessment (NATA), which estimated the annual average exposure to air toxics for the US at the census tract level.^{17,18} We selected the 2005 NATA estimates as this represents a mid-point for births included in our study. Data for the NATA estimates were obtained from EPA, state, and local air toxics inventories. Estimates from mobile sources (i.e., motor vehicles, nonroad engines, and equipment) and activity, fuel, and vehicle data were also incorporated into the models. To determine exposure to benzene using the NATA estimates, we assigned the census tract of the geocoded maternal residence at delivery to

each child and classified benzene into quartiles based on the distribution of benzene in the study population.

We used modified Poisson regression with robust error variance to estimate prevalence proportion ratio (PPR) for the association between benzene exposure and congenital anomalies using complete case analysis. We used a directed acyclic graph (DAG) to select confounders from variables with potential causal pathways between benzene and congenital anomalies, including urbanization, maternal smoking, history of fetal loss, family history of anomalies, gestational age at delivery, race/ethnicity, prenatal care (as a surrogate for prenatal vitamin use), parity (number of previous live births), maternal age, birthweight, maternal education (as a surrogate for socioeconomic status), maternal body mass index, gender, and year of birth. All covariates, with the exception of urbanization, were obtained from the birth certificate. Urbanization was obtained from the 2000 United States Census at the census block level.¹⁹ Maternal education and smoking were the minimally sufficient set of variables identified from the DAG. We also evaluated race/ethnicity as an effect modifier of the association between the exposures and anomalies by including an interaction term in the model, with $p < 0.05$ indicating a statistically significant interaction.

Analyses included evaluation of the relationship between benzene exposures and anomalies classified as CCHD, NTD, and oral clefts (Table 1). Because of heterogeneity within these groupings, we also evaluated specific types of CCHDs, NTDs, and oral clefts in an exploratory analysis. CCHDs are conditions targeted for newborn screening through pulse oximetry in OBDR and have been evaluated in previous studies.^{10,20,21} CCHDs include the following defects: common truncus/truncus arteriosus, transposition of the great arteries, double outlet right ventricle, Tetralogy of Fallot, single ventricle, pulmonary valve atresia and stenosis, tricuspid valve atresia and stenosis, Ebstein anomaly, hypoplastic left heart syndrome, coarctation of aorta, interrupted aortic arch, total anomalous pulmonary venous connection. We also evaluated specific NTDs (spina bifida and anencephaly) and oral clefts (cleft lip and cleft palate).

We conducted several sub-analyses of the association between benzene and the anomalies of interest to evaluate potential biases and limitations of the data. These included 1) excluding those birth addresses that geocoded to ZIP code centroid, 2) restriction to years of birth within two years of the 2005 benzene estimates (2003–2007), 3) restriction to isolated defects, and 4) the impact of residential mobility during pregnancy on exposure misclassification related to air pollution. Previous studies in North America estimated that 12%–33% of mothers change residence during pregnancy.^{22–25} We evaluated the potential impact of residential mobility in our study using published sensitivity and specificity estimates from a case-control study of benzene and NTDs in Texas, which obtained information on both residence at birth (index measure) and at conception (the “true” status).²⁴ To estimate associations corrected for exposure misclassification, we compared births exposed to ambient benzene above the median to below the median value ($0.57 \mu\text{g}/\text{m}^3$) and applied the sensitivity and specificity estimates reported by Lupo et al.²⁴ for children with and without anomalies (sensitivity=91%, specificity=91%). Statistical analyses were conducted in SAS v. 9.4.

RESULTS

The highest benzene levels in Oklahoma were located in the major metropolitan areas (Figure 1). The median estimated maternal ambient benzene exposure concentration in Oklahoma was $0.57\mu\text{g}/\text{m}^3$ (interquartile range $0.54\mu\text{g}/\text{m}^3$), which was lower than the US median exposure concentration at $0.83\mu\text{g}/\text{m}^3$ (interquartile range $0.73\mu\text{g}/\text{m}^3$). We observed a higher percentage of males for CCHD and oral clefts, a lower percentage receiving prenatal care for children with NTDs, and lower gestational age at delivery and lower birth weight for all three anomaly types compared to those without anomalies (Table 2). There was no difference in geocoding level (street, ZIP code, and city/state level) and congenital anomaly status (CCHD $p=0.49$, NTD $p=0.92$, oral clefts $p=0.06$).

