**In Utero** and Early-Life Exposure to Ambient Air Toxics and Childhood Brain Tumors: A Population-Based Case–Control Study in California, USA

Ondine S. von Ehrenstein,1 Julia E. Heck,2 Andrew S. Park,2 Myles Cockburn,3 Loraine Escobedo,3 and Beate Ritz2

1Department of Community Health Sciences, and 2Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California, USA; 3Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA

**Background:** Little is known about the influence of environmental factors on the etiology of childhood brain tumors.

**Objectives:** We examined risks for brain tumors in children after prenatal and infant exposure to monitored ambient air toxics.

**Methods:** We ascertained all cases of medulloblastoma, central nervous system primitive neuroectodermal tumor (PNET), and astrocytoma before 6 years of age diagnosed in 1990–2007 from the California Cancer Registry and selected controls randomly from birth rolls matched by birth year. Exposures to air toxics during pregnancy/infancy for 43 PNET, 34 medulloblastoma, and 106 astrocytoma cases and 30,569 controls living within 5 mi of a monitor were determined. With factor analysis we assessed the correlational structures of 26 probable carcinogenic toxics, and estimated odds ratios by brain tumor type in logistic regression models.

**Results:** PNETs (≤38 cases) were positively associated with interquartile range (IQR) increases in prenatal exposure to acetaldehyde [odds ratio (OR) = 2.30; 95% CI: 1.44, 3.67], 1,3-butadiene (OR = 2.23; 95% CI: 1.28, 3.88), benzene, and toluene; and with IQR increases in exposure during the first year of life to ortho-dichlorobenzene (OR = 3.27; 95% CI: 1.17, 9.14), 1,3-butadiene (OR = 3.15; 95% CI: 1.57, 6.32), and benzene. All exposures except ortho-dichlorobenzene loaded on the same factor. Medulloblastoma (≤30 cases) was associated with prenatal exposure to polycyclic aromatic hydrocarbons (PAHs combined: OR = 1.44; 95% CI: 1.15, 1.80). Exposures to lead and some PAHs during the first year of life were positively associated with astrocytoma, but the confidence intervals included the null value (e.g., for lead, OR = 1.40; 95% CI: 0.97, 2.03).

**Conclusions:** Our data suggest that in utero and infancy exposures to air toxics generated by industrial and road traffic sources may increase the risk of PNET and medulloblastoma, with limited support for increased risks for astrocytoma in children up to age 6.

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**Introduction**

Brain tumors are the most frequent solid tumors in children and the most common cause of childhood cancer deaths (Baldwin and Preston-Martin 2004). Among infants up to 36 months of age, the usually fast growing embryonal tumors medulloblastoma and central nervous system (CNS) primitive neuroectodermal tumor (PNET) are the most frequent brain neoplasms; among all children up to age 15 years, astrocytoma is the most common form of glioma (McKeen-Cowdin et al. 2013) and the most common brain tumor subtype overall (Gurney 1999). Medulloblastoma is believed to arise from the precursor cells of the external granule layer of the developing cerebellum. PNets form in the cerebrum and is composed of poorly differentiated neuroepithelial cells (MacDonald 2008). Medulloblastoma/PNET incidence is highest in infancy, declines slowly until age 5 years with a steep decline thereafter, whereas astrocytoma is reported to peak twice, at ages 5 and 13 years (Gurney 1999; McKeen-Cowdin et al. 2013).

Although several genetic syndromes are associated with an increased risk for brain tumors, these syndromes are thought to account for <5% of all cases (Baldwin and Preston-Martin 2004). Non-genetic risk factors still remain largely unknown. Although environmental influences are thought to play a key role in the development of childhood brain tumors, beyond high doses of ionizing radiation (IARC 2012), no environmental factor is an established risk factor. Suspected environmental factors include exposure to pesticides (Greenop et al. 2013; Sears Nielsen et al. 2010), parental occupational exposures (Cordier et al. 2001, 2004), paternal hobbies (Rosso et al. 2008), and maternal cured meat consumption and other dietary factors (Bunin et al. 2006; Sears Nielsen et al. 2011). Several studies have examined effects of maternal and paternal smoking, but findings are equivocal (Boffetta et al. 2000; Brooks et al. 2004; Milne et al. 2013).

