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Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood

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Abstract

There are few established causes of leukemia, the most common type of cancer in children. Studies in adults suggest a role for specific environmental agents, but little is known about any effect from exposures in pregnancy to toxics in ambient air. In our case-control study, we ascertained 69 cases of acute lymphoblastic leukemia (ALL) and 46 cases of acute myeloid leukemia (AML) from California Cancer Registry records of children < age 6, and 19,209 controls from California birth records within 2km (1.3 miles) (ALL) and 6km (3.8 miles) (AML) of an air toxics monitoring station between 1990–2007. Information on air toxics exposures was taken from community air monitors. We used logistic regression to estimate the risk of leukemia associated with one interquartile range increase in air toxic exposure. Risk of ALL was elevated with 3rd trimester exposure to polycyclic aromatic hydrocarbons (OR=1.16, 95%CI 1.04, 1.29), arsenic (OR=1.33, 95%CI 1.02, 1.73), benzene (OR=1.50, 95%CI 1.08, 2.09), and three other toxics related to fuel combustion. Risk of AML was increased with 3rd trimester exposure to chloroform (OR=1.30, 95%CI 1.00, 1.69), benzene (1.75, 95%CI 1.04, 2.93), and two other traffic-related toxics. During the child's first year, exposure to butadiene, ortho-xylene, and toluene increased risk for AML and exposure to selenium increased risk for ALL. Benzene is an established cause of leukemia in adults; this study supports that ambient exposures to this and other chemicals in pregnancy and early life may also increase leukemia risk in children.

Keywords

Childhood leukemia; pregnancy; polycyclic aromatic hydrocarbons; benzene; toluene; lead; chloroform; xylenes; arsenic; childhood cancer epidemiology

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Introduction

Leukemia is the most common cancer type in children, with 5,000 new cases expected in the US in 2012 (Howlader et al., 2012). The most common type of childhood leukemia is acute lymphoblastic leukemia (ALL), which accounts for 78% of cases in childhood, followed by acute myeloid leukemia (AML) which makes up 16% of childhood leukemias (Ries et al., 1999). Established causes of childhood leukemia including genetic predisposition, ionizing radiation, and chemotherapeutic agents are estimated to explain < 10% of cases, leaving the majority of cases with an unresolved etiology (IARC, 2012a, 2012d; Strahm and Malkin, 2006).

In adults, occupational exposure to benzene, 1,3 butadiene, and formaldehyde, as well as employment in certain industries such as rubber manufacturing, are established causes of hematopoietic cancers (IARC, 2012c). Although there are many fewer studies of children, researchers have observed excess risk for leukemias with maternal employment in machinery production and the textile industry and with maternal occupational exposure to vehicle exhaust, paints, pigments, lacquers, toluene, carbon tetrachloride, wood dust, and benzene (Magnani et al., 1990; McKinney et al., 1991; Reid et al., 2011; Schuz et al., 2000; Shu et al., 1988; Shu et al., 1999; Vianna et al., 1984).

Less is known about whether exposure to the lower levels of chemicals that pregnant mothers and children are exposed to in everyday life (“ambient exposures”) increase risk for leukemia. Recently, two studies by our group observed increases in ALL in children with greater exposure to traffic-related pollution during the mother’s pregnancy period (Ghosh et al., 2013; Heck et al., 2013d). Of the other studies on this topic with high quality exposure assessment, a majority have found similar results (Amigou et al., 2011; Crosignani et al., 2004; Feychting et al., 1998; Raaschou-Nielsen et al., 2001; Vinceti et al., 2012; Weng et al., 2008).

The initiating steps of carcinogenesis of some types of leukemia have been previously demonstrated in studies that identified hallmark chromosome translocations in the bloodspots of newborns (Wiemels et al., 1999; Wiemels et al., 2002). Due to the fetus’ greater vulnerability to toxins (Selevan et al., 2000), environmental exposures occurring during the perinatal period may be of most relevance to leukemia risk. Using a population-based sample, the purpose of the present study was to further examine possible traffic-related and other pollution effects by investigating the influence of specific air toxics on leukemia risk.

Materials and methods

The Air Pollution and Childhood Cancer Study (APCC) is a large population-based study, which is described in detail elsewhere (Heck et al., 2013a). In brief, cases were selected from children younger than age 6 who were listed in the California Cancer Registry between 1990 and 2007. We chose to restrict to this young age because our primary hypothesis was that exposures during the perinatal period would be of the most etiologic relevance. Using first name, last name, date of birth, and social security number when available, we matched

cases to California birth certificates (89% matching rate). The majority of cases that were not matched to a birth certificate were likely born out of state (Urayama et al., 2009). Controls, frequency-matched by year of birth to all childhood cancer cases in the parent APCC study, were selected at random from California birth certificates for the same time period (20:1 matching). After linkage with California death records, we excluded 1,550 controls who died of other causes in childhood (<age 6). There were 9,234 children lacking information on gestational age on their birth certificates that were excluded from the present study. We additionally excluded 71 likely non-viable births among controls (< 500 g birthweight or < 20 weeks gestational age) and 494 children whose home address was listed as being outside of California.