We observed no association between benzene exposure and the specific anomalies of CCHDs, NTDs, and oral clefts when analyzing quartiles of benzene exposure after adjustment for maternal education and smoking (Table 3). Although results of analyses of specific CCHDs included the null value of 1.0, the PPR was elevated among several CCHDs including common truncus (4th quartile PPR: 1.45, 95% CI: 0.67, 3.17), double outlet right ventricle (4th quartile PPR: 1.81, 95% CI: 0.66, 4.96), single ventricle (4th quartile PPR: 1.46, 95% CI: 0.80, 2.68), pulmonary valve atresia and stenosis (4th quartile PPR: 1.48, 95% CI: 0.67, 3.27), and total anomalous pulmonary venous connection (4th quartile PPR: 1.56, 95% CI: 0.87, 2.81) (Table 4). Results for specific NTDs were near the null value of 1.0 (spina bifida) or below 1.0 (anencephaly) and not statistically significant. However, we observed an increased prevalence of cleft lip alone among those exposed to the second quartile of benzene compared to the first (PPR: 1.50, 95% CI: 1.05, 2.13). The prevalence was also elevated in the fourth quartile, but attenuated and not statistically significant (PPR: 1.30, 95% CI: 0.90, 1.87). Cleft palate alone was not associated with benzene exposure.

In our sub-analysis excluding those whose residence at birth was geocoded to the ZIP code centroid ($n=140,211$), results were not meaningfully different in the analysis adjusted for maternal education and smoking (CCHD 4th quartile PPR: 1.06, 95% CI: 0.85, 1.32; NTD 4th quartile PPR: 0.96, 95% CI: 0.63, 1.47; Oral clefts 4th quartile PPR: 0.87, 95% CI: 0.67, 1.13). After restricting to years of birth surrounding the 2005 benzene estimates (2003–2007), we observed stronger results for CCHD (4th v. 1st quartile adjusted PPR: 1.14, 95% CI: 0.88, 1.49), but little difference for NTD (4th v. 1st quartile adjusted PPR: 0.83, 95% CI: 0.48, 1.43) or oral clefts (4th v. 1st quartile adjusted PPR: 0.86, 95% CI: 0.63, 1.18). Results for isolated defects were based on smaller numbers for each anomaly type and were similar in magnitude to the results of both isolated and non-isolated anomalies after adjustment (CCHD 4th quartile PPR: 1.13, 95% CI: 0.64, 1.99, $n=98$; NTD 4th quartile PPR: 1.04, 95% CI: 0.58, 1.87, $n=90$; oral clefts 4th quartile PPR: 0.85, 95% CI: 0.66, 1.10, $n=560$). After evaluating the potential impact of exposure misclassification due to residential mobility between conception and birth, we estimate that our observed results were underestimated, with misclassification biasing results towards the null (CCHD PPR: 1.03, 95% CI: 0.92, 1.16; NTD PPR: 0.93, 95% CI: 0.73, 1.17; oral clefts PPR: 0.74, 95% CI: 0.64, 0.85).

DISCUSSION

In our analysis of CCHDs, NTDs, and oral clefts we observed no association between benzene and these anomaly types. However, when evaluating specific CCHDs, we observed elevated, though non-statistically significant, point estimates for many types of CCHDs. We also observed an association between benzene levels in the second quartile and cleft lip alone, though there was no association among the third and fourth quartiles compared to the first quartile. Among those with non-isolated defects, Tanner et al.¹⁰ observed an elevated prevalence of cleft lip among those exposed to the fourth quartile of benzene exposure compared to the first, though not statistically significant (4th quartile adjusted PPR: 1.79, 95% CI: 0.52, 6.30). In addition, the authors observed similar, though non-significantly increased prevalence for isolated double-outlet right ventricle (Adjusted PPR: 1.34, 95% CI: 0.89, 2.00) and common truncus (truncus arteriosus) (Adjusted PPR: 1.47, 95% CI: 0.79, 2.74) among those exposed to the fourth quartile of benzene compared to the first. Our results did not support the findings from Texas case-control studies of benzene and NTDs.⁷⁸ However, the high exposure category in Texas was higher than the maximum levels observed in Oklahoma (Texas 4th quartile: >2.86–7.44 µg/m³; Oklahoma 4th quartile: 0.87–2.03 µg/m³). The maximum observed benzene levels in both states was lower than the EPA's minimal risk levels. While health effects at higher levels of benzene have been observed,²⁶²⁷ it is also important to understand potential health effects of lower levels of benzene.²⁸ In addition, we used a more recent version of the EPA's NATA model (2005 v. 1999), with the primary difference being the incorporation of additional dispersion models to estimate benzene exposure.¹⁷