Air toxics are defined by the U.S. Environmental Protection Agency (EPA) as pollutants that may cause serious health effects or adverse environmental and ecological effects, and are also known as hazardous air pollutants (HAPs). Many of these are common in urban air mixtures [e.g., polycyclic aromatic hydrocarbons (PAHs) or organic solvents] and are suspected or known carcinogens (IARC 2013), and have also been found to have adverse effects on the developing CNS (Calderón-Garcidueñas et al. 2008; Levesque et al. 2011). One previous study relied on modeled annual average HAPs and reported little association for gliomas (Reynolds et al. 2003).

To the best of our knowledge, no study to date has investigated perinatal exposure to monitored air toxics and specific subtypes of childhood brain tumors. Here we report on a California state-wide case–control study of childhood brain tumors and prenatal and infant exposure to monitored ambient air toxics, including PAHs, aromatic and chlorinated solvents, other volatile organic compounds, and several metals.

**Methods**

**Study Design and Population**

We ascertained all cases of medulloblastoma [International Classification of Disease Oncology (ICD-O) code 9470), PNET (ICD-O code 9473), and astrocytoma [International Classification of Childhood Cancer, version 3 (ICCC-3) code 032] before age 6 years diagnosed in 1990–2007, from the California Cancer Registry (http://www.ccrcal.org). The overall study design has been described elsewhere (Heck et al. 2013a). In brief, we attempted to match all cancer cases to a California birth certificate (received from the Office of Vital Records, California Department of Public Health) using first and last names and dates of birth (89% matching rate). Controls without a cancer diagnosis

Address correspondence to O.S. von Ehrenstein, University of California, Los Angeles, P.O. Box 951772, Los Angeles, CA 90095-1772 USA. Telephone (310) 206-5324. E-mail: ovehren@ucla.edu

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before age 6 years were randomly selected from California birth rolls and frequency matched (20:1) by year of birth to all childhood cancer cases for the same time period. Date of birth and gestational age of each child were retrieved from birth certificates. From the entire cohort, 74 cases and 12,035 controls had missing gestational age and were excluded.

Human subjects research required for this study was approved by the institutional review boards of the University of California, Los Angeles, and the California Health and Human Services Agency; informed consent was waived because there was no contact with study subjects. Confidentiality was maintained by using only de-identified data in the analyses.

**Exposure Assessment**

Residential addresses, as listed on the birth certificate, were geocoded using our open-source geocoder with manual correction of unmatched addresses (Goldberg et al. 2008) and used to classify exposure throughout pregnancy and during the first year of life. Exact home addresses were recorded on electronic birth certificates from 1998; before 1998, only ZIP codes were available, and we geocoded the ZIP code centroid for those children. The California Air Resources Board (CARB) has maintained an air toxics monitoring network since 1990, which collects 24-hr integrated samples of ambient air concentrations every 12 days. The 31 monitors (5-mi radius) were located across the state, positioned primarily near heavily trafficked highways, in industrial or in agriculturally intense regions at locations selected to be representative for the area (for map, see Cox et al. 2010). Using latitude/longitude locations provided by CARB, we determined the distance from each monitor to each home or ZIP code centroid, and participants were assigned pollutant values based upon the measurements taken at the nearest monitor. Based on categorization as “established, possible, or probable carcinogens” by the IARC (2013), we identified an initial set of 42 substances. For each toxic, we included children who had at least one reading for each full month of pregnancy and, because the last month of pregnancy rarely is exactly 1 month in length, with at least one reading within the last 30 days of pregnancy. We included in the analysis all subjects with geocoded addresses within < 5 mi from a CARB air toxics station to balance exposure misclassification with increasing distance from a station against sample size limitations. We further restricted the sample to children with gestational ages and birth weight considered viable (146–323 days, 500–6,800 g), and removed 719 controls because of death before age 6 years by matching to California death records. This resulted in 43 PNETs, 34 medulloblastomas, 106 astrocytomas, and 30,569 controls in the final sample (actual numbers of cases included in analyses varied and were less, due to missing information on exposure or covariates). For each pollutant, we included only children in the analysis who had at least one reading for each full month within the time period of interest. We included substances for which a minimum of 20 cases for each brain cancer type had values for the entire pregnancy average (i.e., at least one measurement for each month of pregnancy) assigned at 5 mi, resulting in 26 substances considered herein. Cases diagnosed during the first year of life were excluded from first year models. Time-specific exposure averages were generated based on birth date and gestational age as retrieved from birth certificates; we determined averages for each trimester, the entire pregnancy period, and the first year of life.