We geocoded home addresses, as listed on birth certificates, with a manual resolution process for unmatched addresses, as previously described (Goldberg et al., 2008). Full addresses (number and street) were available on electronic birth certificates starting in 1998. Prior to that date, electronic records only included zip code, thus we geocoded everyone to the zip code centroid. We conducted sensitivity analyses to determine whether the use of zip code centroid instead of addresses changed estimates in models.

The state of California has conducted community-based environmental monitoring of air toxics since 1985, with data available from 1990. Air monitors collect 24-hour samples every 12 days. While air monitors are located across the state, most are sited near heavy industry, busy freeways, or in agriculturally intense rural regions (for map, see (Cox et al., 2008)). Across the study period, monitors were located at 39 different sites. The number of air toxics that are collected has changed over time (ranging between ~60 to 189), and not every air toxic was collected at every monitor, with many collected only in certain years or at specific monitors. Of the available toxics, we selected 42 for the present study because they had been listed as established or suspected carcinogens by the International Agency for Research on Cancer (IARC, 2011). We additionally created a new variable, total polycyclic aromatic hydrocarbons (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].

We ascertained the gestational age of each child from birth certificates, and calculated the start and end date of each trimester (estimating the trimesters as days 1–90, 91–181, and 181+ of the pregnancy). Time-specific exposure averages were calculated based upon the gestational age and date of birth of each child, with estimates generated for each trimester, the entire pregnancy period, and the child's first year of life. In calculating first year of life exposures, we excluded children diagnosed with leukemia prior to age 1. For each pollutant, we included children in the analysis who had at least one 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. Only children who lived within a specific radius around a monitor were included in analyses, and we examined different radii around the monitors to evaluate consistency in effect estimates across distances. Our goal was to choose the smallest radii that allowed for adequate sample size for estimating effects for most pollutants. Here we report results for 2km (~1.3 miles) (ALL) and 6km (~3.8 miles) (AML) buffer areas. This excluded 2,584 cases (ALL), 394 cases

(AML) and 142,188 controls from the original study that lived outside the 2K and 6K radii. In the interest of having adequate sample sizes, we report only upon the air toxics for which a minimum of 20 cases had values assigned at the respective distance.

Because air toxics frequently arise from the same sources, pollutant measurements are sometimes correlated with one another. Correlations between the pollutants in this study have been previously reported (Heck et al., 2013c). To address this issue, we conducted factor analysis with varimax rotation in order to group highly correlated toxics together. The air toxics loaded to four main factors (eigenvalues > 1) with the remaining air toxics not loading to any factor. Results are presented with correlated toxics loading on each factor grouped together.

We used unconditional logistic regression adjusted for the matching variable, birth year, to compare demographic and other characteristics of cases and controls. We then used unconditional logistic regression to estimate the risk of leukemia from each interquartile range increase in air toxic exposure, for each pollutant separately. Interquartile ranges for these pollutants have been previously published (Heck et al., 2013b). Models adjusted for birth year, maternal race/ethnicity (White non-Hispanic/Hispanic/Other), mother's birth place (US/ foreign), parity (0/1+ prior pregnancies), and neighborhood socioeconomic index. Neighborhood socioeconomic index was created by principal components analysis as a single, 5- level measure based on seven census-level indicators of socioeconomic status (education, median household income, percent living 200% below poverty, percent blue-collar workers, percent older than 16 years without employment, median rent, and median house value) (Heck et al., 2012; Yost et al., 2001). These characteristics have been associated with ALL, AML, and/or exposure to air pollution (Abdullaev et al., 2000; Altieri et al., 2006; Howe et al., 2006; Johnson et al., 2008; Pastor et al., 2004). We also examined adjustment for maternal race/ethnicity using a 4-level variable (White non-Hispanic/Black non- Hispanic/Hispanic/Other), but results were nearly identical to those seen with the 3-level race/ethnicity level variable. We considered additional adjustment for child's sex, rural/urban area of residence, and maternal age, but as these did not change effect estimates by > 5%, they were left out of final models (Greenland, 1989).

Although it has not been established that socioeconomic status is independently associated with childhood leukemia (Adam et al., 2008; Carozza et al., 2010; Poole et al., 2006), we conducted sensitivity analyses to examine the effect of adjustment for two other socioeconomic measures, maternal educational attainment and the type of health insurance used to pay for prenatal care (private insurance vs. Medi-Cal, other governmental sources or self-pay). The inclusion of these variables in regressions did not change point estimates by more than 5%.

Results

Analyses of ALL included 69 cases and 2,994 controls who lived within 2km of an air pollution monitor, and analyses of AML included 46 cases and 19,209 controls living within 6km of an air monitor. Children excluded from analyses because they were residing outside the 6km buffer were more likely to live in rural counties (19.9% vs. 4.5%).

Demographic characteristics of participants are shown in Table 1. Children of Hispanic mothers and children from families with greater parity had a higher risk of ALL.

In the first trimester, an average of 6.9 air toxic measurements was used to calculate an individual's exposure; a similar number was used in the second (mean=6.9) and third (mean=7.3) trimesters. Risk of ALL from pregnancy exposure to air toxics is shown in Table 2. ALL was associated with increased 3rd trimester exposure to PAHs, 1,3 butadiene, benzene, meta/para-xylene, arsenic, and lead. Higher exposure to 1,3 butadiene and benzo(g,h,i)perylene across all of pregnancy also increased risk. Third trimester exposure to benzene, toluene, meta/para-xylene, and chloroform increased the risk for AML (Table 3).

