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An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring

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Abstract

Little is known about the etiology of neuroblastoma, the most common cancer in infancy. In this study, we examined maternal exposure to ambient air toxics in pregnancy in relation to neuroblastoma in the child. We ascertained all cases of neuroblastoma listed in the California Cancer Registry 1990-2007 that could be linked to a California birth certificate, and controls were selected at random from California birth records. Average air toxics exposures during pregnancy were determined based upon measures from community-based air pollution monitors. The study included 75 cases and 14,602 controls who lived with 5 kilometers of an air pollution monitor, and we additionally examined results for those living within a smaller radius around the monitor (2.5 km). Logistic regression was used to determine the risk of neuroblastoma with one interquartile range increase in air toxic exposure. Neuroblastoma risk was increased with higher maternal exposure to carbon tetrachloride (OR=2.65, 95%CI 1.07, 6.53) and polycyclic aromatic hydrocarbons (OR=1.39, 95%CI 1.05, 1.84), particularly indeno(1,2,3-cd)pyrene and dibenz(a,h)anthracene. Hexavalent chromium was associated with neuroblastoma at the 5 km distance (OR=1.32, 95%CI 1.00, 1.74) but not at the 2.5 km distance. This is one of the first studies to report associations between neuroblastoma and these air toxics.

Keywords

Air pollution; Benzene; Embryonal neoplasms; Neuroblastoma; Prenatal Exposure; Childhood cancer epidemiology; Risk factors

Introduction

Neuroblastoma is the most common malignancy in children less than one year of age. Incidence peaks in infancy (52 cases per million children)(U.S. Cancer Statistics Working

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Group., 2013) and drops rapidly thereafter, with nearly all cases diagnosed before age 5. Arising from tissues of the neural crest, it is a cancer of the sympathetic nervous system, with the most common site of tumors being the adrenal glands (40% of cases), and the remainder of tumors primarily occurring elsewhere in the abdomen or chest. Five-year survival is good for children diagnosed in infancy (83%), but poorer for children diagnosed ages 1-4 (55%) and at ages 5 and older (40%) (Ries et al., 1999).

As is the case with several childhood cancers, there are no established risk factors for neuroblastoma, although the early diagnosis would suggest that factors occurring in pregnancy are likely important in its development. There is some suggestion of increased risks with low birthweight, paternal smoking, and maternal pregnancy intake of alcohol or certain prescription medications (Heck et al., 2009). Previous studies have additionally suggested increased risk for neuroblastoma with parental occupational exposure to wood dusts, hydrocarbons, pesticides, lead, petroleum, coal tar and soot (Kerr et al., 2000; Olshan et al., 1999). Given that a fetus is more vulnerable to environmental exposures in comparison to an adult, pregnancy exposures to air toxins may contribute to risk (Selevan et al., 2000). In this exploratory study, we examined the relation between maternal exposure to ambient air toxics in pregnancy and diagnosis of neuroblastoma in the child.

Materials and Methods

This study has been described in detail elsewhere (Heck et al., 2013a). In brief, we ascertained all cases of neuroblastoma [International Classification of Childhood Cancer, version 3 (ICCC-3) code 041] among California residents younger than age 6 that were diagnosed 1990-2007 (born 1990-2007) and listed in the California Cancer Registry. Using a probabilistic linkage program (LinkPlus, Atlanta, GA), we attempted to match all cases to a California birth certificate using first and last names and dates of birth, (89% matching rate); it is likely that many of the unmatched cases were born outside of the state (Urayama et al., 2009), although incompleteness of birthplace information in the Cancer Registry did not allow us to assess this. Controls, frequency matched by year of birth to all childhood cancer cases for the same time period, were randomly selected from California birth records of children who had no cancer diagnosis before age 6. We matched children to California death records in order to exclude controls (n=1522) who had died of other causes prior to age 6. As this was a record-linkage study, we did not seek informed consent from individual subjects. The study received approvals from the human subjects protection boards of the University of California, Los Angeles and the Committee for the Protection of Human Subjects for the State of California.

