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## Prenatal Exposure to Air Toxics and Malignant Germ Cell Tumors in Young Children

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Running title: Air toxics and childhood germ cell tumors

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**Objective:** To assess prenatal air toxics exposure and risk for childhood germ cell tumors (GCTs) by histological subtype (yolk sac tumor and teratoma). **Methods:** In this case-control study, GCT cases <6 years ( $n=243$ ) identified from California Cancer Registry records were matched by birth year to cancer-free population controls ( $n=147,100$ ), 1984-2013. Routinely monitored air toxic exposures were linked to subjects' birth address. Logistic regression estimated GCT risks per interquartile range increase in exposure. **Results:** Prenatal exposure to various highly-correlated, traffic-related air toxics during the second trimester increased GCT risk, particularly 1,3-butadiene (odds ratio [OR]=1.51; 95% confidence interval [CI]=1.01, 2.26) and meta/para-xylene (OR=1.56; 95% CI=1.10, 2.21). Analyses by subtype indicated elevated ORs for yolk sac tumors but not teratomas. **Conclusion:** Our estimated ORs are consistent with positive associations between some prenatal traffic-related air toxics and GCT risk, notably yolk sac tumors.

**Key words:** yolk sac tumor; childhood; cancer; toxicity; air pollutants; risk factor; epidemiology; pregnancy; vehicle emissions; BTEX

## INTRODUCTION

Germ cell tumors (GCTs) are a heterogeneous group of neoplasms believed to arise from primordial germ cells; while they share a similar origin, pediatric GCT histologies have differential methylation patterns, suggesting different etiologies and risk factor profiles.<sup>1,2</sup> These tumors are rare, comprising 3.5% of all cancers in children under the age of 15.<sup>3</sup> In the United States, the GCT incidence rate in children is approximately 6.0 per million.<sup>4</sup> In early childhood, the two most common histologic subtypes of GCTs are teratomas and yolk sac tumors.<sup>5</sup>

With the exception of cryptorchidism and race/ethnicity, there are few established risk factors for childhood GCTs;<sup>6,7</sup> however, some data suggest risk factors differ by histologic subtype in young children (ie, teratomas and yolk sac tumors).<sup>8</sup> In a recent study of California children, our group observed a weak but positive relationship between traffic-related air pollution exposure in pregnancy (assessed using the California LINE Source [CALINE4] dispersion model) and risk for childhood GCTs, specifically teratomas. We observed similar positive associations when assessing exposure based on measures of traffic density within 500m of the child's residence.<sup>9</sup> However, in a separate analysis of children residing in Los Angeles County, we did not detect associations with teratomas or any GCTs when using a Land Use Regression (LUR) model to assess prenatal air pollution exposure.<sup>10</sup>

There are few studies on perinatal exposure to air pollution and GCT risk in children under 15 years old. A case-control study of 272 GCT cases examined exposure to engine exhausts in the perinatal period, reporting possible increased risk for male (odds ratio [OR]=1.7, 95% confidence interval [CI]=0.7-4.0) but not female (OR=0.9; 95% CI=0.4-1.8) children. In the same study, perinatal exposure to "industry dusts" was weakly related to increased GCT risk among female cases only (OR=1.5, 95% CI=0.9-2.4).<sup>11</sup> A Spanish study including 120 GCT

cases found no association between proximity to urban areas with traffic pollution and childhood GCT risk.<sup>12</sup> Neither of these publications stratified GCTs by subtype. Some studies of young men and adults have reported that paternal exposure to metalwork and maternal exposure to hexachlorobenzene and polychlorinated biphenyls increase offspring risk for testicular cancer.<sup>13,</sup>

14

Using a cancer and birth registry-based sample of young California children, this population-based case-control study examines the relationship between prenatal exposure to ambient air toxics and risk for malignant GCTs, and includes analyses that consider histologic subtype (ie, yolk sac tumors and teratomas).

## METHODS

Childhood cancer cases diagnosed <6 years were ascertained from California Cancer Registry records, 1988-2013. Cancer-free controls were frequency matched to childhood cancer cases by birth year, but otherwise randomly selected from California birth records in the main case-control study, which included all reported cancers <6 years as described in detail elsewhere.<sup>15</sup>

GCT cases were classified based on the International Classification of Childhood Cancer, Version 3 (ICCC-3) codes 101-105 ( $n=451$ ). Histological subtypes of GCTs were identified via the International Classification of Diseases for Oncology, Version 3 (ICD-O-3); yolk sac tumors (ICD-O-3 code 9071;  $n=181$ ) and malignant teratomas (ICD-O-3 codes 9080-9084 with malignant behavior code;  $n=216$ ) were the most common in our young study population. Fifty-four cases were not coded as either a teratoma or a yolk sac tumor (mixed germ cell tumors,  $n=26$ ; germinomas,  $n=16$ ; other,  $n=12$ ).

Air toxics were selected for inclusion in our study if they were listed as established or suspected carcinogens by the International Agency for Research on Cancer, or if they were primarily emitted from traffic combustion (ie, benzene, toluene, ethyl benzene, and xylenes [BTEX]). Air toxic exposure during pregnancy was assessed using monitoring data from the California Air Resources Board (CARB)'s Air Toxics Program, as previously described in detail.<sup>16</sup> The CARB air toxics monitoring program was established in 1984. In the CARB toxics monitoring network, 24-hour integrated samples of ambient air concentrations are collected approximately every 12 days. Monitors are located across the state, primarily positioned near heavily trafficked highways in industrial or agriculturally intense regions; locations are selected in order to be representative for the area.<sup>17</sup> Air toxics in the vicinity of our study population residences were monitored at up to 30 sites; not all toxics or criteria pollutants were collected across the entire study period (at all or any sites), and CARB monitors do not necessarily collect data on the same agents at every monitor.

Using the latitude and longitude of each monitoring station as provided by CARB, we determined the distance from each monitor to each home or zip code centroid. Prior to 1998, home location was based on zip code centroid, which was calculated using an open source geocoder with manual correction of unmatched addresses.<sup>18</sup> From 1998, residential addresses at birth were geocoded based on birth certificates as available, otherwise zip code centroid was used. On the birth record, parents are asked to provide a residential address (street and house number) rather than a PO Box. For analyses using a buffer distance of 3 kilometers (km), distance was determined by zipcode centroid for 58,497 records, and by exact address for 88,846 records. For analyses using a buffer distance of 4km, distance was determined by zipcode centroid for 62,709 records, and by exact address for 92,739 records.