**Statistical Analyses**

We employed Pearson’s correlation coefficients to examine collinearity across pollutants and pregnancy periods. We used factor analysis (varimax rotation) to create a correlation matrix for all 26 included exposures. This matrix helped us identify patterns of covariation of pollutants in our data that might represent common sources such as road traffic, or indicate mixtures of toxics in ambient air potentially acting together to increase cancer risks. Substances loading on the same factor were assigned to the same factor, and the sum of square loadings was transformed into a rotated factor score that was assigned to each record in the study.

| Characteristic | PNET (n = 43) | Medulloblastoma (n = 34) | Astrocytoma (n = 106) | Controls (n = 30,569) |
|---------------|--------------|------------------------|----------------------|----------------------|
| Mother’s race/ethnicity | | | | |
| Non-Hispanic white | 14 (32.6) | 13 (38.2) | 47 (44.3) | 7,728 (25.3) |
| Hispanic of any race | 20 (46.5) | 14 (41.2) | 40 (37.7) | 16,169 (52.9) |
| Other/not specified | 9 (20.9) | 7 (20.6) | 19 (17.5) | 6,972 (21.8) |
| Mother’s age (years) | | | | |
| < 20 | 4 (9.3) | 6 (17.7) | 14 (13.2) | 3,591 (11.8) |
| 20–24 | 11 (25.6) | 9 (26.5) | 18 (17.0) | 7,616 (24.9) |
| 25–29 | 16 (37.2) | 10 (29.4) | 27 (25.5) | 8,301 (27.2) |
| 30–35 | 7 (16.3) | 8 (23.5) | 35 (33.0) | 6,913 (22.6) |
| ≥ 35 | 5 (11.6) | 1 (2.9) | 12 (11.3) | 4,146 (13.6) |
| Missing | 0 | 0 | 2 (0.01) | |
| Source of payment for prenatal care | | | | |
| Public (Medi-Cal) | 24 (55.8) | 14 (41.2) | 50 (47.2) | 16,624 (54.4) |
| Private | 19 (44.2) | 19 (55.9) | 56 (52.8) | 13,671 (44.7) |
| Missing | 0 | 1 (2.9) | 0 | 274 (0.9) |
| Maternal education (years) | | | | |
| ≤ 8 | 8 (18.6) | 0 (0) | 12 (11.3) | 4,746 (15.5) |
| 9–11 | 5 (11.6) | 7 (20.6) | 13 (12.3) | 6,315 (20.7) |
| 12 | 14 (32.6) | 11 (32.4) | 30 (28.3) | 8,432 (27.6) |
| 13–15 | 9 (20.9) | 8 (23.5) | 29 (27.4) | 5,856 (18.5) |
| ≥ 16 | 7 (16.3) | 8 (23.5) | 22 (20.8) | 5,101 (16.7) |
| Missing | 0 | 0 | 0 | 319 (1.0) |
| Urban* | Yes | 39 (90.7) | 33 (97.1) | 100 (94.3) | 28,807 (94.2) |
| No | 4 (9.3) | 1 (2.9) | 6 (5.7) | 1,762 (5.8) |
| USA born | Yes | 19 (44.2) | 23 (67.7) | 63 (59.4) | 14,388 (47.1) |
| No | 24 (55.8) | 11 (32.4) | 43 (40.6) | 16,181 (52.9) |
| Child sex | | | | |
| Male | 27 (62.8) | 21 (61.8) | 50 (47.2) | 15,499 (50.7) |
| Female | 16 (37.2) | 13 (38.2) | 56 (52.8) | 15,070 (49.3) |
| Parity | | | | |
| 0 | 20 (46.5) | 14 (41.2) | 45 (42.5) | 12,249 (40.1) |
| ≥ 1 | 23 (53.5) | 20 (58.8) | 61 (57.6) | 18,315 (59.9) |
| Missing | 0 | 0 | 0 | 5 (0.01) |
| Preterm birth | | | | |
| Preterm | 6 (14.0) | 4 (11.8) | 12 (11.3) | 3,296 (10.8) |
| Term | 37 (86.1) | 30 (88.2) | 94 (88.7) | 27,273 (89.2) |
| Census-based SES** | | | | |
| 1 | 15 (34.9) | 7 (20.6) | 26 (24.5) | 9,483 (31.0) |
| 2 | 13 (30.2) | 8 (23.5) | 25 (23.6) | 7,397 (24.2) |
| 3 | 6 (14.0) | 6 (17.7) | 22 (20.8) | 5,476 (17.9) |
| 4 | 8 (18.6) | 8 (23.5) | 22 (20.8) | 5,407 (17.7) |
| 5 | 1 (2.3) | 5 (14.7) | 11 (10.4) | 2,806 (9.2) |