We utilized the birth address, as listed on the birth certificate, to estimate exposure to air toxics. Geocoding was done using our open-source geocoder with manual correction of unmatched addresses (Goldberg et al., 2008). In the latter years of the study (1998-2007), exact home addresses were available on electronic birth certificates. Prior to 1998, only zipcodes were available, and we therefore geocoded the zipcode centroid for those children.

The California Air Resources Board's Air Toxics Program has maintained an air toxics monitoring network since 1985 (with data available from 1990), which measures ambient concentrations of air toxics, collecting 24-hour integrated samples every 12 days from each monitor. The number of toxics collected has varied over time, ranging from ~60-189; many air toxics were only collected during certain years and/or at specific monitors. We selected 42 air toxics to examine in the present study because they have been categorized as established, possible, or probable carcinogens by the International Agency for Research on Cancer (IARC, 2011). Although the 39 air monitors were located across the state, they were primarily positioned either near heavily trafficked highways, in industrial areas, or in

agriculturally intense rural regions (for map, see (Cox et al., 2010)). Using latitude/longitude locations provided by the California Air Resources Board, we determined the distance from each monitor to each family's home, and participants were assigned pollutant values based upon the measurements of the nearest monitor. We additionally explored measures generated with kriging, but saw little meaningful difference in effect estimates (unpublished data). When pollutant values fell below the level of detection, participants were assigned a value equivalent to half of the level of detection.

From birth certificates, we obtained the date of birth and the gestational age of each child. We excluded 39 cases and 9,059 controls who were missing information on length of gestation, and 71 controls with extreme or implausible gestational ages (<140 days or >320 days). Time-specific exposure averages were generated based on gestation dates, and we determined averages for each trimester and the entire pregnancy period. Because trimester-specific values did not differ substantially, we report results for the entire pregnancy period only.

For each pollutant, we included children in the analysis who had at least 1 reading for each full month of the pregnancy, and because the last month of pregnancy rarely is exactly one month in length, with at least one reading within the last 30 days of pregnancy (N=6701 children were excluded due to missing data). Children were included in analyses who lived within a specific radius around a monitor, and we examined different radii (5km, 4km, 3km and 2.5km) around the monitors to examine consistency in effect estimates across distances. Here we report results for 5km and 2.5km buffer areas. In the interest of having adequate sample sizes, we report only upon the 26 air toxics for which a minimum of 30 cases had values assigned at 5 kilometers.

Air toxics that arise from the same sources are generally highly correlated. We previously conducted principal components factor analyses with varimax rotation to assess correlations between toxics,(Heck et al., 2013b) and we present results here with the highly correlated toxics grouped together. In the factor analysis, air toxics loaded to two main factors (eigenvalues>1). The first factor consisted of traffic-related toxics ("BTEX," a term which includes benzene, 1,3 butadiene, toluene, ethyl benzene, and xylenes) as well as pollutants that were correlated with BTEX because they tend to be emitted more often in urban areas (lead, perchloroethylene, and styrene) (Agency for Toxic Substances and Disease Registry., 2007; Mielke et al., 2010; Turnbull et al., 2011). The second factor included all of the polycyclic aromatic hydrocarbons (PAHs). We additionally created a new variable, total PAHs, which consisted of the sum of all PAH values [benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene, dibenz(a,h)anthracene, benzo(g,h,i)perylene, and benzo(a)pyrene]. The remaining air toxics were not as strongly correlated with each other and did not load on a factor. We examined correlations between air toxics. We assessed the interquartile range for each pollutant among controls.