This study focused on risk associated with prenatal exposure to ambient air toxics because (1) we only had information on address at birth and (2) many cases have early diagnoses and there is an expectation that prenatal exposures may be of most relevance.<sup>19,20</sup> Dates of birth and gestational ages, estimated using date of last menses, were obtained from birth certificates and used to calculate developmental period-specific exposure averages for each trimester and the entire pregnancy.

Subjects were assigned air toxic exposure values according to measurements taken at the nearest monitor. We additionally explored measures generated with kriging, but saw little meaningful difference in effect estimates (unpublished data). For each air toxic, we included children who had at least 1 reading for each full month of pregnancy. Subjects were only included in our analyses if they were born 1984+ and lived within a specified radius around an air monitoring station. In order to balance exposure misclassification with increasing distance from a station against sample size limitations, we used a buffer distance of 3km for analyses of all GCTs; in subgroup analyses of yolk sac tumors and teratomas, a 4km buffer distance was implemented to increase sample size.

Unconditional logistic regression was used to estimate ORs and 95% CIs for GCT risk with each interquartile range increase in air toxics exposure, separately for each toxic and developmental period. Selection of covariates was based on the literature and associations seen in our previous analyses.<sup>8,21-24</sup> Crude models controlled for the matching variable (birth year), while adjusted models additionally controlled for maternal age (continuous), maternal race/ethnicity (non-Hispanic white vs. all others), and a five-level neighborhood socioeconomic status (SES) index.<sup>25</sup> We also explored adjustment for two additional socioeconomic variables: maternal years of education and source of payment for prenatal care (private insurance

[including Health Maintenance Organizations and Blue Cross-Blue Shield] and other payment methods [government aid programs, worker's compensation, Title V, and self-pay]);<sup>8</sup> and adjusted for race/ethnicity using more detailed indicator variables for non-Hispanic whites, Hispanics of any race, and Asian/Pacific Islanders. These additional adjustments did not change estimated ORs by at least 10% and therefore were left out of final models.

Several air toxics are generated from the same sources and therefore would be correlated. Among controls, we assessed correlations across toxics measures and report Pearson correlation coefficients and descriptive statistics for each toxic across the entire pregnancy period (for both 3km and 4km buffer distances, see Supplementary Tables 1-4). In order to identify highly correlated toxics, we employed factor analysis using principal components extraction with varimax rotation. We grouped toxics by factor, with loadings >0.80; factor one consisted of 14 pollutants we categorized as traffic-related air toxics and factor two was comprised of six polycyclic aromatic hydrocarbons. Fifteen pollutants were not loaded on a factor.

All statistical analyses were conducted using SAS, Version 9.4 (Cary, North Carolina).

## **RESULTS**

We identified 243 GCT cases and 147,100 controls born 1984+ and residing within 3km of air monitoring stations. In subgroup analyses, we identified 99 yolk sac tumor cases, 125 teratoma cases, and 155,191 controls born 1984+ and living within 4km of air monitoring stations. While population characteristics have been previously described in detail,<sup>8</sup> we present select demographic characteristics in Table 1. Maternal non-white race/ethnicity was more common among yolk sac tumor cases and less common among teratoma cases, but there was little difference between cases and controls with respect to maternal age and neighborhood SES.



Exposure to several traffic-related air toxics in the second trimester was associated with an elevated risk for all GCTs in offspring, particularly exposure to meta/para-xylene and 1,3-butadiene (Table 2). Second trimester exposure to ortho-xylene, para-dichlorobenzene, and ortho-dichlorobenzene was positively associated with GCT risk in offspring. For ortho-dichlorobenzene, entire pregnancy exposure was also associated with increased GCT risk. We observed an increased risk for GCTs with exposure to formaldehyde in the first trimester and the entire pregnancy.

Exposure to BTEX and 1,3-butadiene in the second trimester was associated with an increased risk for yolk sac tumors (Table 3). ORs were similar or elevated for BTEX when assessing exposure throughout pregnancy, with the highest OR estimated for ethyl benzene. Yolk sac tumor risk was also positively associated with second trimester exposure to ortho-dichlorobenzene, para-dichlorobenzene, strontium, and chromium, as well as exposure to formaldehyde in the first trimester and the entire pregnancy.

Estimated ORs for prenatal exposure to air toxics and teratomas were imprecise and no meaningful associations were detected (Supplementary Table 5).

## **DISCUSSION**

This record linkage study suggests that ambient exposure to some traffic-related air toxics during the second trimester is associated with an increased risk for GCT development in young children, particularly yolk sac tumors. Our previous findings have been inconsistent. In one study of California children, we detected associations with GCTs when using CALINE4 air pollution modeling of carbon monoxide or traffic density to assess traffic exposure in the first trimester, but not for monitored particulate matter ( $\leq 2.5\mu\text{m}$  in aerodynamic diameter;  $\text{PM}_{2.5}$ ).<sup>9</sup> The CALINE4 model focuses on local exposure to traffic emissions, while  $\text{PM}_{2.5}$  has multiple

sources in California, including traffic, but also construction or agricultural dust and sea salt. Consequently, traffic density, measured PM, and CALINE4 traffic models can be poorly correlated depending on the region.<sup>26</sup> In contrast to the current study results, our CALINE4 analysis estimated an increased risk for teratomas rather than yolk sac tumors;<sup>9</sup> however, carbon monoxide was not associated with GCTs overall or either subtype in the present analysis. Additionally, in a separate registry-based study of Los Angeles County children only, we observed no association with all GCTs or teratomas when using a LUR model to assess prenatal traffic-related air pollution exposure (ie, nitric oxide, nitrogen dioxide, and nitrogen oxides); we did not have the sample size to estimate associations with yolk sac tumors.<sup>10</sup> Similarly, null associations with nitric oxide, nitrogen dioxide, and nitrogen oxides were observed in the present study.