Differences to 100% due to rounding; data is retrieved from birth certificates unless otherwise indicated.

*Urban/rural data based on census tract 2000 data (U.S. Census Bureau 2013). Census-based block-group level SES indicator variable, 1 = lowest SES, 5 = highest SES.
might also be proxies for each other because of their high correlation. Whenever several agents loading on the same factor show similar and consistent results for the association with brain cancer, we believe that it supports the argument that either the whole mixture or at least a component of this mixture increases cancer risk. Unconditional logistic regression was used to estimate odds ratios (ORs) per interquartile-range (IQR) increase in pregnancy exposures for each toxicant during each trimester, the entire pregnancy, and the first 12 months of life. Selection of potential confounding variables was based upon previous knowledge (Baldwin and Preston-Martin 2004; McKean-Cowdin et al. 2013) as well as our own previous examination of demographic and perinatal factors related to cancer status in our data (data not shown). We adjusted all models for birth year (matching variable), and further adjusted models for maternal age, race/ethnicity, place of birth, parity (primapara vs. one or more previous births), offspring sex, and preterm birth (< 37 weeks vs. ≥ 37 weeks) did not change the estimates of interest > 3% (data not shown) and thus were not retained in final models.

We present complete case analyses. Associations were evaluated based on the magnitudes of ORs and the width and position of the 95% confidence interval (CI) in relation to the null value. We have chosen not to adjust for multiple comparisons, based in part on the fact that all considered substances were selected a priori based on their classification as carcinogens by IARC (2013). Thus, the models presented equal the number of comparisons we conducted. Additionally, we also conducted sensitivity analyses (adding additional variables to the models mentioned above, restricting for term birth). All analyses were done with SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

Most demographic characteristics were similar among cases and controls, except that more PNET and medulloblastoma case children were boys (Table 1), which is consistent with national data (Ostrom et al. 2015). Mean (± SD) age in years at diagnosis for PNET, medulloblastoma, and astrocytoma was 2.5 ± 1.6, 2.0 ± 1.5, and 2.5 ± 1.8, respectively. The means, standard deviation, and factor loadings (> 0.6) of the air toxics are displayed in Table S1.