We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression with SAS 9.1 (SAS, Cary, NC). Logistic regression analyses assessed the neuroblastoma risk per one interquartile range increase in pollutant-specific exposure. Analyses were conducted for each pollutant separately. Selection of potential confounding variables was based upon literature review as well as our own examination of demographic and perinatal factors related to neuroblastoma status in our data (Heck et al., 2009). Demographic and socioeconomic information of participants was taken from birth certificates and from US Census data. We adjusted for mother's age (continuous), mother's race/ethnicity (White non-Hispanic, Hispanic, other), birth year, and a socioeconomic indicator, the method of payment for prenatal care (private health insurance vs. Medi-Cal/ other government-sponsored health insurance/self-pay), which we have previously observed

is a reasonable proxy for family income (Ritz et al., 2007). We adjusted for maternal race/ethnicity because the child's race/ethnicity was not available on birth certificates in all years of the study. We additionally examined mother's race/ethnicity with non-Hispanic Blacks as a separate group; however, since the results were largely similar, we consolidated this variable into three categories. Additional adjustment for other socioeconomic indicators (maternal educational attainment and neighborhood socioeconomic index, as described previously (Heck et al., 2012)) did not change effect estimates by 10% and were left out of final models. In California, air toxics releases are related to race, Latino ethnicity, and to a lesser degree, socioeconomic status (Pastor et al., 2004).

We additionally conducted logistic regression analyses to examine risks by quartile of pollutant exposure, with quartiles set by the distribution among controls. All regression analyses adjusted for the same variables listed above. We also examined stratified estimates by the age of child, examining the youngest children (<12 months and <6 months at diagnosis) separately.

Results

There were 75 cases and 14,602 controls included in the present study because they lived within 5 km of an air toxics monitor and had measurement values for at least one pollutant. This excluded 147,763 children (781 cases and 146,763 controls) because they did not live within 5 km of an air toxics monitor. Excluded children were more likely to live in a rural county (20% vs. 4%) and to have a mother who was White non-Hispanic (35% vs. 26%) and born in the US (56% vs. 50%). Correlations between air toxics are shown in supplemental table 1. Neuroblastoma cases were distributed across the state, with cases present within the 5 km buffer distance of nearly every monitor.

Population characteristics are shown in Table 1. In comparison to controls, the mothers of children with neuroblastoma were more likely to be White non-Hispanic, to be older, and to have had their prenatal care paid by private insurance.

Mean, interquartile ranges, and percentiles for pollutants are shown in Table 2. Results for the air toxics analyses are shown in Table 3. PAHs were positively associated with neuroblastoma at all buffer distances. In particular, dibenz(a,h)anthracene, indeno(1,2,3-cd)pyrene, and total PAHs were related to increased disease odds. Carbon tetrachloride odds increased steadily for smaller distance radii: at 5 km, the odds ratio (OR) was 2.65 (95%CI 1.07, 6.53), and rose to 3.72 (95%CI 1.20, 11.60) at 4 km, to 6.52 (95%CI 1.54, 27.6) at 3 km, and 7.87 (95%CI 1.37, 45.3) at 2.5 km.

Although hexavalent chromium was associated with an increased odds of neuroblastoma at 5km, the effect estimate dropped to null at 2.5 km. At the 4km distance, the odds ratio was 1.37 (95%CI 1.01, 1.86), and at 3km, the odds ratio was 1.45 (95%CI 1.07, 1.97).

In comparison to children at the lowest quartile of carbon tetrachloride exposure, children in the 4^{th} quartile had sharply elevated odds (2^{nd} quartile: OR=0.39, 95% CI 0.03, 4.37; 3^{rd} quartile: OR=1.68, 95% CI 0.21, 13.50; 4^{th} quartile: OR=8.85, 95% CI 1.19, 66.0). For PAHs, the point estimates were increased across the quartiles in comparison to the lowest one, with confidence limits crossing the null (2nd quartile: OR=1.50, 95% CI 0.39, 15.84; 3rd quartile: 1.63, 95% CI 0.38, 6.90; highest quartile: OR=1.35, 95%CI 0.27, 6.71).

When we stratified by trimester of exposure, effect estimates were similar across time periods, with overlapping confidence intervals (supplemental table 2). When we examined stratified estimates by age, the point estimates tended to be highest among the children diagnosed at younger ages (Supplemental Table 3).