Though the existing literature for benzene exposure and congenital anomalies is limited, a meta-analysis of other air pollutants (primarily particulate matter >10 microns in diameter [PM₁₀], sulfur dioxide [SO₂], nitrogen dioxide [NO₂], carbon monoxide, and ozone) and congenital anomalies (primarily cardiac defects and oral cleft defects) observed small effects of NO₂ and both coarctation of the aorta (combined OR: 1.17, 95% CI: 1.00, 1.36) and tetralogy of Fallot (combined OR: 1.20, 95% CI: 1.02, 1.42), PM₁₀ and atrial septal defects (combined OR: 1.14, 95% CI: 1.01, 1.28), SO₂ and coarctation of the aorta (combined OR: 1.07, 95% CI: 1.01, 1.13) and tetralogy of Fallot (combined OR: 1.03, 95% CI: 1.01, 1.05).²⁹ The authors observed no association with oral clefts for any of the pollutants evaluated. However, in an updated meta-analysis including these studies, Chen et al.³⁰ observed only one statistically significant finding between NO₂ and coarctation of the aorta (combined OR: 1.20, 95% CI: 1.02, 1.41), with the association between O₃ and cleft lip approaching significance (combined OR: 1.17, 95% CI: 0.98, 1.41). Air pollution is complex to study due to the multiple types of air pollutants, which are frequently co-linear, and multiple methods of measuring air pollutants, which include using air monitoring stations and model-based estimates.³¹³² While estimates of exposure to air pollutants varies depending on the exposure classification method used, a recent study compared multiple methods of measuring benzene and observed minimal changes in exposure concentration.³² In addition, the complexity of congenital anomalies, which are heterogeneous even among specific categories of anomalies, may have differing etiologies.³¹ The heterogeneity of both air

pollution and congenital anomalies, in addition to the rarity of individual anomalies makes it difficult to evaluate these specific associations at a state level.

A strength of our study is the availability of data from an active, population-based birth defects registry. The Centers for Disease Control and Prevention requires quality assessments of the OBDR data. Quality improvement methods used by OBDR include the use of registered nurses to identify and abstract cases through strong quality procedures.³³ In comparison to other active NBDPN registries, OBDR is similar to or stronger in completeness, timeliness, and accuracy of the data (personal communication). In addition, including data on congenital anomalies for the entire State of Oklahoma allowed us to evaluate CCHDs, NTDs, and oral clefts separately. Furthermore, the use of the EPA's 2005 NATA estimates for benzene at the census tract level allowed us to evaluate the exposure accounting for multiple sources of benzene exposure, including traffic, Toxics Release Inventory sites, and other point and non-point sources in Oklahoma. Using the NATA estimates provides an advantage over modeling benzene from monitor data based on a previous study, which demonstrated poor reliability between interpolated benzene estimates and EPA-modeled data used in the NATA estimates.³⁴

Although the OBDR is population-based, it only contains children diagnosed with a major congenital anomaly who were hospitalized from birth to age six years (with signs/symptoms or a diagnosis of an eligible diagnosis prior to the second birthday). Anomalies diagnosed in children after discharge from the birthing hospital who were never hospitalized will not be reported to the registry and are more likely to be minor. However, because the OBDR only includes major anomalies, under-ascertainment of minor anomalies would have a minimal impact on the results. While we conducted multiple statistical tests to evaluate the relationship between benzene and specific CCHDs, NTDs, and oral clefts, these analyses were exploratory and hypothesis generating, thus we did not adjust for multiple comparisons.³⁵ Therefore, it is possible that the elevated prevalence of cleft lip within the second quartile of benzene exposure, but not at higher levels of exposure, was due to chance. Survival bias was another concern in this study. Children with certain anomalies, such as CNS anomalies, may not survive to delivery, and thus, would not link with a birth certificate to classify exposure. This could potentially underestimate the association if exposure is related to severe anomalies with high prenatal mortality. Obtaining information on covariates from the birth certificate provided information on all children at birth. However, we were limited to variables reported on the birth certificate in our analysis and the reliability and validity of behavioral risk factors, including maternal smoking, may be poor.³⁶