The air monitoring data used in this study differs from the above in that it includes more air toxics and all possible sources of ambient pollution, which include traffic in California but also other combustion sources (airplanes, boats, other machinery). In 2009, 26% of ambient butadiene arose from on-road mobile sources, with 27% from other mobile sources, 25% from natural sources, 1% from stationary sources, and 21% was generated area-wide (eg, from industry sources, refineries, wildfires, etc).<sup>17</sup> Thus, the exposure used in the analysis presented here should not be viewed as a proxy for traffic pollution only.

Our mixed results for subtypes across studies indicate that specific toxics may be responsible for risk increases and that relevant substances or toxic mixtures might vary by subtype. Even though air monitors measure the contributions from all possible emission sources, the accuracy of measurements taken at one site in estimating exposure to persons residing within

a distance of 3-4km is dependent on decay, topography, and other characteristics (eg, housing, meteorology, activity patterns).

In the present report, we detected positive associations with various highly-correlated traffic-related air toxics, specifically second trimester exposure to BTEX. These toxics are suspected endocrine disruptors, and exposure *in utero* may be particularly relevant for childhood cancer risk due to the fetus's increased vulnerability to environmental toxicants.<sup>20</sup> Toluene exposure is associated with decreased levels of testosterone, follicle stimulating hormone, and luteinizing hormone; and exposure to benzene, ethyl benzene, and toluene are associated with the activation of oxidative stress pathways.<sup>27</sup> In humans, gonadal development begins during the sixth week of gestation and continues into the second trimester, when several androgen-dependent processes take place.<sup>28</sup> For males, the second trimester is a critical period of development because the number of Sertoli and germ cells exponentially increases and internal/external genitalia are established; disturbance of testicular development in the second trimester has been linked to adverse reproductive outcomes later in life.<sup>28</sup> The endocrine system plays a critical role in fetal gonadal development and interruption of hormonal function in developing tissues is associated with an increased risk for cryptorchidism, a strong risk factor for childhood GCTs.<sup>29</sup>

The impact of endocrine disrupting chemicals on testicular development is well-documented in animal studies.<sup>29</sup> In mice, pregnancy exposure to high levels of toluene and acrolein (an environmental pollutant arising from the combustion of fuels and other sources) decreased fetal testosterone synthesis, which can lead to maldevelopment of the testes.<sup>30,31</sup> Similarly, components of air pollution (eg, diesel exhaust), are associated with retardation of gonadal cell migration and germ cell differentiation disorders in mice.<sup>32</sup> In humans, however, the

epidemiologic evidence is less clear and based on older populations (>13 years). An Italian study of 103 testicular GCT cases suggested increased risks with paternal (OR=1.33; 95% CI=0.65, 2.70) but not maternal (OR=0.97; 95% CI=0.23, 4.07) exposure to endocrine disrupting chemicals during preconception or pregnancy.<sup>33</sup> Similarly, a Canadian study of 343 testicular GCT cases found paternal preconception occupation as a metalworker (OR=3.28; 95% CI=1.03, 10.52) and exposure to metal products (OR=5.77; 95% CI=1.53, 21.77) were associated with increased testicular cancer risk in offspring.<sup>14</sup> Conversely, a Nordic registry-based study of 8,112 testicular GCT cases found little evidence supporting an association between parental exposure to heavy metals/welding fumes and cancer risk in offspring; however, it did report a positive association with paternal exposure to high levels of chromium (OR=1.37; 95% CI=1.05-1.79).<sup>34</sup> As stated above, the literature is limited with respect to GCTs in younger children and perinatal exposure to air pollution.<sup>11, 12</sup> Our results are not directly comparable with previous studies that did not investigate GCT subtypes; additionally, studies of populations >13 years include histological subtypes less frequently observed in young children (<6 years).

In California, race/ethnicity appears to be a more important factor than socioeconomic status in predicting exposure to air pollution.<sup>35</sup> Race/ethnicity is associated with GCT risk, particularly yolk sac tumors, with children of Asians/Pacific Islanders and Hispanics showing the highest risk for tumor development.<sup>8</sup> Yet, in this study effect estimates for all GCTs and yolk sac tumors did not change after adjustment for race/ethnicity (neither white vs. non-white race/ethnicity, nor more detailed race/ethnicity variables), or adjustment for other SES indicators (whether measured by maternal education, health insurance type, or neighborhood-level SES). With respect to teratoma risk, adjustment for these variables further lowered ORs already below 1.00, though estimates remained imprecise.

Limitations of this study include exposure misclassification due to residential mobility during pregnancy, estimated to occur in 9-32% of families.<sup>36</sup> However, moves are typically local (<10km, usually resulting in similar levels of air pollutant exposure) and most often happen during the second trimester. In this study, addresses were collected from birth certificates, but misclassification would be similar for cases and controls as residential address is likely to be recalled with equivalent accuracy. The use of zip code centroids (birth years 1984-1997) introduced some misclassification to estimates, but a sensitivity analysis restricting to births 1998+ did not change effect estimates by more than 10% (not shown). Most California children (>95%) live in large urban areas,<sup>37</sup> where the relatively smaller size of zip codes (eg, in metropolitan Los Angeles, 2-4km in diameter) would limit misclassification compared with exposure measurements in rural areas where zip codes are much larger. Even so, any misclassification from utilizing zip code centroids for exposure assessment is assumed non-differential and would bias estimates towards the null. Lack of information on cryptorchidism diagnoses in this population did not allow us to assess the role of this important risk factor. Small sample size for GCT subtypes limited our analysis by requiring the use of a larger buffer distance to assess exposure. Yet, our study was not affected by recall bias or selective participation due to its record- and population-based nature. Further, our study was strengthened by the relatively large number of GCT cases and the assessment of exposure to multiple air toxics over a long period of time.

In sum, although we have seen mixed results with various air pollutants and their measures by subtype and exposure assessment strategy, our group's studies on this topic do suggest some evidence for positive associations.<sup>9, 10</sup> Further investigation in other populations may be warranted.

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**TABLE 1.** Select Characteristics for All GCT Cases and Controls with an Exposure Buffer Distance of 3km, and for Yolk Sac Tumor and Teratoma Cases and Controls with an Exposure Buffer Distance of 4km.