Discussion

In this large, population-based study we observed increased risks of neuroblastoma from maternal exposure to polycyclic aromatic hydrocarbons and carbon tetrachloride in pregnancy. There are few other studies of ambient exposure to air toxics in pregnancy and childhood neuroblastoma. A study of Texas children observed no risk increase for neuroblastoma (OR=1.2, 95%CI 0.8, 1.6) from exposure to hazardous air pollutant releases (Thompson et al., 2008). The Texas study summed across all emissions data from specific industries (petroleum refineries and related industries, chemical industries, and plastics production) to assess risk and therefore no information was available on specific chemicals, making results difficult to compare to the present study.

Air toxics differ considerably in their stability in ambient air. Both PAHs and hexavalent chromium were measured as particles in our study, and the typical size of the PAHs that we examined would suggest that they remain airborne for several days or longer (Agency for Toxic Substances and Disease Registry., 2012). Hexavalent chromium particles can remain airborne for 7-10 days and are subject to long-range transport (Kimbrough et al., 1999). Carbon tetrachloride, which is a gas, does not degrade readily in the atmosphere. Thus, all of the air toxics associated with neuroblastoma in the present study have fairly low reactive decay across distances.

Carbon tetrachloride is a halogenated hydrocarbon, and the primary sources of its releases in California are chemical product manufacturing and petroleum refining. In the past, carbon tetrachloride was used as a pesticide, however it has not been registered for pesticide use in California since 1987, e.g. before the start of the present study. Although its use in indoor products has been discontinued in the US, carbon tetrachloride persists in the atmosphere for many years. Over the course of the present study, most of the emissions in California occurred in three counties, Los Angeles, Contra Costa and Orange (Alexis et al., 2002; Cox et al., 2010); therefore it is possible that our findings may represent some other geographically-associated factor common in those counties. Nonetheless it is well documented that carbon tetrachloride affects the sympathetic nervous system (Calvert and Brody, 1960). Its mechanism of causing carcinogenicity is not fully established, but it induces DNA adducts, double-strand breaks and micronucleated cells, perhaps as a result of oxidative stress and lipid peroxidation (Eastmond, 2008). Carbon tetrachloride has been linked to liver tumors in experimental studies, and in humans, some studies have linked it to NHL among exposed workers. Research on its developmental effects is limited (International Agency for Research on Cancer., 1999).

One previous study has reported results for carbon tetrachloride in relation to neuroblastoma. That study, in which information on occupational exposures was collected via parental interview, observed no increased risk with the father’s occupational exposure (OR= 0.4, 95%CI 0.2, 1.2)(De Roos et al., 2001) but did not report on maternal exposure, perhaps due to a having a small number of exposed mothers. It should be noted that any effects transpiring due to paternal exposure would occur via a different biologic mechanism than exposures which occurred in pregnancy, as was our hypothesis in this study.

We observed increased risk of neuroblastoma with exposure to PAHs. PAHs arise from a variety of sources in the environment, including bitumen, coal dust, coal tar, creosotes, fuel combustion, mineral oils, petroleum refining, wood smoke, coke production, and tobacco smoke. There are not previous reports, to our knowledge, of neuroblastoma in relation to PAH exposure. However, other studies have reported elevated effect estimates for maternal occupational exposures that involve PAH exposure, such as petroleum, creosote, and coal soot (Kerr et al., 2000). Its role as a developmental toxicant is supported by evidence that

inhalation exposure of PAH causes reduced fetal growth and adduct formation in cord blood (Perera et al., 2005; Tang et al., 2006). The primary routes of carcinogenicity arise from the metabolism of PAHs to highly reactive species that result in DNA adducts and genotoxic effects such as sister chromatid exchanges and DNA damage. In studies in adults, workers exposed to PAHs have excesses of lung, laryngeal, and renal cell carcinomas (IARC, 2012b).