In addition, there is a potential for exposure misclassification due to residential mobility and the ecologic level of the benzene estimates. We assumed that the residence at the child's birth was the same as that during early pregnancy when congenital anomalies develop, which may result in exposure misclassification. Adjusting our estimates for potential exposure misclassification due to residential mobility allowed us to assess the potential impact on the association, which indicates our results may be biased towards the null. Although the NATA estimates account for commuting between census tracts based on US Census data, misclassification may still exist for mothers who do not work in the home, which could result in an over or underestimate of the association. NATA provides estimates

of benzene at the census tract level, which prohibited us from evaluating individual-level benzene exposure. Although biomarkers can be measured from urine, breath, and serum, measurement is limited to recent exposures.⁴ Ambient benzene has decreased approximately 66% in the US from 1994 through 2009.³⁷ In addition, the availability of annual benzene estimates from NATA prohibited us from evaluating seasonal variability in exposure, though this is an important consideration for future studies. Because we did not have information on maternal occupation during pregnancy, we were also unable to account for occupational benzene exposure. Benzene was only available for one year in the 2005 NATA and the EPA advises against combining multiple NATA assessments.¹⁸ When we restricted our analysis to births in the years surrounding the NATA estimates (2003–2007), our results were strengthened for CCHDs, indicating our results may be biased towards the null.

In summary, we did not observe an association between benzene exposure and CCHDs, NTDs, or oral clefts. We observed an association with cleft lip among those exposed to the second quartile of benzene and elevated PPRs, although not significantly, for several CCHDs, but not NTDs. This study was one of the first to evaluate the relationship between benzene and specific types of CCHD, NTD, and oral clefts, though our power to detect an association was limited. As a next step, we plan to evaluate the relationship between exposure to natural gas wells and congenital anomalies in Oklahoma, a state with considerable oil and gas development.³⁸ Future studies would benefit from pooling results from multiple states and evaluating other air pollutants to better understand the relationship between air pollution and specific congenital anomalies.

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What this study adds:

What is already known about this subject? Although the biologic mechanism for benzene to be a cause of congenital anomalies is unknown, benzene crosses the placenta and levels in the fetus can be higher than those in the mother.

What are the new findings? We observed no associations between benzene exposure and anomaly classifications of critical congenital heart defects, neural tube defects, or oral clefts. When specific anomalies were examined, the prevalence of cleft lip increased among those exposed to the second quartile of benzene compared to the first, but there was no evidence of a dose-response relationship.

How might this impact on policy or clinical practice in the foreseeable future? This is one of the first studies to evaluate the relationship between benzene and specific anomalies. Future studies would benefit from pooling results from multiple states and evaluating other air pollutants.

Figure 1. Distribution of ambient benzene exposure among Oklahoma births, 1997–2009. Source of Oklahoma Freeways is the Federal Highway Administration, National Transportation Atlas.

Table 1.

Centers for Disease Control and Prevention British Pediatric Association (CDC BPA) codes included for analysis of specific congenital anomaly types.

Anomaly Type	CDC BPA Codes
Critical congenital heart defects (CCHD) (combined)	745000-745019, 745100-745119, 745130-745159, 745190-745199, 745200-745219, 745300-745309, 746000-746009, 746200-746299, 746700-746799, 747100-747199, 747215-747217, 747285, 747420-747429, 746840, 747310-747319,
Common truncus (truncus arteriosus or TA)	745000-745019
Transposition of the great arteries (TGA)	745100-745119, 745190-745199
Double outlet right ventricle (DORV)	745130-745159
Single ventricle	745300-745309
Pulmonary valve atresia and stenosis	746000-746009
Tricuspid valve atresia and stenosis	746100
Ebstein anomaly	746200-746299
Hypoplastic left heart syndrome	746700-746799
Coarctation of aorta	747100-747199
Tetralogy of Fallot (TOF)	745200-745219, 746840, 747310-747319
Interrupted aortic arch (IAA)	747215-747217, 747285
Total anomalous pulmonary venous connection (TAPVC)	747420-747429
Neural Tube Defects	741000-741999, 742300-742399
Spina Bifida	741000-741999, excluding anencephaly
Anencephaly	740000-740109
Cleft Lip/Palate	749000-749299
Cleft palate only	749000-749099
Cleft lip only	749100-749199