Table 2. Adjusted* odds ratios for in utero and first-year-of-life exposure to air toxics and primitive neuroectodermal tumors in children by age 6 years residing within 5 mi of monitoring stations at birth, California, birth years 1990–2007.

| Air toxic | Prenatal | 1st year of life |
|-----------|----------|------------------|
| IQR Case/control (n) | OR*95% CI | Case/control (n) | OR*95% CI |
| Factor 1 | Aromatic solvents | | | |
| Toluene (ppbV) | 2.196 37/32,149 | 2.14 (1.38, 3.32) | 30/22,528 | 2.19 (1.32, 3.65) |
| ortho-Xylene (ppbV) | 0.388 37/32,033 | 1.83 (1.22, 2.74) | 30/22,376 | 1.88 (1.15, 3.07) |
| Ethyl benzene (ppbV) | 0.178 35/23,267 | 1.59 (1.13, 2.26) | 28/21,648 | 1.75 (1.12, 2.73) |
| 1,3-Butadiene (ppbV) | 2.57 38/27,189 | 2.23 (1.28, 3.88) | 31/25,888 | 3.15 (1.57, 6.32) |
| Chlorinated solvents | | | | |
| Perchloethylene (ppbV) | 1.216 38/27,199 | 2.14 (1.12, 4.06) | 31/25,698 | 2.42 (1.09, 5.37) |
| Trichloroethylene (ppbV) | 0.054 36/25,168 | 1.52 (1.13, 2.04) | 28/22,657 | 1.68 (1.14, 2.49) |
| Toluene (ppbV) | 0.453 34/25,412 | 1.14 (0.93, 1.40) | 29/23,758 | 1.13 (0.85, 1.49) |
| Other | | | | |
| Hexavalent chromium (ng/m³) | 0.134 26/16,944 | 1.23 (0.89, 1.78) | 21/14,038 | 1.11 (0.68, 1.82) |
| Lead (ng/m³) | 20.048 26/19,765 | 1.38 (0.85, 2.25) | 20/16,880 | 1.34 (0.74, 2.44) |
| Styrene (ppbV) | 0.137 29/20,001 | 1.31 (0.88, 1.94) | 21/17,132 | 1.12 (0.72, 2.25) |
| Acetaldehyde (ppbV) | 0.900 34/25,361 | 2.30 (1.44, 3.67) | 29/23,343 | 2.12 (1.05, 4.24) |
| Methylene chloride (ppbV) | 0.732 26/18,999 | 1.58 (1.12, 2.17) | 19/15,850 | 1.67 (1.20, 2.32) |
| Factor 2 | PAHs (ng/m³) | | | |
| Benzo[ghi]fluoranthene | 1.049 29/21,368 | 1.06 (0.73, 1.55) | 20/17,862 | 1.03 (0.53, 2.01) |
| Benzo[a]pyrene | 0.077 32/20,416 | 0.96 (0.68, 1.37) | 21/18,834 | 1.14 (0.73, 1.77) |
| Benzo[k]fluoranthene | 0.192 30/22,416 | 1.00 (0.71, 1.42) | 21/18,834 | 1.11 (0.68, 1.84) |
| Indeno[1,2,3-cd]pyrene | 0.233 29/21,368 | 1.04 (0.71, 1.52) | 20/17,862 | 1.03 (0.51, 2.05) |
| Benzo[al]pyrene | 0.157 30/22,416 | 0.93 (0.66, 1.31) | 21/18,834 | 1.08 (0.72, 1.65) |
| Dibenz[a,l]anthracene | 0.015 29/21,368 | 0.81 (0.56, 1.19) | 20/17,862 | 0.83 (0.48, 1.45) |
| Benzo[b,ghi]perylene | 0.448 29/21,368 | 1.58 (0.95, 2.63) | 20/17,862 | 1.73 (0.72, 4.10) |
| Other (ppbV) | | | | |
| Chloroform | 0.017 37/25,534 | 1.48 (1.07, 2.05) | 30/23,792 | 1.50 (1.01, 2.21) |
| ortho-Dichlorobenzene | 0.076 32/21,053 | 1.51 (0.75, 3.04) | 23/18,040 | 3.07 (1.17, 9.14) |
| para-Dichlorobenzene | 0.039 32/21,121 | 1.25 (0.96, 1.63) | 23/18,093 | 1.12 (0.72, 1.73) |
| Formaldehyde | 1.334 34/25,361 | 1.32 (1.00, 1.75) | 29/23,585 | 1.68 (1.18, 2.43) |