The elevated risk for hexavalent chromium was only observed at 5 km and not at 2.5 km, with a very small sample size at the 2.5 km distance. This may suggest the finding was due to chance. Hexavalent chromium is an established carcinogen based upon studies of workers in industries with high exposure (i.e. chromate production, chromium electroplating, smelting) with excesses of lung cancer and cancers of the nose and nasal sinuses. Lymphocytes of workers exposed to hexavalent chromium compounds showed elevated frequencies of DNA strand breaks, sister chromatid exchanges, and micronuclei (IARC, 2012a). Occupational studies have also noted sperm abnormalities among exposed workers (Kumar et al., 2005). In studies of pregnant mice, hexavalent chromium causes low birthweight and fetal loss (Kanojia et al., 1998; Trivedi et al., 1989). Although no prior epidemiologic studies have reported on hexavalent chromium in relation to neuroblastoma, elevated effect estimates for neuroblastoma risk has been seen with maternal employment in metalwork, although small numbers of exposed mothers resulted in imprecise estimates (OR=1.6, 95%CI 0.5, 4.8)(Olshan et al., 1999).

In studies that reported on maternal occupational exposures in pregnancy, positive associations have also been reported for exposure to acetone and insecticides and neuroblastoma (Kerr et al., 2000). Similar to the present study, no associations were previously observed with maternal occupational exposure to diesel fuel nor with maternal employment as a mechanic or service station attendant (De Roos et al., 2001; Olshan et al., 1999). In two other studies by our group, we observed no association between neuroblastoma and exposure to traffic-related air pollution in pregnancy or early childhood (Ghosh et al., 2013; Heck et al., 2013c). The present study found similar results, although when we stratified by age at diagnosis, we observed higher point estimates for BTEX among children diagnosed at a younger age.

Limitations of this study include an inability to assess individual levels of PAH exposure, which in addition to outdoor air exposures is additionally dependent upon dietary and indoor air sources (tobacco smoke, emissions from household heat sources, charbroiled meat consumption etc.). However, previous research has noted that for the higher molecular weight PAHs we examined in the present study [benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-cd)pyrene, dibenz(a,h)anthracene, benzo(g,h,i)perylene], indoor measurements of PAHs are strongly correlated with outdoor concentrations (Naumova et al., 2002). A further limitation of the study was our inability to stratify patients by the International Neuroblastoma Staging System (INSS). Stage 4S, an enigmatic form of neuroblastoma, may have a unique etiology but we were unable to examine these types of tumors in our study. We are also limited by the reliance upon birth address to assess exposures throughout pregnancy. Between 9-30% of families move in pregnancy, with most moves occurring in the 2nd trimester, which likely affects the accuracy of early pregnancy exposure estimates (Bell and Belanger, 2012); however most moves are local (<10km), which may limit biases from misclassification errors. Geocoding methods were based upon the place of birth and thus errors are expected to be non-differential.

Despite the large sample size for a childhood cancer study, the rarity of this disease, combined with the small number of air toxics monitoring stations, meant that there were small numbers of cases with exposure measurements for many given pollutants. This

lessened statistical power and increased the likelihood of spurious associations; nonetheless, it would not be appropriate to adjust for multiple comparisons in our study (Goldberg and Silbergeld, 2011). A comparison of participants in the present study to the overall sample of children in the parent study (born during the same time period) showed that, perhaps due to the larger number of urban residents, children in the present study included more Hispanics (52% vs. 47%), more children without private health insurance (56% vs. 49%), and fewer US-born mothers (50% vs. 55%). A limitation of the study was having only a small amount of information on air toxics exposures of rural children, due to fewer air monitors and low population density in rural areas. Rural communities often have high levels of hazardous air pollutant exposures due to pesticide spraying.