Table 2.
Distribution of birth characteristics by congenital anomaly status, Oklahoma births, 1997-2009.

Anomaly Type	Critical Congenital Heart Defects		Neural Tube Defects		Oral Clefts		No Congenital Anomaly	
N	N=1123	%	N=283	%	N=797	%	N=603,783	%
Prevalence (per 10,000 live births) ^a (95% confidence interval)	17.9 (16.8, 18.9)		4.5 (4.0, 5.0)		12.7 (11.8, 13.6)			
Gender	N	%	N	%	N	%	N	%
Female	477	42.5	139	49.1	313	39.3	296232	49.1
Male	646	57.5	144	50.9	484	60.7	307541	50.9
Unknown	0	0.0	0	0.0	0	0.0	10	0.0
Race/Ethnicity	N	%	N	%	N	%	N	%
Non-Hispanic White	752	67	197	69.6	556	69.8	401256	66.5
Non-Hispanic African American	88	7.8	20	7.1	39	4.9	56724	9.4
Non-Hispanic American Indian	129	11.5	22	7.8	104	13.0	63645	10.5
Non-Hispanic Asian/Unknown ^b	32	2.8	<6 ^c	1.8	20	2.5	15530	2.6
Hispanic	122	10.9	39	13.8	78	9.8	66628	11.0
Maternal Age	N	%	N	%	N	%	N	%
<20	138	12.3	36	12.7	132	16.6	89584	14.8
20-34	862	76.8	221	78.1	603	75.7	465279	77.1
35+/Unknown ^b	123	11	26	9.2	62	7.8	48920	8.1
Prenatal Care	N	%	N	%	N	%	N	%
Prenatal care	1037	92.3	251	88.7	749	94.0	570774	94.5
No Prenatal Care	22	2.0	6	2.1	11	1.4	7141	1.2
Unknown	64	5.7	26	9.2	37	4.6	25868	4.3
Gestational Age at Birth	N	%	N	%	N	%	N	%
<37 weeks	205	18.3	90	31.8	111	13.9	48026	8.0
37-39 weeks	616	54.9	148	52.3	439	55.1	329252	54.5
40+ weeks	258	23.0	36	12.7	214	26.9	208107	34.5
Unknown	44	3.9	9	3.2	33	4.1	18398	3.0

Anomaly Type	Critical Congenital Heart Defects				Neural Tube Defects				Oral Clefts				No Congenital Anomaly			
N	N=1123	%	N	%	N=283	%	N	%	N=797	%	N	%	N=603,783	N	%	
Prevalence (per 10,000 live births) ^a (95% confidence interval)		17.9 (16.8, 18.9)				4.5 (4.0, 5.0)				12.7 (11.8, 13.6)						
Birth Weight																
<1500	33	2.9	41	14.5	27	3.4	5749	1.0								
1500-2499	176	15.7	50	17.7	95	11.9	30306	5.0								
2500-3999	845	75.2	177	62.5	620	77.8	516026	85.5								
4000+/Unknown ^b	69	6.1	15	5.3	55	6.9	51702	8.6								
Maternal Tobacco																
Yes	159	14.2	44	15.5	153	19.2	95806	15.9								
No	894	79.6	222	78.4	588	73.8	466638	77.3								
Unknown	70	6.2	17	6.0	56	7.0	41339	6.8								
Maternal Education																
Less than High School	250	22.3	64	22.6	200	25.1	138101	22.9								
High School	442	39.4	101	35.7	314	39.4	218819	36.2								
More than High School/Unknown ^b	431	38.4	118	41.7	283	35.5	246863	40.9								
Urbanization																
Rural	317	28.2	88	31.1	229	28.7	156588	25.9								
Urban	806	71.8	195	68.9	568	71.3	447195	74.1								

^aThe number of live births for the prevalence estimate includes all singleton children born in Oklahoma from 1997-2012 who geocoded to the ZIP code level or better (n=628,121).