<b>Characteristic</b>	<b>Exposure Buffer Distance: 3km</b>		<b>Exposure Buffer Distance: 4km</b>			
	<b>All GCTs</b>		<b>Controls</b> <i>(n=155,191)</i>	<b>Yolk Sac Tumor Cases</b> <i>(n=99)</i>	<b>Teratoma Cases</b> <i>(n=125)</i>	
	<b>Controls</b> <i>(n=147,100)</i>	<b>Cases</b> <i>(n=243)</i>				
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>
Maternal race						
White	102,863 (69.9)	168 (69.1)	107,531 (69.3)	60 (60.6)	96 (76.8)	
Non-White	44,237 (30.1)	75 (30.9)	47,660 (30.7)	39 (39.4)	29 (23.2)	
Neighborhood-level SES index						
Low	41,380 (28.1)	70 (28.8)	43,143 (27.8)	29 (29.3)	37 (29.6)	
Medium-low	36,678 (24.9)	64 (26.3)	38,961 (25.1)	24 (24.2)	35 (28.0)	
Medium	28,826 (19.6)	37 (15.2)	30,562 (19.7)	14 (14.1)	15 (12.0)	
Medium-high	21,861 (14.9)	45 (18.5)	23,253 (15.0)	21 (21.2)	23 (18.4)	
High	18,143 (12.3)	27 (11.1)	19,052 (12.3)	11 (11.1)	15 (12.0)	
Missing	212 (0.1)	0 (0.0)	220 (0.1)	0 (0.0)	0 (0.0)	
Maternal age, M ± SD	27.6 ±0.02	27.0 ±0.39	27.6 ±0.02	27.7 ±0.66	26.5 ±0.50	
Missing	15	0	16	0	0	

GCT, germ cell tumor; km, kilometer; M, mean; SD, standard deviation; SES, socioeconomic status.

**TABLE 2.** ORs and 95% CIs for a One Interquartile Range Increase in Prenatal Exposure to Ambient Air Toxics and GCTs in Young California Children (1984-2013).

Exposure agent	All GCTs		Exposure Window (Buffer Distance: 3km)		
	Cases (n=243)	Controls (n=147,100)	First Trimester	Second Trimester	Entire Pregnancy
			OR [95% CI]*	OR [95% CI]*	OR [95% CI]*
<i>Factor 1: Traffic-related air toxics</i>					
Benzene	18	13,365	0.76 [0.42, 1.36]	1.25 [0.86, 1.81]	1.00 [0.59, 1.71]
1,3-Butadiene	18	13,362	0.74 [0.40, 1.39]	1.51 [1.01, 2.26]	1.22 [0.64, 2.33]
Dichloromethane	17	12,249	0.93 [0.61, 1.41]	0.89 [0.56, 1.42]	0.92 [0.54, 1.58]
Ethyl benzene	15	11,313	0.84 [0.51, 1.39]	1.25 [0.95, 1.65]	1.21 [0.67, 2.17]
Meta/Para-xylene	14	10,547	1.10 [0.67, 1.78]	1.56 [1.10, 2.21]	1.45 [0.92, 2.28]
Ortho-xylene	16	11,935	0.94 [0.58, 1.52]	1.35 [0.97, 1.87]	1.18 [0.77, 1.82]
Lead	16	9535	0.92 [0.59, 1.45]	1.10 [0.76, 1.60]	0.95 [0.57, 1.60]
Perchloroethylene	17	12,305	0.92 [0.64, 1.32]	1.02 [0.84, 1.24]	0.96 [0.68, 1.36]
Styrene	14	8081	0.58 [0.28, 1.21]	0.98 [0.68, 1.42]	0.67 [0.34, 1.34]
Toluene	16	12,081	1.00 [0.59, 1.69]	1.38 [0.91, 2.11]	1.23 [0.72, 2.10]
Carbon monoxide	72	46,208	1.00 [0.77, 1.30]	1.11 [0.88, 1.41]	1.05 [0.79, 1.39]
Nitric oxide	69	44,031	0.98 [0.79, 1.23]	1.05 [0.86, 1.29]	1.00 [0.74, 1.34]
Nitrogen dioxide	72	44,667	0.87 [0.61, 1.24]	0.89 [0.62, 1.27]	0.81 [0.56, 1.19]
Nitrogen oxides	69	43,644	0.96 [0.73, 1.26]	1.03 [0.79, 1.33]	0.95 [0.68, 1.33]
<i>Factor 2: Polycyclic aromatic hydrocarbons</i>					
Benzo(a)pyrene	14	9932	0.76 [0.42, 1.37]	1.02 [0.77, 1.35]	0.78 [0.41, 1.47]
Benzo(b)fluoranthene	15	11,533	0.58 [0.26, 1.30]	0.94 [0.68, 1.30]	0.60 [0.29, 1.22]
Benzo(g,h,i)perylene	15	11,067	0.49 [0.21, 1.19]	1.02 [0.67, 1.55]	0.68 [0.33, 1.43]
Benzo(k)fluoranthene	15	11,533	0.63 [0.30, 1.31]	0.91 [0.65, 1.28]	0.59 [0.28, 1.24]
Dibenz(a,h)anthracene	15	11,067	0.80 [0.53, 1.19]	0.94 [0.78, 1.14]	0.62 [0.30, 1.28]
Indeno(1,2,3-cd)pyrene	15	11,067	0.58 [0.26, 1.28]	0.99 [0.73, 1.35]	0.74 [0.39, 1.41]
<i>Toxics not loaded on a factor</i>					
Acetaldehyde	16	12,610	0.35 [0.15, 0.82]	0.69 [0.36, 1.33]	0.46 [0.21, 0.97]
Carbon tetrachloride	15	8864	0.63 [0.29, 1.37]	0.62 [0.33, 1.17]	0.62 [0.38, 1.02]
Chloroform	17	12,571	1.02 [0.64, 1.65]	1.17 [0.76, 1.81]	1.17 [0.73, 1.86]
Chromium	16	9853	1.03 [0.68, 1.55]	1.19 [0.90, 1.56]	1.08 [0.76, 1.52]
Formaldehyde	16	12,610	1.28 [1.12, 1.47]	1.28 [0.74, 2.24]	1.50 [1.12, 2.00]
Nickel	16	9856	1.08 [0.66, 1.75]	1.07 [0.65, 1.77]	0.99 [0.58, 1.67]
Ortho-dichlorobenzene	15	8971	1.51 [0.66, 3.44]	1.97 [0.97, 4.03]	2.85 [1.14, 7.13]
Phosphorus	15	8074	1.03 [0.79, 1.36]	0.97 [0.69, 1.35]	1.01 [0.75, 1.35]
Para-dichlorobenzene	15	8996	0.86 [0.48, 1.54]	1.30 [0.99, 1.70]	1.05 [0.71, 1.55]
Strontium	16	9389	1.23 [0.81, 1.88]	1.24 [0.83, 1.84]	1.21 [0.65, 2.24]
Trichloroethylene	17	12,353	0.88 [0.67, 1.16]	0.97 [0.82, 1.14]	0.92 [0.73, 1.16]
Ozone	87	53,279	1.02 [0.78, 1.34]	0.82 [0.62, 1.09]	0.84 [0.64, 1.12]
PM <sub>10</sub>	56	42,014	1.16 [0.86, 1.55]	1.04 [0.76, 1.43]	0.97 [0.67, 1.40]
PM <sub>2.5</sub>	33	23,282	1.26 [0.85, 1.88]	0.80 [0.49, 1.30]	0.77 [0.44, 1.37]
Sulfur	16	9784	1.12 [0.67, 1.87]	1.16 [0.68, 1.98]	0.98 [0.45, 2.12]