Strengths of the study include the population-based ascertainment strategy and the record-linkage approach, allowing the study to be free of selection or recall biases. This is one of the few studies of neuroblastoma to date in relation to pregnancy environmental exposures, with detailed information available on specific carcinogens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We studied exposure to ambient air toxics in pregnancy and neuroblastoma in the child
- Air toxics measures came from community air pollution monitors near the birth address
- Cases were ascertained from the California Cancer Registry
- Carbon tetrachloride, polycyclic aromatic hydrocarbons, and hexavalent chromium increased neuroblastoma risk

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Table 1

Characteristics of the population

Demographic characteristics	Cases Number (%)	Controls Number (%)	OR[a](95%CI)
Mother's race/ethnicity			
Hispanic of any race	31 (41.3)	7672 (52.5)	Reference
White non-Hispanic	30 (40.0)	3808 (26.1)	1.95 (1.17, 3.22)
Other/not specified	14 (18.7)	3122 (21.4)	1.11 (0.59, 2.09)
Mother's Age			
19 or less	8 (10.7)	1837 (12.6)	0.86 (0.40, 1.84)
20-29	39 (52.0)	7684 (52.6)	Reference
30-34	16 (21.3)	3179 (21.8)	1.00 (0.56, 1.78)
35+	12 (16.0)	1901 (13.0)	1.25 (0.65, 2.40)
Missing	0	1 (0.0)	
Maternal Educational attainment (years)			
8 or less	7 (9.3)	2240 (15.3)	0.67 (0.28, 1.60)
9-11	20 (26.7)	3103 (21.3)	1.40 (0.75, 2.64)
12	19 (25.3)	4132 (28.3)	Reference
13-15	13 (17.3)	2659 (18.2)	1.07 (0.53, 2.17)
16+	15 (20.0)	2301 (15.8)	1.44 (0.73, 2.85)
Missing	1 (1.3)	167 (1.1)	
Neighborhood Socioeconomic Index			
1 (Lowest)	14 (18.7)	4265 (29.2)	Reference
2	21 (28.0)	3969 (27.2)	1.61 (0.82, 3.16)
3	21 (28.0)	2415 (16.5)	2.65 (1.35, 5.23)
4	14 (18.7)	2605 (17.8)	1.62 (0.77, 3.14)
5 (Highest)	5 (6.7)	1348 (9.2)	0.99 (0.94, 1.04)
Sex			
Male	44 (58.7)	7370 (50.5)	Reference
Female	31 (41.3)	7232 (49.5)	0.72 (0.45, 1.14)

Demographic characteristics	Cases Number (%)	Controls Number (%)	OR[a](95%CI)
Birth Weight (g)			
2499 or less	6 (8.0)	876 (6.0)	1.46 (0.63, 3.38)
2500-3999	58 (77.3)	12302 (84.3)	Reference
4000+	11 (14.7)	1413 (9.7)	1.65 (0.86, 3.15)
Missing	0	11 (0.1)	
Gestational Age			
Very Preterm (<33 weeks)	0 (0.0)	288 (2.0)	-----
Preterm (33-36 weeks)	6 (8.0)	1309 (9.0)	0.88 (0.38, 2.03)
Term (37-42 weeks)	65 (86.7)	12446 (85.2)	Reference
Post-term (43+ weeks)	4 (5.3)	559 (3.8)	1.36 (0.50, 3.76)
Source of payment for prenatal care			
Medi-Cal/other			
government/self-pay	36 (48.0)	8046 (55.1)	Reference
Private insurance	39 (52.0)	6423 (44.0)	1.36 (0.86, 2.14)
Missing	0	133 (0.9)	

[a]Adjusted for year of birth (matching variable)

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Table 2

Air toxics measures (1990-2007)