We excluded cases diagnosed before age 1 in analyses of exposures in the child's first year, reducing case sample sizes slightly (Table 4). In infancy, ALL was positively associated with exposure to selenium, while AML was positively associated with exposure to 1,3 butadiene, ortho-xylene, and toluene.

In additional sensitivity analyses we compared the influence of using zip code centroid instead of home addresses on results; for some of the pollutants, we observed much larger point estimates during time periods for which exact address data was available. For example, for benzene and ALL, the OR when zip code centroid only was available was 1.37 (95%CI 0.93, 2.01) while for address data it was 2.69 (95%CI 1.28, 5.67). However for several air toxics, such as total PAHs, the ALL point estimates were similar no matter whether zip code centroid (OR=1.16) or home address (OR=1.18) was used.

Discussion

Using a case-control sample of linked cancer registry and birth records, we investigated associations between air toxics exposures in pregnancy and early life in relation to leukemia in young children. We examined known or suspected carcinogens based upon, in most instances, studies of adults that are occupationally exposed to high levels of these agents. Our study suggests that at the relatively lower levels these agents are encountered in ambient air, they are still acting as carcinogens. We observed that exposure to several air toxics during the 3rd trimester, and some in the child's first year, was associated with increased risk for ALL and AML. In early pregnancy, lymphoid-hematopoietic progenitor cells migrate from intraembryonic mesenchyme to fetal liver and fetal spleen, and in late gestation, relocate to bone marrow and thymus, which are the primary lymphopoietic sites for B-cells and T-cells, respectively. Late gestation is also a time period of rapid proliferation of both B-cells and T-cells (Holladay and Smialowicz, 2000; Holsapple et al., 2003); immune system development then continues postnatally. As has been previously hypothesized, there are likely to be critical windows in fetal development which increase susceptibility to toxicants (Dietert et al., 2000; Holladay and Smialowicz, 2000); our data suggest that the 3rd trimester and early life may be critical periods of vulnerability.

As previously reported (Amigou, et al., 2011; Crosignani, et al., 2004; Feychting, et al., 1998; Ghosh, et al., 2013; Heck, et al., 2013d; Vinceti, et al., 2012; Weng, et al., 2008), we observed associations with both AML and ALL in relation to the components of traffic

exhaust. Benzene is an established cause of leukemia in adults (mostly myelogenous, although there is some evidence for lymphoblastic leukemia as well) (IARC, 2012c). Benzene appears to exert genotoxic effects on precursor cells in bone marrow, causing a variety of genetic abnormalities. A study in mice observed *in utero* exposure to benzene increases occurrences of micronuclei and DNA recombination events in hematopoietic tissue (Lau et al., 2009). These changes may occur through oxidative cellular damage which is disruptive to signaling pathways (Badham et al., 2010). Toxics from traffic pollution are able to cross the human placenta, as shown by evidence of bulky DNA adducts and micronuclei in cord blood among newborns exposed *in utero* (Pedersen et al., 2009).

Our findings also support the results of an earlier study which observed excesses of leukemia with maternal occupational exposure to toluene (Shu, et al., 1999). However, benzene, toluene, ethyl benzene, and the xylenes (collectively referred to as “BTEX”) are strongly correlated in our study because they largely arise from the same source, fossil fuel combustion. These strong correlations make it difficult to discern which pollutant may be most relevant for leukemia development. Correlations between BTEX and other toxics loading onto our second factor (perchloroethylene, lead, carbon tetrachloride, hexavalent chromium) can be explained part by the contribution of gasoline combustion to emissions of several of the other chemicals; for example, 52% of hexavalent chromium emissions in California arise from fuel combustion (Cox et al., 2010). Lead is likely correlated with BTEX due to its continuing presence in gasoline that is used by small propeller aircraft (“avgas”) and racing fuels (Agency for Toxic Substances and Disease Registry, 2012). Despite the fact that lead appears to act synergistically with other mutagens in vitro, studies linking it to cancer have been limited in number. It is a known reproductive toxicant; however at present evidence is lacking that it is a leukemogen (Landrigan et al., 2000). Other air toxics are correlated with BTEX likely due to greater releases in urban areas (Turnbull et al., 2011). Perchloroethylene is a solvent used in dry cleaning and manufacturing, while carbon tetrachloride releases in California result from chemical manufacturing and petroleum refining (Cox, et al., 2010).

We observed increased risk of ALL 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. Only one PAH, benzo(a)pyrene, has been classified as an established human carcinogen, based upon the results of experimental studies as well as biological plausibility (IARC, 2012c). PAH exposure in ambient air is associated with chromosomal aberrations in cord blood (Bocskay et al., 2005), and immune system dysfunction is observed in mice exposed to PAHs *in utero* (Holladay and Smialowicz, 2000). To our knowledge, this is the first human study to report on a potential association between childhood leukemia and PAH exposure.