CI, confidence interval; GCT, germ cell tumor; km, kilometers; OR, odds ratio; PM, particulate matter.

\*ORs adjusted for birth year, maternal age, maternal race, and neighborhood-level socioeconomic status.

**TABLE 3.** ORs and 95% CIs for a One Interquartile Range Increase in Prenatal Exposure to Ambient Air Toxics and Yolk Sac Tumors in Young California Children (1984-2013).

Exposure agent	Yolk Sac Tumors		Exposure Window (Buffer Distance: 4km)		
	Cases (n=99)	Controls (n=155,191)	First	Second	Entire
			Trimester	Trimester	Pregnancy
			OR [95% CI]*	OR [95% CI]*	OR [95% CI]*
<i>Factor 1: Traffic-related air toxics</i>					
Benzene	10	21,762	1.06 [0.49, 2.30]	1.68 [1.02, 2.78]	1.76 [0.89, 3.47]
1,3-Butadiene	10	21,770	0.97 [0.43, 2.19]	1.80 [1.02, 3.16]	2.08 [0.85, 5.07]
Dichloromethane	9	20,308	1.07 [0.84, 1.36]	1.05 [0.83, 1.35]	1.31 [0.85, 2.02]
Ethyl benzene	9	18,508	1.15 [0.76, 1.75]	1.41 [1.09, 1.84]	2.29 [1.17, 4.49]
Meta/Para-xylene	8	17,007	1.06 [0.53, 2.10]	1.59 [1.02, 2.49]	1.58 [0.86, 2.90]
Ortho-xylene	9	19,402	1.28 [0.70, 2.33]	1.77 [1.16, 2.71]	1.89 [1.08, 3.32]
Lead	9	15,839	0.97 [0.55, 1.69]	1.19 [0.74, 1.89]	1.13 [0.59, 2.13]
Perchloroethylene	9	20,057	1.05 [0.81, 1.36]	1.08 [0.90, 1.28]	1.17 [0.80, 1.71]
Styrene	7	13,205	0.83 [0.37, 1.89]	1.05 [0.68, 1.63]	0.87 [0.36, 2.14]
Toluene	9	19,602	1.36 [0.71, 2.59]	1.82 [1.10, 3.03]	2.13 [1.05, 4.31]
Carbon monoxide	40	65,064	1.01 [0.70, 1.45]	1.09 [0.77, 1.53]	0.93 [0.60, 1.42]
Nitric oxide	41	64,220	0.97 [0.71, 1.31]	1.00 [0.75, 1.33]	0.78 [0.51, 1.20]
Nitrogen dioxide	42	64,729	0.77 [0.47, 1.26]	0.69 [0.42, 1.14]	0.57 [0.33, 0.99]
Nitrogen oxides	41	63,593	0.93 [0.65, 1.35]	0.95 [0.66, 1.36]	0.73 [0.46, 1.17]
<i>Factor 2: Polycyclic aromatic hydrocarbons</i>					
Benzo(a)pyrene	7	16,477	0.92 [0.50, 1.67]	0.85 [0.42, 1.72]	0.90 [0.40, 2.06]
Benzo(b)fluoranthene	9	19,188	0.67 [0.27, 1.70]	0.81 [0.40, 1.63]	0.71 [0.29, 1.70]
Benzo(g,h,i)perylene	9	18,355	0.55 [0.19, 1.65]	0.89 [0.43, 1.85]	0.77 [0.28, 2.15]
Benzo(k)fluoranthene	9	19,188	0.74 [0.33, 1.64]	0.83 [0.44, 1.57]	0.73 [0.31, 1.72]
Dibenz(a,h)anthracene	9	18,355	0.71 [0.35, 1.47]	0.42 [0.09, 2.08]	0.40 [0.09, 1.67]
Indeno(1,2,3-cd)pyrene	9	18,355	0.63 [0.23, 1.71]	0.81 [0.38, 1.72]	0.75 [0.30, 1.84]
<i>Toxics not loaded on a factor</i>					
Acetaldehyde	9	20,708	0.26 [0.07, 0.94]	0.68 [0.27, 1.72]	0.54 [0.20, 1.46]
Carbon tetrachloride	7	14,421	0.73 [0.21, 2.47]	0.25 [0.07, 0.83]	0.33 [0.13, 0.87]
Chloroform	9	20,498	1.12 [0.59, 2.11]	1.33 [0.80, 2.21]	1.38 [0.78, 2.45]
Chromium	10	16,339	1.09 [0.71, 1.66]	1.27 [0.99, 1.61]	1.20 [0.92, 1.58]
Formaldehyde	9	20,708	1.31 [1.15, 1.50]	1.45 [0.81, 2.61]	1.60 [1.20, 2.13]
Nickel	10	16,347	1.06 [0.56, 2.00]	1.36 [0.86, 2.14]	1.20 [0.71, 2.02]
Ortho-dichlorobenzene	8	14,606	1.69 [0.52, 5.46]	2.50 [0.96, 6.48]	2.79 [0.71, 10.96]
Phosphorus	8	13,249	0.85 [0.44, 1.63]	1.04 [0.73, 1.50]	0.95 [0.58, 1.55]
Para-dichlorobenzene	8	14,645	1.11 [0.70, 1.75]	1.43 [1.07, 1.91]	1.29 [0.88, 1.89]
Strontium	10	15,469	1.02 [0.52, 2.01]	1.42 [0.97, 2.08]	1.19 [0.57, 2.48]
Trichloroethylene	9	20,127	0.90 [0.64, 1.27]	0.95 [0.75, 1.21]	0.95 [0.73, 1.23]
Ozone	51	75,509	1.02 [0.72, 1.44]	0.79 [0.54, 1.15]	0.81 [0.57, 1.17]
PM <sub>10</sub>	30	58,633	1.22 [0.82, 1.80]	0.95 [0.60, 1.49]	0.85 [0.51, 1.44]
PM <sub>2.5</sub>	17	33,394	1.49 [0.86, 2.58]	0.72 [0.34, 1.50]	0.64 [0.28, 1.49]
Sulfur	10	16,098	1.09 [0.58, 2.04]	1.34 [0.74, 2.44]	0.98 [0.37, 2.60]