Agent	Mean (Standard Deviation)	Inter-Quartile Range	Minimum	10th Percentile	25th Percentile	75th Percentile	90th Percentile	Maximum
Ortho-xylene (ppbV)	0.478 (0.316)	0.389	0.053	0.169	0.242	0.629	0.950	1.984
Toluene (ppbV)	2.778 (1.684)	2.124	0.337	1.063	1.481	3.604	5.563	10.830
Ethyl Benzene (ppbV)	0.287 (0.168)	0.228	0.100	0.149	0.278	0.436	0.604	1.300
1,3-Butadiene (ppbV)	0.367 (0.175)	0.158	0.022	0.092	0.155	0.384	0.548	0.910
Benzene (ppbV)	1.268 (0.830)	1.197	0.151	0.410	0.591	1.788	2.574	4.600
Meta/para-xylene (ppbV)	0.993 (0.548)	0.616	0.141	0.445	0.599	1.213	1.765	3.791
Styrene (ppbV)	0.159 (0.122)	0.139	0.050	0.053	0.068	0.207	0.350	1.378
Lead (ng/m3)	21.360 (17.488)	18.143	2.318	6.391	8.913	27.174	45.600	87.158
Perchloroethylene (ppbV)	0.186 (0.198)	0.177	0.009	0.035	0.057	0.234	0.487	1.845
Total PAHs (ng/m3)	1.476 (1.128)	1.090	0.164	0.486	0.723	1.814	2.808	12.885
Benzo(k)fluoranthene (ng/m3)	0.109 (0.102)	0.081	0.020	0.035	0.048	0.129	0.210	1.097
Benzo(a)pyrene (ng/m3)	0.214 (0.230)	0.168	0.020	0.053	0.084	0.251	0.445	2.449
Benzo(b)fluoranthene (ng/m3)	0.266 (0.241)	0.202	0.023	0.080	0.120	0.321	0.513	2.519
Indeno(1,2,3-cd)pyrene (ng/m3)	0.318 (0.254)	0.245	0.024	0.097	0.153	0.397	0.607	3.189
Dibenz(a,h)anthracene (ng/m3)	0.036 (0.036)	0.016	0.020	0.020	0.021	0.038	0.058	0.691
Benzo(g,h,i)perylene (ng/m3)	0.559 (0.353)	0.446	0.047	0.191	0.296	0.741	1.058	2.799
Ortho-dichlorobenzene (ppbV)	0.108 (0.040)	0.079	0.050	0.059	0.071	0.150	0.150	0.276
Para-dichlorobenzene (ppbV)	0.144 (0.038)	0.038	0.100	0.100	0.115	0.152	0.188	0.519
Trichloroethylene (ppbV)	0.069 (0.108)	0.043	0.010	0.012	0.016	0.059	0.184	1.021
Carbon tetrachloride (ppbV)	0.105 (0.019)	0.034	0.072	0.084	0.090	0.124	0.132	0.145
Formaldehyde (ppbV)	2.725 (1.135)	1.277	0.744	1.479	1.936	3.212	4.174	8.111
Selenium (ng/m3)	1.533 (0.666)	0.716	0.750	1.000	1.045	1.762	2.421	4.737
Chloroform (ppbV)	0.034 (0.013)	0.016	0.010	0.019	0.025	0.041	0.052	0.126
Chromium (total) (ng/m3)	5.056 (2.478)	3.005	1.182	2.316	3.350	6.350	7.696	30.136
Hexavalent chromium (ng/m3)	0.189 (0.101)	0.135	0.096	0.100	0.110	0.245	0.313	1.514
Acetaldehyde (ppbV)	1.371 (0.661)	0.864	0.286	0.645	0.863	1.727	2.435	4.082
Nickel (ng/m3)	4.851 (2.187)	3.193	1.077	2.304	3.182	6.381	7.726	18.571

Table 3

Risk of neuroblastoma with one interquartile increase in air toxic exposure during the pregnancy period, at 5K and 2.5K radii around air pollution monitors [a]