We additionally observed associations between ALL and exposure to arsenic in the 3rd trimester, although arsenic measurements were correlated with PAH levels. In our study, the highest levels of ambient arsenic were measured in the San Joaquin valley and other inland counties, possibly from its use in pesticide formulations (Baker et al., 1996), however emissions may also arise from smelters, coal burning and other industrial processes (Agency

for Toxic Substances and Disease Registry, 2007). Arsenic is a cause of lung, skin and bladder cancers in adults (IARC, 2012b), and it passes through the placenta and is a developmental toxicant, causing fetal loss and birth defects (Vahter, 2009). However a previous study of airborne arsenic, which arose primarily from industrial coal burning, did not find increases in childhood leukemia (Engel and Lamm, 2008).

Chloroform is used in pesticide formulations, as a solvent, and is emitted into the atmosphere as a byproduct from bleaching of paper pulp and in water chlorination. Chloroform is an established carcinogen in animals, but data on its carcinogenicity in humans are limited (IARC, 1999). It is a developmental toxicant and is associated with fetal death and growth retardation in animals; it also causes sperm abnormalities (US EPA, 2001). A small number of studies have observed excesses of leukemia from exposure to trihalomethanes or chloroform in drinking water (Infante-Rivard et al., 2001; Vinceti et al., 2004), however little is known regarding putative effects from ambient air exposure. The associations we observed with chloroform may have been in part driven by the moderate correlations with BTEX pollutants (r~0.21–0.60).

The largest anthropogenic sources of airborne selenium are from the combustion of fossil fuels and in copper production and refining. It is also used in insecticide formulations and in the glass and rubber industries. Studies of selenium exposure have shown both increases and decreases in cancer; it should be noted that selenium releases from industrial sources are likely inorganic, while naturally occurring dietary sources are likely organic (Vinceti et al., 2013). In our study the highest selenium levels occurred in the South Coast Air Basin (which includes Los Angeles), San Diego, the Bay Area, and the San Joaquin Valley. The adverse health effects of selenium include impacts on endocrine function and on the metabolism of growth hormones and insulin-like growth factor-1. However, ambient selenium has not previously been linked to leukemia, and results may be due to chance.

The stability in ambient air of the toxics that we examined is quite variable. Benzene has relatively low reactive decay, while 1,3 butadiene, toluene, and the xylenes are quite reactive, which suggests the findings that we observed for benzene would be the most reliable. Chloroform is also quite stable, while selenium species released in air react rapidly with sulfur dioxide and are reduced to elemental selenium. The size of PAHs (0.4–1.1 μm), which were measured as particulates in our study, would suggest that they may remain airborne for several days or longer. Lead particulates vary in size, but tend to be deposited < 10km from emission sources (Agency for Toxic Substances and Disease Registry, 2012). Traffic emissions are believed to have relatively narrow impact zones of highest exposures, ranging from 300 meters downwind during daytime with good mixing (Zhu et al., 2002) to up to 2600 meters before sunrise with a stable atmosphere (Hu et al., 2009).

We were limited by our reliance on the birth address to estimate exposures, as ambient air near workplaces or while commuting would also be important. We attempted to account for this in part by adjusting for parity, a proxy indicator of whether mothers may have worked outside the home during pregnancy. In addition, between 10–30% of families move addresses during pregnancy, although most moves are local (< 10km) and occur during the 2nd trimester; thus, exposure misclassification would be most concerning for 1st trimester

estimates (Bell and Belanger, 2012). We were further limited by the distance from home addresses to monitors, with some misclassification of exposure expected from the use of monitors that were situated up to 6km from the home, in the case of AML analyses. We also lacked information on parental smoking status, as tobacco use was not collected on California birth certificates until 2007. Tobacco use in pregnancy is lower in California than in other states, in part because of the large numbers of Latina mothers, who are much less likely to smoke while pregnant than women of other ethnic groups (California Department of Public Health Tobacco Control Program, 2006). We were also not able to assess individual level PAH exposure, which in addition to outdoor air exposures is dependent on dietary and indoor air sources (tobacco smoke, emissions from household heat sources, charbroiled meat consumption etc.). However, previous research has noted that for the PAHs we examined in the present study, indoor measurements of PAHs are strongly correlated with outdoor concentrations (Naumova et al., 2002). Results should be interpreted with caution due to the large number of statistical tests, with some results likely due to chance.

Although levels of many air toxics are dropping in California due to changes in gasoline formulations (Cox, et al., 2008), poor air quality is common in many parts of the world due to rapid growth. Strengths of the present study include the population-based design with many years of data collection for airborne toxic pollutants and no response or recall biases since it was based on record linkage only. We observed increases in ALL and AML with maternal and early life exposure to benzene and several other pollutants. Benzene is a known leukemogen and the higher odds ratio we observed when exact home address was available suggest its effects may be also occurring from ambient air exposures. Our results also support earlier research which has observed increases in cancer risk with exposure to traffic pollution (International Agency for Research on Cancer and World Health Organization, 1989). Our other findings, on arsenic, lead, chloroform, selenium, and PAHs have not been reported previously and necessitate replication in other studies.