CI, confidence interval; km, kilometers; OR, odds ratio; PM, particulate matter.

\*ORs adjusted for birth year, maternal age, maternal race, and neighborhood-level socioeconomic status.





**Supplementary Table 3.** Descriptive statistics for air toxic measures among controls residing within 3km of air monitoring stations in California (1984-2013).

Agent	Mean (Standard Deviation)		Inter-Quartile Range	Minimum	10th Percentile	25th Percentile	75th Percentile	90th Percentile	Maximum
1,3-Butadiene (ppbV)	0.230	(0.147)	0.176	0.022	0.078	0.125	0.301	0.428	0.982
Benzene (ppbV)	0.967	(0.736)	0.661	0.140	0.363	0.496	1.157	1.891	6.105
Carbon monoxide (ppmV)	0.987	(0.584)	0.672	0.002	0.414	0.563	1.234	1.807	4.614
Dichloromethane (ppbV)	0.572	(0.463)	0.449	0.050	0.129	0.243	0.692	1.044	6.183
Ethyl benzene (ppbV)	0.308	(0.154)	0.177	0.100	0.135	0.188	0.365	0.471	1.300
Meta/Para-xylene (ppbV)	1.013	(0.533)	0.591	0.132	0.451	0.638	1.229	1.805	3.791
Nitric oxide (ppmV)	28.136	(21.537)	26.005	0.304	7.182	12.293	38.298	61.405	141.767
Nitrogen oxides (ppbV)	53.788	(31.778)	41.940	3.137	20.728	29.347	71.286	103.316	202.484
Nitrogen dioxide (ppbV)	25.385	(11.556)	17.157	1.350	12.545	16.519	33.676	42.269	65.760
Ortho-xylene (ppbV)	0.372	(0.245)	0.239	0.053	0.157	0.214	0.452	0.647	1.984
Lead (ng/m <sup>3</sup> )	15.712	(13.097)	11.658	2.417	5.524	7.500	19.158	29.681	87.611
Perchloroethylene (ppbV)	0.135	(0.155)	0.108	0.006	0.031	0.050	0.158	0.296	1.813
Styrene (ppbV)	0.128	(0.106)	0.101	0.050	0.052	0.060	0.160	0.253	1.378
Toluene (ppbV)	2.206	(1.326)	1.513	0.252	0.960	1.295	2.808	3.805	10.830
Benzo(a)pyrene (ng/m <sup>3</sup> )	0.158	(0.139)	0.121	0.025	0.048	0.071	0.192	0.299	1.495
Benzo(b)fluoranthene (ng/m <sup>3</sup> )	0.236	(0.216)	0.164	0.028	0.074	0.107	0.271	0.500	2.357
Benzo(g,h,i)perylene (ng/m <sup>3</sup> )	0.457	(0.283)	0.345	0.040	0.169	0.253	0.598	0.822	2.585
Benzo(k)fluoranthene (ng/m <sup>3</sup> )	0.099	(0.086)	0.066	0.025	0.035	0.046	0.113	0.200	1.027
Dibenz(a,h)anthracene (ng/m <sup>3</sup> )	0.039	(0.027)	0.015	0.025	0.025	0.026	0.042	0.055	0.692
Indeno(1,2,3-cd)pyrene (ng/m <sup>3</sup> )	0.273	(0.207)	0.199	0.027	0.090	0.135	0.334	0.533	3.189
Acetaldehyde (ppbV)	1.231	(0.553)	0.683	0.300	0.626	0.817	1.500	1.948	4.248
Carbon tetrachloride (ppbV)	0.097	(0.014)	0.011	0.072	0.085	0.088	0.099	0.125	0.146
Chloroform (ppbV)	0.035	(0.013)	0.015	0.011	0.022	0.027	0.042	0.053	0.126
Chromium (ng/m <sup>3</sup> )	4.969	(3.435)	2.727	1.182	2.227	3.115	5.842	7.211	31.318
Formaldehyde (ppbV)	2.848	(1.129)	1.330	0.811	1.530	2.074	3.404	4.395	17.805
Nickel (ng/m <sup>3</sup> )	4.639	(2.466)	2.528	1.167	2.238	2.950	5.478	7.217	19.182
Ortho-dichlorobenzene (ppbV)	0.114	(0.040)	0.076	0.050	0.057	0.074	0.150	0.150	0.276
Ozone (ppmV)	0.039	(0.011)	0.014	0.011	0.026	0.032	0.046	0.054	0.093
PM <sub>10</sub> (ng/m <sup>3</sup> )	34.617	(14.123)	18.812	7.704	19.109	23.571	42.383	54.048	105.955
PM <sub>2.5</sub> (ng/m <sup>3</sup> )	17.520	(5.716)	8.994	3.149	10.407	12.960	21.954	25.130	42.399
Phosphorus (ng/m <sup>3</sup> )	63.997	(50.310)	26.276	2.762	26.500	39.571	65.848	117.483	395.625
Para-dichlorobenzene (ppbV)	0.143	(0.034)	0.032	0.100	0.104	0.118	0.150	0.176	0.519
Sulfur (ng/m <sup>3</sup> )	877.935	(328.042)	519.040	210.917	515.200	608.182	1127.220	1336.840	2229.470
Strontium (ng/m <sup>3</sup> )	13.831	(6.540)	8.458	1.410	6.278	9.000	17.458	22.818	47.000
Trichloroethylene (ppbV)	0.061	(0.107)	0.034	0.010	0.012	0.015	0.049	0.151	0.949

**Supplementary Table 4.** Descriptive statistics for air toxic measures among controls residing within 4km of air monitoring stations in California (1984-2013).