	5 kilometers			2.5 kilometers		
Air toxic	**N cases/ controls**	**Model 1 OR**	**Model 2 OR (95% CI)**	**N cases/ controls**	**Model 1 OR**	**Model 2 OR (95% CI)**
Traffic-related and other correlated pollutants						
Ortho-xylene	59/11554	1.18	1.30 (0.87, 1.95)	20/3499	0.84	0.88 (0.39, 1.96)
Toluene	59/11612	1.22	1.35 (0.89, 2.04)	20/3532	0.78	0.82 (0.35, 1.90)
1,3-Butadiene	74/13110	0.95	1.06 (0.70, 1.62)	23/3987	1.21	1.27 (0.60, 2.68)
Ethyl Benzene	58/11122	1.01	1.09 (0.78, 1.51)	19/3353	0.78	0.81 (0.40, 1.62)
Benzene	74/13115	1.21	1.36 (0.82, 2.25)	23/3988	1.24	1.32 (0.52, 3.37)
Meta/para-xylene	43/7904	0.84	0.87 (0.58, 1.33)	16/2426	0.94	0.94 (0.50, 1.78)
Styrene	48/9718	1.13	1.22 (0.84, 1.78)	15/2940	0.95	1.00 (0.46, 2.18)
Lead	51/9679	1.04	1.10 (0.79, 1.52)	16/2924	1.17	1.13 (0.62, 2.05)
Perchloroethylene	67/12041	1.02	1.06 (0.84, 1.33)	21/3635	1.00	1.01 (0.62, 1.64)
Polycyclic aromatic hydrocarbons (PAHs)						
Total PAHs	49/10142	1.13	1.12 (0.86, 1.46)	18/3135	1.40	1.39 (1.01, 1.91)
Benzo(k)fluoranthene	56/10676	1.14	1.13 (0.96, 1.33)	20/3296	1.18	1.18 (0.91, 1.51)
Benzo(a)pyrene	56/10676	1.15	1.13 (0.98, 1.31)	20/3296	1.16	1.15 (0.91, 1.46)
Benzo(b)fluoranthene	56/10676	1.13	1.12 (0.93, 1.35)	20/3296	1.20	1.19 (0.91, 1.58)
Indeno(1,2,3-cd)pyrene	49/10142	1.16	1.15 (0.90, 1.47)	18/3135	1.40	1.39 (1.05, 1.84)
Dibenz(a,h)anthracene	49/10142	1.08	1.08 (1.01, 1.14)	18/3135	1.11	1.11 (1.03, 1.20)
Benzo(g,h,i)perylene	49/10142	0.98	1.02 (0.66, 1.58)	18/3135	1.62	1.62 (0.84, 3.13)
Other air toxics						
Ortho-dichlorobenzene	53/10175	1.08	1.21 (0.62, 2.37)	17/3065	0.44	0.45 (0.12, 1.67)
Para-dichlorobenzene	53/10213	1.00	1.04 (0.80, 1.37)	17/3083	0.76	0.77 (0.40, 1.52)
Trichloroethylene	67/12086	0.95	0.98 (0.87, 1.10)	21/3639	1.03	1.05 (0.88, 1.26)
Carbon tetrachloride	40/7443	2.55	2.65 (1.07, 6.53)	12/2245	7.90	7.87 (1.37, 45.34)
Formaldehyde	67/12105	0.86	0.91 (0.67, 1.23)	19/3625	0.91	0.92 (0.52, 1.63)
Selenium	44/9288	0.86	0.88 (0.61, 1.28)	14/2807	1.00	0.95 (0.50, 1.80)
Chloroform	69/12257	1.11	1.12 (0.86, 1.47)	22/3693	1.29	1.27 (0.82, 1.96)
Chromium (total)	52/9727	1.01	1.06 (0.75, 1.49)	16/2943	0.80	0.77 (0.37, 1.58)
Hexavalent chromium	35/8237	1.34	1.32 (1.00,1.75)	9/2468	1.00	1.00 (0.25, 4.00)
Acetaldehyde	67/12105	1.15	1.22 (0.87, 1.73)	19/3625	1.36	1.37 (0.72, 2.63)
Nickel	52/9730	0.97	1.08 (0.71, 1.66)	16/2944	0.73	0.67 (0.29, 1.56)

[a] Model 1 adjusts for birth year (matching variable). Model 2 adjusts for birth year, mother's age, mother's race/ethnicity, and the method of payment for prenatal care