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Table 1

Demographic characteristics of participants

	ALL			AML		
	Controls† N (%)	Cases N (%)	Crude OR* (95% CI)	Controls† N (%)	Cases N (%)	Crude OR* (95% CI)
Mother's race/ethnicity						
White non-Hispanic	861 (28.8)	18 (26.1)	Referent	5025 (26.2)	14 (30.4)	Referent
Hispanic	1450 (48.4)	40 (58.0)	1.40 (0.79, 2.46)	9970 (51.9)	23 (50.0)	0.78 (0.40, 1.51)
Other/unknown	683 (22.8)	11 (15.9)	0.78 (0.37, 1.66)	4214 (21.9)	9 (19.6)	0.75 (0.32, 1.73)
Mother's birthplace						
U.S.	1599 (53.5)	36 (52.2)	Referent	9499 (49.5)	26 (56.5)	Referent
Other country	1392 (46.5)	33 (47.8)	1.06 (0.66, 1.72)	9692 (50.5)	20 (43.5)	0.75 (0.42, 1.35)
Parity						
No prior pregnancies	1171 (39.1)	27 (39.1)	Referent	7673 (40.0)	19 (41.3)	Referent
1+ prior pregnancies	1823 (60.9)	42 (60.9)	0.99 (0.61, 1.61)	11533 (60.0)	27 (58.7)	0.95 (0.53, 1.71)
Neighborhood socioeconomic index						
Q1 (low)	458 (15.3)	5 (7.2)	Referent	5891 (30.7)	10 (21.7)	Referent
Q2	991 (33.1)	22 (31.9)	1.91 (0.72, 5.11)	4602 (24.0)	11 (23.9)	1.47 (0.62, 3.46)
Q3	800 (26.7)	30 (43.5)	3.27 (1.26, 8.50)	3551 (18.5)	9 (19.6)	1.53 (0.62, 3.76)
Q4	662 (22.1)	11 (15.9)	1.43 (0.49, 4.15)	3264 (17.0)	8 (17.4)	1.57 (0.62, 4.00)
Q5 (high)	83 (2.8)	1 (1.4)	1.27 (0.15, 11.14)	1901 (9.9)	8 (17.4)	2.62 (1.03, 6.65)

*Odds ratios adjust for birth year (matching variable)

†Control sample sizes differ between ALL and AML analyses because of differing radii around air monitors: 2km for ALL and 6km for AML.

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Table 2

Risk of ALL from one interquartile range increase in air toxics exposure during each pregnancy period

	N	1st trimester OR (95% CI)		2nd trimester OR (95% CI)		3rd trimester OR (95% CI)		Entire pregnancy OR (95% CI)	
	Cases/ Controls	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]
1st factor									
total PAHs	53/2159	0.97	0.95 (0.82, 1.11)	1.04	1.04 (0.94, 1.14)	1.15	1.16 (1.04, 1.29)	1.17	1.17 (0.94, 1.45)
Benzo(k)fluoranthene	56/2263	0.97	0.96 (0.84, 1.09)	1.01	1.01 (0.94, 1.10)	1.06	1.07 (1.00, 1.14)	1.08	1.08 (0.92, 1.28)
Benzo(b)fluoranthene	56/2263	0.96	0.95 (0.83, 1.09)	1.01	1.01 (0.93, 1.11)	1.07	1.08 (1.00, 1.16)	1.08	1.09 (0.91, 1.30)
Benzo(a)pyrene	56/2263	0.96	0.95 (0.84, 1.07)	1.01	1.01 (0.94, 1.08)	1.06	1.06 (1.00, 1.13)	1.06	1.07 (0.92, 1.24)
Indeno(1,2,3-cd)pyrene	53/2159	0.96	0.94 (0.81, 1.10)	1.02	1.02 (0.93, 1.13)	1.16	1.16 (1.03, 1.31)	1.13	1.12 (0.91, 1.39)
Dibenz(a,h)anthracene	53/2159	0.96	0.95 (0.86, 1.05)	0.99	0.99 (0.93, 1.05)	1.11	1.12 (1.02, 1.22)	0.99	0.98 (0.89, 1.09)
Benzo(g,h,i)perylene	53/2159	0.99	0.96 (0.78, 1.18)	1.12	1.12 (0.95, 1.31)	1.28	1.27 (1.08, 1.48)	1.62	1.63 (1.13, 2.34)
Arsenic	22/981	0.70	0.71 (0.46, 1.11)	1.06	1.07 (0.79, 1.46)	1.28	1.33 (1.02, 1.73)	1.07	1.12 (0.71, 1.76)
2nd factor									
1,3-Butadiene	66/2626	0.97	0.91 (0.67, 1.25)	1.23	1.17 (0.88, 1.54)	1.60	1.54 (1.19, 1.99)	1.94	1.76 (1.09, 2.86)
Ethyl benzene	57/2199	1.01	0.95 (0.75, 1.21)	0.98	0.92 (0.7, 1.21)	1.23	1.19 (0.97, 1.46)	1.17	1.06 (0.74, 1.51)
Ortho-xylene	57/2297	0.90	0.84 (0.60, 1.17)	1.05	0.99 (0.72, 1.35)	1.32	1.29 (0.99, 1.68)	1.17	1.07 (0.70, 1.62)
Benzene	66/2627	0.94	0.85 (0.58, 1.26)	1.25	1.16 (0.80, 1.67)	1.61	1.50 (1.08, 2.09)	1.67	1.44 (0.84, 2.48)
Toluene	59/2313	1.03	0.95 (0.68, 1.32)	1.09	1.02 (0.73, 1.42)	1.28	1.22 (0.90, 1.65)	1.24	1.11 (0.71, 1.74)
Styrene	46/1932	0.92	0.85 (0.60, 1.19)	0.96	0.89 (0.65, 1.22)	1.03	1.01 (0.83, 1.23)	0.99	0.87 (0.58, 1.32)
Meta/para-xylene	37/1613	1.10	1.07 (0.84, 1.37)	1.05	1.04 (0.75, 1.43)	1.35	1.33 (1.05, 1.69)	1.42	1.38 (0.92, 2.08)
Perchloroethylene	59/2373	1.01	0.97 (0.69, 1.37)	1.09	1.06 (0.76, 1.48)	1.16	1.13 (0.84, 1.52)	1.13	1.08 (0.72, 1.61)
Lead	54/2091	1.15	1.06 (0.74, 1.51)	1.27	1.19 (0.84, 1.70)	1.48	1.42 (1.02, 1.96)	1.51	1.38 (0.89, 2.13)
Hexavalent chromium	47/1758	1.24	1.18 (0.85, 1.63)	1.14	1.12 (0.97, 1.29)	1.09	1.07 (0.86, 1.33)	1.32	1.27 (0.89, 1.81)
Carbon tetrachloride	37/1425	1.09	1.01 (0.47, 2.20)	0.99	0.94 (0.46, 1.90)	0.86	0.80 (0.40, 1.59)	0.97	0.90 (0.41, 1.97)
3rd factor									
Nickel	54/2106	1.08	0.95 (0.66, 1.37)	1.17	1.06 (0.77, 1.47)	0.98	0.85 (0.59, 1.23)	1.09	0.92 (0.60, 1.41)
Chromium	54/2105	1.08	1.00 (0.73, 1.36)	1.17	1.12 (0.88, 1.43)	1.03	0.95 (0.70, 1.28)	1.12	1.02 (0.73, 1.44)
4th factor									
Para-dichlorobenzene	49/2025	0.95	0.94 (0.76, 1.16)	1.00	1.01 (0.85, 1.21)	1.02	1.01 (0.82, 1.24)	1.00	0.99 (0.76, 1.30)
Chloroform	62/2419	0.88	0.85 (0.64, 1.12)	1.02	0.98 (0.76, 1.28)	1.03	1.00 (0.78, 1.28)	0.97	0.91 (0.65, 1.28)