Agent	Mean (Standard Deviation)		Inter-Quartile Range	Minimum	10th Percentile	25th Percentile	75th Percentile	90th Percentile	Maximum
1,3-Butadiene (ppbV)	0.229	(0.146)	0.180	0.022	0.078	0.123	0.304	0.420	1.013
Benzene (ppbV)	0.971	(0.744)	0.691	0.140	0.357	0.487	1.178	1.965	6.206
Carbon monoxide (ppmV)	0.986	(0.573)	0.675	0.002	0.412	0.565	1.241	1.787	4.614
Dichloromethane (ppbV)	0.578	(0.490)	0.462	0.050	0.128	0.238	0.700	1.050	6.518
Ethyl benzene (ppbV)	0.306	(0.151)	0.184	0.100	0.133	0.183	0.367	0.467	1.300
Meta/Para-xylene (ppbV)	0.995	(0.524)	0.576	0.126	0.445	0.629	1.205	1.742	3.791
Nitric oxide (ppmV)	27.760	(21.020)	24.349	0.199	7.309	12.659	37.008	60.277	141.767
Nitrogen oxides (ppbV)	53.616	(30.920)	39.155	3.137	21.156	30.149	69.304	101.446	202.484
Nitrogen dioxide (ppbV)	25.650	(11.379)	16.978	1.350	12.878	16.941	33.918	42.049	65.760
Ortho-xylene (ppbV)	0.368	(0.241)	0.239	0.053	0.155	0.211	0.450	0.650	1.984
Lead (ng/m <sup>3</sup> )	16.009	(13.511)	12.479	2.417	5.414	7.474	19.952	31.800	93.071
Perchloroethylene (ppbV)	0.134	(0.154)	0.109	0.006	0.030	0.049	0.157	0.298	1.837
Styrene (ppbV)	0.127	(0.106)	0.102	0.050	0.052	0.058	0.160	0.255	1.378
Toluene (ppbV)	2.177	(1.328)	1.523	0.236	0.931	1.264	2.786	3.796	10.830
Benzo(a)pyrene (ng/m <sup>3</sup> )	0.161	(0.149)	0.122	0.025	0.047	0.070	0.192	0.304	1.510
Benzo(b)fluoranthene (ng/m <sup>3</sup> )	0.238	(0.220)	0.166	0.025	0.075	0.107	0.273	0.515	2.519
Benzo(g,h,i)perylene (ng/m <sup>3</sup> )	0.456	(0.283)	0.346	0.040	0.173	0.253	0.599	0.816	2.585
Benzo(k)fluoranthene (ng/m <sup>3</sup> )	0.099	(0.088)	0.067	0.025	0.035	0.046	0.114	0.207	1.098
Dibenz(a,h)anthracene (ng/m <sup>3</sup> )	0.039	(0.027)	0.015	0.025	0.025	0.026	0.041	0.057	0.692
Indeno(1,2,3-cd)pyrene (ng/m <sup>3</sup> )	0.272	(0.208)	0.198	0.027	0.090	0.134	0.332	0.539	3.189
Acetaldehyde (ppbV)	1.218	(0.563)	0.681	0.286	0.617	0.795	1.476	1.948	4.248
Carbon tetrachloride (ppbV)	0.097	(0.015)	0.012	0.072	0.085	0.088	0.100	0.125	0.146
Chloroform (ppbV)	0.035	(0.012)	0.014	0.010	0.022	0.027	0.041	0.051	0.126
Chromium (ng/m <sup>3</sup> )	4.965	(3.289)	2.548	1.182	2.364	3.257	5.805	7.087	32.000
Formaldehyde (ppbV)	2.816	(1.131)	1.336	0.744	1.505	2.025	3.361	4.335	17.805
Nickel (ng/m <sup>3</sup> )	4.649	(2.427)	2.534	1.077	2.208	2.966	5.500	7.211	19.500
Ortho-dichlorobenzene (ppbV)	0.113	(0.040)	0.077	0.050	0.057	0.073	0.150	0.150	0.276
Ozone (ppmV)	0.039	(0.011)	0.014	0.009	0.026	0.032	0.046	0.054	0.100
PM <sub>10</sub> (ng/m <sup>3</sup> )	34.512	(13.859)	18.369	7.704	19.300	23.781	42.150	53.714	105.955
PM <sub>2.5</sub> (ng/m <sup>3</sup> )	17.528	(5.583)	8.778	3.149	10.555	13.104	21.882	24.980	43.716
Phosphorus (ng/m <sup>3</sup> )	60.647	(44.844)	24.826	2.762	25.684	39.091	63.917	110.077	395.625
Para-dichlorobenzene (ppbV)	0.142	(0.034)	0.033	0.100	0.100	0.117	0.150	0.173	0.519
Sulfur (ng/m <sup>3</sup> )	858.320	(329.921)	512.109	200.545	502.963	598.800	1110.910	1333.750	2229.470
Strontium (ng/m <sup>3</sup> )	13.617	(6.325)	7.780	1.289	6.150	9.175	16.955	22.000	47.000
Trichloroethylene (ppbV)	0.063	(0.112)	0.034	0.010	0.011	0.015	0.048	0.160	1.021



**Supplementary Table 5.** Odds ratios and 95% confidence intervals for the relationship between one interquartile range increase in exposure to ambient air toxics and teratomas.<sup>a, b, c</sup>