^bThe Unknown category was combined with the smallest category to ensure confidentiality following Oklahoma State Department of Health policies requiring suppression of categories with <6 observations.

^cCategories with <6 observations suppressed following Oklahoma State Department of Health policies (Non-Hispanic Asian/Unknown with neural tube defects).

Table 3.

Association between maternal ambient benzene exposure and types of anomalies, Oklahoma, 1997-2009.

Quartiles of Benzene	Critical Congenital Heart Defects N=1123		Neural Tube Defects N=283		Oral Clefts N=797	
	Unadjusted PPR (95% CI)	Adjusted ^a PPR (95% CI)	Unadjusted PPR (95% CI)	Adjusted ^a PPR (95% CI)	Unadjusted PPR (95% CI)	Adjusted ^a PPR (95% CI)
0.11-<0.33 µg/m ³	Reference	Reference	Reference	Reference	Reference	Reference
0.33-<0.57 µg/m ³	1.03 (0.87, 1.22)	1.03 (0.87, 1.22)	1.02 (0.74, 1.41)	0.99 (0.71, 1.39)	1.06 (0.88, 1.28)	1.09 (0.90, 1.32)
0.57-<0.87 µg/m ³	1.04 (0.88, 1.23)	1.04 (0.88, 1.24)	0.97 (0.70, 1.34)	0.95 (0.67, 1.35)	0.81 (0.67, 0.99)	0.87 (0.71, 1.08)
0.87-2.03 µg/m ³	1.05 (0.89, 1.23)	1.05 (0.88, 1.24)	0.93 (0.66, 1.29)	0.93 (0.66, 1.31)	0.80 (0.65, 0.97)	0.82 (0.67, 1.01)

^a Adjusted for maternal education and smoking

PPR: Prevalence proportion ratio, 95% CI: 95% confidence interval

Table 4.

Association between maternal ambient benzene exposure and specific critical congenital heart defects, neural tube defects, and oral clefts for quartiles of benzene exposure.

	N with Anomalies	Unadjusted PPR (95% CI)	Adjusted^a PPR (95% CI)
Specific Critical Congenital Heart Defects			
Common truncus	54		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.27 (0.59, 2.71)	1.40 (0.64, 3.06)
0.57-<0.87 µg/m ³		0.67 (0.27, 1.64)	0.77 (0.30, 1.94)
0.87-2.03 µg/m ³		1.59 (0.77, 3.28)	1.45 (0.67, 3.17)
Transposition of the great arteries	159		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		0.92 (0.59, 1.43)	0.94 (0.60, 1.48)
0.57-<0.87 µg/m ³		1.08 (0.71, 1.66)	1.02 (0.65, 1.59)
0.87-2.03 µg/m ³		0.91 (0.58, 1.42)	0.90 (0.56, 1.43)
Double outlet right ventricle	38		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.53 (0.54, 4.28)	1.56 (0.56, 4.38)
0.57-<0.87 µg/m ³		2.19 (0.83, 5.75)	2.32 (0.89, 6.06)
0.87-2.03 µg/m ³		1.68 (0.61, 4.61)	1.81 (0.66, 4.96)
Single ventricle	82		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.23 (0.67, 2.26)	1.15 (0.61, 2.17)
0.57-<0.87 µg/m ³		0.74 (0.37, 1.48)	0.72 (0.35, 1.47)
0.87-2.03 µg/m ³		1.38 (0.76, 2.49)	1.46 (0.80, 2.68)
Pulmonary valve atresia and stenosis	53		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.02 (0.42, 2.44)	1.03 (0.43, 2.47)
0.57-<0.87 µg/m ³		1.71 (0.79, 3.74)	1.55 (0.70, 3.45)
0.87-2.03 µg/m ³		1.61 (0.73, 3.55)	1.48 (0.67, 3.27)
Tricuspid valve atresia and stenosis	45		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.02 (0.44, 2.34)	1.00 (0.43, 2.31)
0.57-<0.87 µg/m ³		0.92 (0.39, 2.16)	0.71 (0.29, 1.76)
0.87-2.03 µg/m ³		1.19 (0.53, 2.65)	1.15 (0.51, 2.56)
Ebstein anomaly	42		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.36 (0.64, 2.87)	1.40 (0.62, 3.13)
0.57-<0.87 µg/m ³		0.59 (0.23, 1.49)	0.57 (0.21, 1.56)
0.87-2.03 µg/m ³		0.59 (0.23, 1.49)	0.56 (0.21, 1.54)