	N	1st trimester OR (95% CI)		2nd trimester OR (95% CI)		3rd trimester OR (95% CI)		Entire pregnancy OR (95% CI)	
	Cases/ Controls	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]
Pollutants that did not load on a factor									
Formaldehyde	58/2521	1.08	1.07 (0.80, 1.43)	1.05	1.06 (0.78, 1.43)	1.14	1.14 (0.87, 1.49)	1.16	1.17 (0.80, 1.70)
Acetaldehyde	58/2521	0.96	0.95 (0.67, 1.35)	1.05	1.06 (0.75, 1.49)	1.13	1.12 (0.82, 1.52)	1.11	1.10 (0.72, 1.69)
Ortho-dichlorobenzene	49/2025	1.08	1.04 (0.67, 1.62)	0.88	0.82 (0.50, 1.35)	1.11	1.06 (0.65, 1.72)	1.08	0.97 (0.50, 1.90)
Trichloroethylene	59/2377	1.00	1.01 (0.90, 1.14)	0.94	0.92 (0.72, 1.19)	1.00	1.01 (0.81, 1.26)	0.98	0.98 (0.79, 1.23)
Selenium	51/2011	0.94	0.94 (0.68, 1.30)	1.10	1.09 (0.85, 1.40)	1.22	1.22 (0.97, 1.53)	1.20	1.19 (0.83, 1.72)
Ethylene dibromide	25/730	0.96	1.01 (0.73, 1.40)	0.85	0.87 (0.58, 1.31)	0.70	0.70 (0.37, 1.33)	0.71	0.74 (0.40, 1.38)

[+] Odds ratios adjust for birth year (matching variable)

[*] Models adjusted for maternal race/ethnicity, birth year, parity, maternal birthplace, and neighborhood socioeconomic index. Included children lived within 2km of an air monitor.

Table 3

Risk of AML from one interquartile range increase in air toxics exposure during each pregnancy period