Agent	Case N	Control N	First trimester			Second trimester			Entire pregnancy		
			OR	LCL	UCL	OR	LCL	UCL	OR	LCL	UCL
<i>Factor 1: Traffic-related air pollutants</i>											
Benzene	18	21762	<b>0.46</b>	0.20	1.04	<b>0.77</b>	0.40	1.46	<b>0.47</b>	0.20	1.13
1,3-Butadiene	19	21770	<b>0.65</b>	0.31	1.35	<b>1.19</b>	0.71	2.01	<b>0.84</b>	0.38	1.88
Dichloromethane	17	20308	<b>0.70</b>	0.35	1.42	<b>0.58</b>	0.25	1.36	<b>0.58</b>	0.23	1.44
Ethyl benzene	17	18508	<b>0.61</b>	0.29	1.26	<b>0.83</b>	0.45	1.52	<b>0.42</b>	0.14	1.24
Meta/Para-xylene	16	17007	<b>0.84</b>	0.46	1.56	<b>1.20</b>	0.78	1.85	<b>1.08</b>	0.64	1.82
Ortho-xylene	19	19402	<b>0.49</b>	0.23	1.06	<b>0.87</b>	0.51	1.49	<b>0.62</b>	0.31	1.24
Lead	15	15839	<b>0.42</b>	0.16	1.13	<b>0.34</b>	0.11	1.03	<b>0.27</b>	0.08	0.90
Perchloroethylene	18	20057	<b>0.63</b>	0.32	1.25	<b>1.06</b>	0.92	1.23	<b>0.88</b>	0.56	1.39
Styrene	13	13205	<b>0.63</b>	0.29	1.37	<b>1.04</b>	0.74	1.47	<b>0.77</b>	0.37	1.59
Toluene	19	19602	<b>0.44</b>	0.19	1.02	<b>0.77</b>	0.40	1.46	<b>0.48</b>	0.21	1.13
Carbon monoxide	57	65064	<b>0.74</b>	0.51	1.09	<b>0.87</b>	0.62	1.22	<b>0.92</b>	0.64	1.31
Nitric oxide	54	64220	<b>0.88</b>	0.67	1.17	<b>1.02</b>	0.80	1.29	<b>1.06</b>	0.78	1.43
Nitrogen dioxide	52	64729	<b>0.79</b>	0.51	1.21	<b>0.95</b>	0.63	1.43	<b>0.91</b>	0.59	1.41
Nitrogen oxides	54	63593	<b>0.83</b>	0.59	1.16	<b>0.98</b>	0.73	1.32	<b>0.99</b>	0.70	1.41
<i>Factor 2: Polycyclic aromatic hydrocarbons</i>											
Benzo(a)pyrene	14	16477	<b>0.60</b>	0.25	1.41	<b>1.09</b>	0.87	1.38	<b>1.04</b>	0.65	1.67
Benzo(b)fluoranthene	16	19188	<b>0.64</b>	0.31	1.33	<b>1.00</b>	0.74	1.36	<b>0.72</b>	0.38	1.36
Benzo(g,h,i)perylene	16	18355	<b>0.55</b>	0.24	1.27	<b>1.10</b>	0.70	1.72	<b>0.82</b>	0.39	1.75
Benzo(k)fluoranthene	16	19188	<b>0.68</b>	0.35	1.33	<b>0.97</b>	0.71	1.32	<b>0.70</b>	0.36	1.35
Dibenz(a,h)anthracene	16	18355	<b>0.83</b>	0.58	1.18	<b>0.99</b>	0.86	1.13	<b>0.80</b>	0.48	1.34
Indeno(1,2,3-cd)pyrene	16	18355	<b>0.61</b>	0.28	1.32	<b>1.05</b>	0.76	1.46	<b>0.82</b>	0.44	1.52
<i>Pollutants not loaded on a factor</i>											
Acetaldehyde	17	20708	<b>0.48</b>	0.22	1.07	<b>0.48</b>	0.21	1.08	<b>0.39</b>	0.17	0.91
Carbon tetrachloride	11	14421	<b>0.82</b>	0.30	2.22	<b>0.78</b>	0.33	1.88	<b>0.79</b>	0.39	1.59
Chloroform	19	20498	<b>0.79</b>	0.44	1.42	<b>0.82</b>	0.46	1.46	<b>0.73</b>	0.39	1.35
Chromium	17	16339	<b>0.63</b>	0.30	1.34	<b>0.67</b>	0.33	1.37	<b>0.63</b>	0.30	1.33
Formaldehyde	17	20708	<b>0.50</b>	0.24	1.08	<b>0.45</b>	0.21	1.01	<b>0.44</b>	0.20	0.96
Nickel	17	16347	<b>0.83</b>	0.45	1.52	<b>0.76</b>	0.40	1.48	<b>0.83</b>	0.46	1.49
Ortho-dichlorobenzene	15	14606	<b>0.63</b>	0.20	2.01	<b>0.97</b>	0.34	2.77	<b>1.21</b>	0.40	3.65
Phosphorus	13	13249	<b>1.02</b>	0.76	1.36	<b>0.83</b>	0.50	1.36	<b>0.96</b>	0.68	1.35
Para-dichlorobenzene	15	14645	<b>0.36</b>	0.12	1.11	<b>1.01</b>	0.60	1.69	<b>0.68</b>	0.35	1.32
Strontium	17	15469	<b>0.78</b>	0.41	1.46	<b>0.64</b>	0.32	1.30	<b>0.68</b>	0.35	1.32
Trichloroethylene	18	20127	<b>0.76</b>	0.48	1.22	<b>0.73</b>	0.43	1.24	<b>0.64</b>	0.33	1.26
Ozone	63	75509	<b>0.98</b>	0.71	1.35	<b>0.84</b>	0.60	1.18	<b>0.81</b>	0.58	1.13
PM <sub>10</sub>	48	58633	<b>1.01</b>	0.72	1.43	<b>1.03</b>	0.73	1.45	<b>1.02</b>	0.69	1.50
PM <sub>2.5</sub>	27	33394	<b>1.08</b>	0.66	1.76	<b>1.00</b>	0.60	1.67	<b>1.19</b>	0.63	2.24
Sulfur	17	16098	<b>0.60</b>	0.30	1.22	<b>0.70</b>	0.36	1.35	<b>0.51</b>	0.21	1.23

<sup>a</sup>Odds ratios adjusted for birth year, maternal age, maternal race, and neighborhood-level socioeconomic status

<sup>b</sup>Cases and controls had to reside within 4km of air monitoring stations in California to be included in analysis

<sup>c</sup>OR=odds ratio; LCL=lower confidence limit; UCL=upper confidence limit