	N with Anomalies	Unadjusted PPR (95% CI)	Adjusted ^a PPR (95% CI)
Hypoplastic left heart syndrome	136		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.15 (0.71, 1.88)	1.17 (0.70, 1.95)
0.57-<0.87 µg/m ³		1.34 (0.84, 2.16)	1.50 (0.91, 2.45)
0.87-2.03 µg/m ³		1.07 (0.65, 1.77)	1.10 (0.65, 1.85)
Coarctation of aorta	297		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		0.86 (0.63, 1.18)	0.85 (0.61, 1.17)
0.57-<0.87 µg/m ³		0.88 (0.64, 1.20)	0.85 (0.61, 1.19)
0.87-2.03 µg/m ³		0.83 (0.60, 1.14)	0.85 (0.61, 1.18)
Tetralogy of Fallot	266		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.10 (0.78, 1.56)	1.06 (0.74, 1.53)
0.57-<0.87 µg/m ³		1.12 (0.80, 1.59)	1.08 (0.75, 1.55)
0.87-2.03 µg/m ³		1.17 (0.83, 1.65)	1.14 (0.80, 1.63)
Interrupted aortic arch	57		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		0.64 (0.31, 1.32)	0.67 (0.32, 1.38)
0.57-<0.87 µg/m ³		0.80 (0.40, 1.57)	0.89 (0.45, 1.79)
0.87-2.03 µg/m ³		0.58 (0.28, 1.22)	0.56 (0.26, 1.22)
Total anomalous pulmonary venous connection	96		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.47 (0.81, 2.68)	1.53 (0.84, 2.78)
0.57-<0.87 µg/m ³		1.34 (0.73, 2.48)	1.39 (0.75, 2.58)
0.87-2.03 µg/m ³		1.56 (0.87, 2.83)	1.56 (0.87, 2.81)
Neural Tube Defects			
Spina Bifida	218		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		1.17 (0.81, 1.70)	1.10 (0.75, 1.62)
0.57-<0.87 µg/m ³		1.09 (0.74, 1.58)	1.01 (0.68, 1.51)
0.87-2.03 µg/m ³		0.97 (0.66, 1.43)	0.93 (0.62, 1.38)
Anencephaly	65		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		0.63 (0.32, 1.26)	0.71 (0.35, 1.45)
0.57-<0.87 µg/m ³		0.67 (0.34, 1.32)	0.80 (0.39, 1.62)
0.87-2.03 µg/m ³		0.81 (0.43, 1.54)	0.92 (0.47, 1.81)
Oral Clefts			
Cleft lip only	475		
0.11-<0.33 µg/m ³		Reference	Reference

	N with Anomalies	Unadjusted PPR (95% CI)	Adjusted ^a PPR (95% CI)
0.33-<0.57 µg/m ³		1.53 (1.09, 2.14)	1.50 (1.05, 2.13)
0.57-<0.87 µg/m ³		0.90 (0.62, 1.32)	0.97 (0.65, 1.44)
0.87-2.03 µg/m ³		1.26 (0.89, 1.79)	1.30 (0.90, 1.87)
Cleft palate only	260		
0.11-<0.33 µg/m ³		Reference	Reference
0.33-<0.57 µg/m ³		0.99 (0.78, 1.26)	1.00 (0.78, 1.29)
0.57-<0.87 µg/m ³		0.86 (0.67, 1.10)	0.89 (0.69, 1.15)
0.87-2.03 µg/m ³		0.73 (0.56, 0.95)	0.76 (0.58, 1.00)

^a Adjusted for maternal education and smoking

PPR: Prevalence proportion ratio, 95% CI: 95% confidence interval