*Adjusted for birth weight, maternal race/ethnicity, maternal age and education, place of birth mother (USA vs. non-USA), and consistent for exposures during all trimesters (e.g., OR = 1.23; 95% CI: 0.85, 1.79). When evaluated by trimester, associations with PAHs were closer to the null but persisted for the first and second trimesters OR = 1.13 (95% CI: 1.01, 1.26) and OR = 1.10 (95% CI: 0.99, 1.22), respectively, for summed PAHs (Table S3). ORs were < 1 for several factor 1 substances, and about 0.99 for factor 2 substances.
Discussion

In this first large population-based childhood brain tumor study investigating ambient air toxics measured at community-based monitoring stations, we found increased risks for embryonal brain tumors in young children related to estimated exposure during fetal and first-year-of-life brain development. PNET risks were associated with prenatal and postnatal exposure of several neurotoxics (butadiene, BTEX, selenium, acetaldehyde, perchloroethylene, trichloroethylene, chloroform), and to first-year exposure of ortho-dichlorobenzene. Medulloblastoma risks were associated with higher prenatal PAH exposures. For astrocytoma we estimated imprecise increases in risk (with the OR around 20% > 1 and the lower 95% CI close to excluding the null) related to exposures to lead and some PAHs in the first year of life. As astrocytoma continues to be diagnosed after later childhood, we may not be capturing the most relevant time period for this tumor in our study of children < 6 years of age.

Very little research on environmental contributions to the etiology of childhood brain cancer has been published, and to our knowledge no prior study has examined prenatal and postnatal exposure to monitored concentrations of common ambient air toxics. One small case-only study (n = 98) considered concentrations of annual chlorinated solvents modeled at the census tract level and reported an interaction between high trichloroethylene and OGG1 rs293795 genotype and childhood medulloblastoma/PNET (Lupo et al. 2012); the case-only study design did not allow the researchers to estimate marginal effects for the chlorinated solvents. The only other study to date we are aware of that considered a range of HAPs and childhood cancers included brain tumors diagnosed in children up to age 15 years (1988–1994). This study relied on county-level modeled annual averages from 1990 using the U.S. EPA HAP emissions model. The authors created different exposure scores combining 25 frequent HAPs, and combining point versus mobile sources of emissions, and they considered cancers at all sites, and differentiated only between leukemias and gliomas. Positive associations were reported for leukemias (OR = 1.32; 95% CI: 1.11, 1.57), and for gliomas the OR was 1.19 (95% CI: 0.96, 1.46); embryonal brain tumors were not considered separately (Reynolds et al. 2003).

A few previous studies have investigated traffic-related exposure in relation to all childhood cancers, including brain tumors, and suggested increased risks for leukemia but found little indication of association for other tumors (Raaschou-Nielsen et al. 2001; Reynolds et al. 2002, 2004). One previous California study of all childhood cancers used density of roadways within 500 ft around the birth address as an indicator of traffic exposure and reported for “higher traffic density” an OR of 1.22 (95% CI: 0.87, 1.70) for combined CNS tumors (Reynolds et al. 2004). In our own recent study of all California childhood cancers assessing traffic related air pollution using CALIFORNIA LINE (CALINE4) Source Dispersion Modeling, we found associations between IQR increases in modeled carbon monoxide estimated using CALINE4 and acute lymphoblastic leukemia and retinoblastoma and estimated an OR of 1.10 (95% CI: 0.93, 1.31) for PNET (Heck et al. 2013c). Employing a land use regression (LUR) model to assess traffic related exposure in Los Angeles County only, we examined PNET and astrocytoma but found no associations (Ghosh et al. 2013). We reported earlier no more than moderate correlations (r = 0.2 to 0.5) between several air toxics including benzene and PAHs and LUR-based measures of nitrogen oxides exposure in Los Angeles County (Ghosh et al. 2012). This indicates that the LUR-based exposure markers may not be good indicators for these air toxics from industry and traffic sources in Los Angeles or for the mixture of air toxics across California, and may explain the differences in findings between the studies using LUR-based exposure estimates versus estimates based on air toxics monitoring data.

