



Systematic Reviews and Meta- and Pooled Analyses

Parental, In Utero, and Early-Life Exposure to Benzene and the Risk of Childhood Leukemia: A Meta-Analysis

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Benzene is an established cause of adult leukemia, but whether it is associated with childhood leukemia remains unclear. We conducted a meta-analysis in which we reviewed the epidemiologic literature on this topic and explored causal inference, bias, and heterogeneity. The exposure metrics that we evaluated included occupational and household use of benzenes and solvents, traffic density, and traffic-related air pollution. For studies of occupational and household product exposure published from 1987 to 2014, the summary relative risk for childhood leukemia was 1.96 (95% confidence interval (CI): 1.53, 2.52; $n = 20$). In these studies, the summary relative risk was higher for acute myeloid leukemia (summary relative risk (sRR) = 2.34, 95% CI: 1.72, 3.18; $n = 6$) than for acute lymphoblastic leukemia (sRR = 1.57; 95% CI: 1.21, 2.05; $n = 14$). The summary relative risk was higher for maternal versus paternal exposure, in studies that assessed benzene versus all solvents, and in studies of gestational exposure. In studies of traffic density or traffic-related air pollution published from 1999 to 2014, the summary relative risk was 1.48 (95% CI: 1.10, 1.99; $n = 12$); it was higher for acute myeloid leukemia (sRR = 2.07; 95% CI: 1.34, 3.20) than for acute lymphoblastic leukemia (sRR = 1.49; 95% CI: 1.07, 2.08) and in studies that involved detailed models of traffic pollution (sRR = 1.70; 95% CI: 1.16, 2.49). Overall, we identified evidence of associations between childhood leukemia and several different potential metrics of benzene exposure.

benzene; cancer; childhood; leukemia; occupation

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; RR, relative risk; sRR, summary relative risk.

Millions of people in the United States and worldwide are exposed to benzene, either in occupational settings or environmentally (1, 2). The International Agency for Research on Cancer has classified benzene as a human carcinogen based primarily on research that linked occupationally exposed workers to elevated risks of acute myeloid leukemia (AML) (3). Children and fetuses might also be exposed to benzene either through air pollution, exposure sources near residences (such as gas stations or automotive repair facilities), maternal workplace exposure during pregnancy, or home use of products that contain benzene. Despite the sufficient evidence linking benzene to leukemia in adults, it is less clear whether there is an association in exposed children.

Childhood cancer is one of the leading causes of death by disease in children (4), and acute leukemia accounts for 30% of childhood malignancies (5). The most common form is acute lymphoblastic leukemia (ALL), with AML being less common but more fatal (6). Risk factors include genetic conditions such as Li-Fraumeni syndrome or Down syndrome, radiation therapy, chemotherapy, and possibly tobacco smoke (5, 7). To date however, the causes of most childhood leukemias are unknown, and no single chemical agent has been conclusively linked to this cancer.

Although the links between benzene and childhood leukemia have been evaluated in several studies (8–12), the results have been mixed. The reasons for this are not well defined but

could be attributed to differences in study design, exposure levels, leukemia subtypes, and the methods used to assess benzene exposure. Another possible reason is that exposures in children might be much lower than occupational exposures in adults. **Studies of low exposures are likely to have relative risks closer to 1.0, and inadequate sample sizes, bias, or confounding can be especially important when increases in relative risks are small (13).**

We examined current epidemiologic studies of parental or childhood exposure to benzene and childhood leukemia. Our goals were to perform a **systematic literature review**, evaluate each study for the basic tenets of epidemiologic validity, and summarize this literature using meta-analysis. Another goal was to evaluate **sources of heterogeneity**, including heterogeneity based on study design, confounding, leukemia subtype, and methods and timing of exposure assessment.

METHODS

Literature search

Two authors conducted independent literature searches. Databases including PubMed, Google Scholar, Medline, and Embase were searched for epidemiologic studies on benzene and childhood leukemia before age 20 years. Key words included childhood cancer, childhood leukemia, childhood ALL, childhood AML, benzene, occupational setting, traffic, traffic density, hazardous air pollution, vehicle exhaust, hydrocarbons, solvents, ambient air, parental occupation and offspring, home exposure, and in utero exposure. The bibliographies of relevant review articles (1, 5, 14–25) and all studies included in the present meta-analysis were also searched.

Study selection

We included studies that were focused on benzene or common sources or surrogates of benzene exposure. **All cohort and case-control studies that provided a relative risk estimate, an estimate of variance, and an assessment of benzene exposure or related surrogates were included.** Studies in which exposures after cancer diagnosis were assessed were excluded. Only studies that were published in peer-reviewed journals were used. Studies of mortality and not incidence were excluded because childhood leukemia is typically not fatal. Studies that involved populations in which all members were exposed to another potential risk factor (e.g., Down syndrome or residence near a nuclear facility) were also excluded.

Two authors evaluated each study and abstracted relative risk estimates independently. Discrepancies were discussed and resolved through consensus. Study inclusion criteria are detailed in the Appendix.