		1st trimester OR (95% CI		2nd trimester OR (95% CI)		3rd trimester OR (95% CI)		Entire pregnancy OR (95% CI)	
	N Cases/Controls	Crude+	Adjusted*	Crude+	Adjusted*	Crude+	Adjusted*	Crude+	Adjusted*
1st factor									
Total PAHs	31/13535	0.86	0.88 (0.63, 1.21)	0.95	0.96 (0.74, 1.24)	1.12	1.13 (0.93, 1.36)	1.03	1.07 (0.69, 1.65)
Benzo(k)fluoranthene	32/14195	1.00	1.01 (0.82, 1.23)	0.93	0.93 (0.72, 1.19)	1.02	1.03 (0.87, 1.21)	0.99	1.00 (0.70, 1.42)
Benzo(b)fluoranthene	32/14195	1.02	1.03 (0.85, 1.25)	0.93	0.94 (0.73, 1.21)	1.03	1.04 (0.87, 1.23)	1.03	1.05 (0.73, 1.50)
Benzo(a)pyrene	32/14195	1.01	1.02 (0.86, 1.21)	0.95	0.95 (0.77, 1.18)	1.03	1.04 (0.90, 1.19)	1.04	1.04 (0.78, 1.40)
Indeno(1,2,3-cd)pyrene	31/13535	0.89	0.90 (0.66, 1.23)	0.95	0.95 (0.73, 1.24)	1.13	1.14 (0.93, 1.38)	1.04	1.07 (0.69, 1.65)
Dibenz(a,h)anthracene	31/13535	0.95	0.95 (0.78, 1.16)	0.89	0.88 (0.67, 1.17)	1.02	1.02 (0.86, 1.22)	0.91	0.91 (0.66, 1.26)
Benzo(g,h,i)perylene	31/13535	0.81	0.83 (0.56, 1.25)	0.96	0.97 (0.70, 1.36)	1.23	1.25 (0.98, 1.61)	1.18	1.28 (0.70, 2.36)
2nd factor									
1,3-Butadiene	41/17296	0.90	0.99 (0.62, 1.58)	1.04	1.13 (0.73, 1.75)	1.34	1.45 (0.99, 2.15)	1.25	1.58 (0.81, 3.09)
Ethyl benzene	36/14768	0.97	1.02 (0.70, 1.49)	0.91	0.95 (0.63, 1.44)	1.06	1.12 (0.79, 1.58)	0.94	1.05 (0.59, 1.85)
Ortho-xylene	39/15310	1.07	1.15 (0.78, 1.71)	1.12	1.20 (0.81, 1.77)	1.28	1.38 (0.95, 1.99)	1.29	1.48 (0.88, 2.47)
Benzene	41/17299	1.00	1.13 (0.64, 2.01)	1.15	1.30 (0.74, 2.28)	1.57	1.75 (1.04, 2.93)	1.51	1.94 (0.89, 4.19)
Toluene	39/15369	1.16	1.25 (0.83, 1.88)	1.22	1.31 (0.88, 1.94)	1.41	1.50 (1.04, 2.16)	1.52	1.78 (1.03, 3.06)
Styrene	36/12773	1.21	1.27 (0.92, 1.75)	1.15	1.20 (0.86, 1.68)	1.07	1.08 (0.92, 1.27)	1.31	1.38 (0.94, 2.03)
Meta/para-xylene	29/10683	0.99	1.03 (0.71, 1.51)	1.14	1.20 (0.86, 1.68)	1.30	1.37 (1.01, 1.85)	1.35	1.51 (0.93, 2.44)
Perchloroethylene	40/15891	0.96	1.02 (0.73, 1.41)	1.03	1.06 (0.82, 1.38)	1.09	1.11 (0.90, 1.36)	1.06	1.16 (0.75, 1.80)
Lead	23/12669	1.03	1.19 (0.71, 2.02)	1.02	1.18 (0.69, 2.00)	0.95	1.09 (0.61, 1.92)	1.04	1.31 (0.66, 2.58)
Carbon tetrachloride	25/9838	0.80	0.83 (0.32, 2.14)	0.88	0.90 (0.37, 2.20)	1.02	1.02 (0.41, 2.52)	0.90	0.92 (0.33, 2.54)
3rd factor									
Nickel	23/12744	0.96	1.02 (0.63, 1.67)	1.17	1.23 (0.80, 1.88)	1.05	1.05 (0.87, 1.28)	1.13	1.21 (0.72, 2.03)
Chromium	23/12737	0.94	0.99 (0.65, 1.52)	1.05	1.08 (0.77, 1.53)	0.99	1.02 (0.71, 1.48)	1.01	1.06 (0.69, 1.62)
4th factor									
Para-dichlorobenzene	35/13473	1.12	1.14 (0.96, 1.35)	1.17	1.19 (1.02, 1.39)	0.68	0.70 (0.43, 1.14)	1.14	1.19 (0.87, 1.65)
Chloroform	40/16185	1.13	1.18 (0.90, 1.56)	1.28	1.32 (1.04, 1.69)	1.24	1.30 (1.00, 1.69)	1.39	1.49 (1.07, 2.07)
Pollutants that did not load on a factor									
Formaldehyde	39/15969	0.82	0.88 (0.62, 1.25)	0.97	1.05 (0.77, 1.43)	1.03	1.11 (0.83, 1.50)	0.93	1.04 (0.71, 1.53)

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		1st trimester OR (95% CI		2nd trimester OR (95% CI)		3rd trimester OR (95% CI)		Entire pregnancy OR (95% CI)	
	N Cases/Controls	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]	Crude[+]	Adjusted[*]
Acetaldehyde	39/15969	0.72	0.78 (0.47, 1.29)	0.96	1.05 (0.67, 1.66)	1.24	1.38 (0.91, 2.08)	0.96	1.13 (0.64, 1.99)
Ortho-dichlorobenzene	35/13419	0.99	1.04 (0.55, 1.95)	1.16	1.21 (0.68, 2.15)	1.36	1.45 (0.84, 2.49)	1.30	1.43 (0.63, 3.23)
Trichloroethylene	40/15947	0.91	0.95 (0.77, 1.17)	0.85	0.89 (0.67, 1.18)	0.94	0.98 (0.80, 1.21)	0.88	0.92 (0.71, 1.20)
Selenium	22/12189	0.78	0.76 (0.43, 1.35)	0.98	0.98 (0.66, 1.46)	1.00	0.99 (0.64, 1.53)	0.89	0.89 (0.49, 1.60)

[+] Odds ratios adjust for birth year (matching variable)

[*] Models adjusted for maternal race/ethnicity, birth year, parity, maternal birthplace, and neighborhood socioeconomic index. Included children lived within 6km of an air monitor.