Our own recent exploratory study (using the same California study as for the brain cancer study) of air toxics and other pollutants and risk of childhood brain tumors (vitamin D, genotypes, maternal and paternal smoking) is in progress.
childhood neuroblastoma \( (n \) cases = 75, \( n \) controls = 14,602), an embryonal malignancy of the sympathetic nervous system, suggested slightly increased risks related to prenatal PAHs and carbon tetrachloride exposure (Heck et al. 2013b). We also found leukemia and retinoblastoma to be positively related to several toxics generated in fuel combustion and traffic, and to chloroform (Heck et al. 2014, 2015), which is in line with our present findings. Factors we identified based on substances with similar loadings may be representative of common or similar emission sources and their complex mixtures of air toxics. It is possible that the combined exposures rather than single substances contribute to CNS tumor risk. The exposures that were most strongly associated with PNET in the present analysis included several substances loading on factor 1 including acetone, toluene, benzene, benzene, and related aromatic solvents, which are generated in fossil fuel burning with primary sources in California being fuel combustion, combustion processes in petroleum refining and oil and gas extraction, coke oven operations, and forest fires (Cox et al. 2010). Selenium additionally is emitted in the production and refining of copper (George 2003). The chlorinated solvents perchloroethylene and trichloroethylene are frequently used in the textile industry and in dry cleaning, whereas chloroform (factor 2) is frequently generated in wastewater treatment (U.S. Geological Survey 2015).

Exposure during the first year of life to ortho-dichlorobenzene (factor 2), which is mainly generated in agricultural pesticide production, was positively associated with PNET. Because most of the substances associated with PNET were highly correlated, our ability to distinguish whether and which specific substances or the mixture of these established or probable carcinogens are responsible for the outcome is limited (Dominici et al. 2010). Future studies need to confirm the associations we reported here and rule out possible residual confounding and to be designed specifically for the purpose of disentangling whether specific toxics or the combination of several toxics increase childhood brain cancer risk.

There was also some suggestion of increased risks for astrocytoma and lead exposure in infancy. Preconceptional paternal occupational lead exposure was inversely associated with astrocytomas and embryonal tumors in a large UK study; however, maternal exposure was not assessed (Keegan et al. 2013). An adult brain cancer study found positive associations with lead (Rajaraman et al. 2006).

Yet data on the risks for childhood brain tumors related to metals are sparse.

Medulloblastoma ORs increased moderately with prenatal exposure to PAHs, which are emitted through coal, wood or fuel burning, petroleum refining, coke production, and tobacco smoke. Little prior research on childhood brain tumors and PAH exposure exists. One study of cancers in children up to age 19 years in relation to maternal prenatal and paternal preconceptional occupational PAH exposure found slight increases related to the latter but not for maternal exposures. However, maternal exposure was rate, and no actual PAH measurements were undertaken (Cordier et al. 2004). The authors reported increased ORs for astroglial tumors (classified using ICD-O codes); we only estimated weak and imprecise associations with exposures during the first three years of life for astrocytoma (classified according to ICCC-3). Cordier et al. (2004) also combined medulloblastoma/PNET into one group, further limiting our ability to compare these results to our study.

Several childhood brain tumor studies investigated parental occupational exposures involving exposures to some toxic air pollutants. Parental occupations related to vehicle exhaust, and maternal exposure to solvents and maternal employment in healthcare (Cordier et al. 1997), as well as in the textile industry, increased risk for PNET and other brain tumors (Cordier et al. 2001). Maternal prenatal and paternal periconceptual exposure to diesel exhaust were related to increased risks for all childhood brain tumors combined by age 5 years, in a case-control study (Peters et al. 2013). A United Kingdom–wide study of paternal occupations found no association with PAH exposure or occupations involving solvents and all CNS tumors combined; however, intrauterine exposure via maternal occupation was not considered (Keegan et al. 2013). Finally, several studies have examined effects of maternal and paternal smoking, but findings are equivocal with positive associations seen for paternal but not maternal smoking during or after pregnancy in an earlier meta-analysis (Boffetta et al. 2000). Positive associations between maternal prenatal smoking and child brain tumors were reported based on prospectively collected data in Sweden (Brooks et al. 2004). Recently, no overall association for parental prepregnancy or prenatal smoking was found; however, there was some indication of increased risks for diagnosis before age 2 years, but the number of young cases was small (Milne et al. 2013). Differential

### Table 4. Adjusted \* odds ratios for in utero and first-year-of-life exposure to air toxics and astrocytoma in children by age 6 years residing within 5 mi of monitoring stations at birth, 1990–2007, California.

| Air toxic | Prenatal OR [95% CI] | 1st Year of life OR [95% CI] |
|-----------|---------------------|-----------------------------|
| Factor 1  |                     |                             |
| Aromatic solvents |                  |                             |
| Toluene (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| ortho-Xylene (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Ethyl benzene (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| 1,2,3-Butadiene (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Benzene (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Chlorinated solvents |                  |                             |
| Perchloroethylene (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Trichloroethylene (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Methylene chloride (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Factor 2  |                     |                             |
| PAHs (ng/m³) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Benzo[a]fluoranthene | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Benzo[k]fluoranthene | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Indeno[1,2,3-cd]pyrene | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Benzo[a]pyrene | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Dibenzo[a,h]anthracene | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Benzo[g,h,i]perylene | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Other (ppbV) | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Chloriform | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| ortho-Dichlorobenzene | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| para-Dichlorobenzene | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |
| Formaldehyde | 1.186 [0.69, 1.99] | 1.186 [0.69, 1.99] |

*Adjusted for birth year, maternal race/ethnicity, maternal age and education, place of birth mother (USA vs. non-USA). \*PAH: Includes sum of average concentrations of six hydrocarbons: benzo[a]pyrene, benzo[a]fluoranthene, benzo[g,h,i]perylene, dibenzo[a,h]anthracene, and indeno[1,2,3-cd]pyrene.*
We do not have data on the percentage of children who moved during the first year of life in our study; however, geocoding methods were based on the place of birth for all children so misclassification is the same for cases and controls. We adjusted our models for important confounders and conducted sensitivity analyses adding additional variables such as parity, child sex, SES indicators, and rural/urban location, which did not change our estimates; yet residual confounding due to unmeasured factors is always possible. Although we relied on a large sample for a childhood cancer study; the rarity of childhood brain tumors combined with the limited number of air toxics monitoring stations resulted in small numbers of cases with exposure measurements and reduced statistical power. Comparing control subjects in the present study to controls in the parent study sample (born during the same time period) but not living within 5 mi of an air monitor, we saw that controls in the present study differed only slightly for most variables except that there were more Hispanics (52.9% vs. 44.4%), more children without private health insurance (54.4% vs. 49.3%), and fewer U.S.-born mothers (47.1% vs. 57.0%) in our sample. Furthermore, a higher percentage was urban (94.2% vs. 79.5), which reflects the fact that we have fewer air toxics monitors and lower population density in rural areas. Thus, we were unable to adequately estimate air toxics exposure and potential risks due to pesticide applications. Among controls missing versus not missing gestational age, fewer indicated private health insurance (35.1% vs. 44.7%) or Hispanic ethnicity (44.9% vs. 52.9%), and more were U.S. born (59.9% vs. 47.1%); other characteristics did not differ. One limitation inherent to the field of childhood brain tumor research is the small number for each tumor type. Strengths of our study include the population based design and record-based approach, which eliminates the drawbacks of recall bias as well as selection bias due to nonparticipation and the ability to differentiate between brain cancer subtypes.

In conclusion, our findings suggest increased risks for the highly malignant and difficult to treat embryonal CNS tumors PNET and medulloblastoma related to in utero and infancy exposure to air toxics emitted from industrial and road traffic sources at ambient concentrations occurring in communities in California.

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