Table 4

Risk of leukemia from one interquartile range increase in air toxics exposure during the child's first year

	ALL			AML		
	N Cases/ Controls†	Crude+	Adjusted*	N Cases/ Controls†	Crude+	Adjusted*
1st factor						
total PAHs	42/1765	1.07	1.05 (0.69, 1.59)	20/11259	1.14	1.22 (0.63, 2.38)
Benzo(k)fluoranthene	45/1863	0.94	0.91 (0.65, 1.28)	20/11878	1.02	1.08 (0.62, 1.87)
Benzo(b)fluoranthene	45/1863	0.94	0.92 (0.64, 1.32)	20/11878	1.02	1.08 (0.59, 1.98)
Benzo(a)pyrene	45/1863	0.94	0.91 (0.67, 1.23)	20/11878	1.05	1.09 (0.67, 1.79)
Indeno(1,2,3-cd)pyrene	42/1765	1.10	1.09 (0.71, 1.68)	20/11259	1.11	1.19 (0.59, 2.41)
Dibenz(a,h)anthracene	42/1765	0.95	0.93 (0.68, 1.27)	20/11259	1.08	1.12 (0.74, 1.69)
Benzo(g,h,i)perylene	42/1765	1.48	1.44 (0.81, 2.54)	20/11259	1.50	1.66 (0.65, 4.19)
Arsenic	14/651	---	-----	8/5532	---	-----
2nd factor						
1,3-Butadiene	61/2502	1.91	1.73 (0.97, 3.08)	25/16316	1.70	2.35 (1.02, 5.39)
Ethyl Benzene	48/2064	1.20	1.05 (0.67, 1.65)	21/13702	1.15	1.32 (0.69, 2.53)
Ortho-Xylene	50/2165	1.17	1.03 (0.61, 1.73)	24/14231	1.57	1.88 (1.02, 3.45)
Benzene	61/2503	1.48	1.23 (0.62, 2.43)	25/16319	1.93	2.61 (0.97, 6.99)
Toluene	52/2184	1.36	1.19 (0.70, 2.02)	24/14309	1.64	2.02 (1.03, 3.94)
Styrene	36/1646	1.16	0.97 (0.57, 1.66)	21/10895	1.50	1.63 (0.93, 2.83)
Meta/para-xylene	32/1503	1.60	1.59 (0.97, 2.61)	14/9724	---	-----
Perchloroethylene	51/2176	1.24	1.21 (0.75, 1.96)	24/14361	1.17	1.30 (0.79, 2.16)
Lead	48/1803	1.56	1.45 (0.83, 2.53)	13/10753	---	-----
Hexavalent chromium	39/1495	0.84	0.70 (0.35, 1.40)	17/10808	---	-----
Carbon tetrachloride	21/775	0.78	0.72 (0.25, 2.08)	6/5177	---	-----
3rd factor						
Nickel	48/1810	1.39	1.24 (0.82, 1.87)	13/10771	---	-----
Chromium	48/1810	1.17	1.09 (0.77, 1.53)	13/10771	---	-----
4th factor						
Para-dichlorobenzene	38/1718	0.96	0.91 (0.62, 1.32)	23/11494	1.35	1.47 (0.96, 2.26)

	ALL			AML		
	N Cases/ Controls†	Crude+	Adjusted*	N Cases/ Controls†	Crude+	Adjusted*
Chloroform	54/2270	1.05	0.98 (0.69, 1.40)	24/15043	1.20	1.33 (0.82, 2.17)
Pollutants that did not load on a factor						
Formaldehyde	50/2317	1.07	1.09 (0.72, 1.65)	22/14790	1.28	1.50 (0.96, 2.35)
Acetaldehyde	50/2317	1.12	1.13 (0.71, 1.80)	22/14790	1.10	1.36 (0.68, 2.72)
Ortho-dichlorobenzene	38/1720	1.04	0.75 (0.27, 2.10)	23/11448	1.27	1.57 (0.44, 5.60)
Trichloroethylene	52/2220	1.14	1.18 (0.94, 1.47)	24/14765	1.01	1.12 (0.87, 1.45)
Selenium	45/1718	1.52	1.53 (1.01, 2.32)	13/10242	---	-----
Ethylene dibromide	19/0	---	-----	9/4943	---	-----

+Odds ratios adjust for birth year (matching variable)

*Models adjusted for maternal race/ethnicity, birth year, parity, maternal birthplace, and neighborhood socioeconomic index.

†Control sample sizes differ because ALL models included children living within 2km of an air monitor while AML models included children living within 6km of an air monitor.

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