Exposure assessment

None of the selected studies involved personal measurements of benzene exposure. **In all studies, exposure levels were based on indirect measures, such as job titles, self-reports of benzene or related product use, or other potential surrogates.** To identify the most appropriate metrics of benzene exposure, we referred to the US Environmental Protection Agency's

Toxicity and Exposure Assessments for Children's Health (26) and the Center for Disease Control and Prevention's Toxicological Profile for Benzene (27). On the basis of this information, we included studies in which the following metrics were assessed: **estimates of occupational exposure based on job titles and expert evaluations that linked job titles to probable high exposure to benzene, aromatic hydrocarbons, solvents, or petroleum products; personal interviews in which self-reported exposure to benzene, aromatic hydrocarbon, solvent, or petroleum products at work or home were assessed; automotive repair or gas station attendant work; residential proximity to high traffic density; models of residential ambient air concentrations of benzene based on traffic density or other factors; or residential proximity to gas stations and automotive repair facilities.** Because some of these metrics might be more accurate indicators of benzene exposure than others, we performed subgroup analyses based on each metric. In addition, because of potential differences in exposure levels and exposure scenarios, studies of occupational and household product use were analyzed separately from studies of proximity to gas stations or studies of traffic-related exposures.

Some publications included relative risk estimates for several different exposure metrics for the same study subjects. In our analysis of occupational and household product exposure, we selected which relative risk to include for each metric in the following order: **benzene, aromatic hydrocarbons, solvents, petroleum products, and related occupations** (e.g., automotive repair). In our analysis of traffic density or ambient air exposure, the selection order was ambient air benzene measurements, traffic-related pollution models (e.g., California Line Source Dispersion Model, version 4), and traffic density.

Tobacco smoke is a major source of benzene exposure in smokers and has been linked to childhood leukemia in some studies, although the increases in risks are usually small and not seen in all studies (7). Because tobacco smoke contains multiple carcinogens and because the association of tobacco smoke with childhood leukemia has been reviewed elsewhere (7, 28), we excluded studies that focused on smoking. Potential confounding by smoking and socioeconomic status was evaluated in subgroup analyses.

Data abstraction

From each study, we abstracted information on **location, dates, study design, sample size, participation rates, exposure assessment, timing of exposure, diagnosis, and statistical adjustments.** Different studies assessed exposure during different life stages. We categorized these exposure periods into **5 time frames: preconception (≥ 2 years before birth), periconception (approximately 1 year before birth), gestation, postnatal (any point after pregnancy), and overall (any or all life stages).** In several studies, separate relative risks for different time periods were provided. For our analyses of occupational and household product exposures, we selected 1 result using the following order: overall, gestational, and postnatal. For studies of paternal occupational exposure, data from the preconception period were selected first because this time frame might involve more direct and higher exposures (i.e., to the gamete). Because a previous analysis of traffic studies suggested that

postnatal exposure was associated with higher risks (29), the selection order in our traffic-related analyses was postnatal, overall, and gestational, although subgroup analyses by exposure period were also performed.

In several studies, separate results by leukemia subtype were provided. When this occurred, we selected a subtype in the following order: AML, all types combined, and ALL. AML was selected first because this is the type most strongly linked to benzene exposure in adults (1, 3, 30); ALL results were also evaluated using subgroup analyses. In 1 study, only results for leukemia and lymphomas combined were reported (31). This study was included because leukemia represented the large majority of cases. Some studies reported separate results for exposures in mothers and fathers combined, either parent, mothers only, or fathers only; in this case, 1 result was selected using the following order: both parents, mother only, either parent, and father only. Several studies also reported separate results for different exposure levels (e.g., low, medium, or high). We extracted the result for the highest exposure level because associations are best initially evaluated in groups with high levels of exposure (13).

Some publications included separate results for several different exposure metrics, several different leukemia types, different parents, or different periods of exposure for the same study subjects. In the analyses of all studies combined, 1 result was selected based on the following factors in the following order: the more direct exposure metric (e.g., benzene exposure was selected before exposure to solvents, occupational exposure before home exposure, or more detailed models of traffic pollution before simple traffic density information); leukemia subtype (e.g., AML, all types combined, and then ALL); highest exposure category; parent (both parents before mother only and mother only before father only); exposure period (as described above); largest number of cases; and statistical adjustment (adjusted before unadjusted) (Web Figures 1 and 2, available at <http://aje.oxfordjournals.org/>). Results that were not selected for the combined analyses were still used in the subgroup analyses when appropriate.

Statistical methods

Summary relative risks were calculated using the fixed- and random-effects methods (32). Heterogeneity was assessed using the methods described by Petitti (33). Some believe that the random-effects model is more conservative than the fixed-effects model because it accounts for variance between studies. However, unlike the fixed-effects model, the random-effects model does not weight studies directly on precision; it assigns smaller, less precise studies greater relative weight than does the fixed-effect model. To weight studies directly on precision while still incorporating between-study variance, we used the fixed-effects model to calculate the summary relative risks and then adjusted their 95% confidence intervals for between-study heterogeneity using the method described by Shore et al. (34). Publication bias was evaluated using funnel plots and the tests described by Begg and Mazumdar (35) and Egger et al. (36). All calculations were performed using Excel 2010 (Microsoft Corporation, Redmond, Washington) or STATA, version 12 (StataCorp LP, College Station, Texas), and all *P* values are 2-sided.

RESULTS

The literature review is summarized in Web Figure 3. The initial literature search yielded 506 articles. Title screenings filtered out obviously unrelated articles and studies that did not include humans, resulting in 354 articles. We then filtered out studies specifically about smoking, as well as additional laboratory, animal, or nonrelevant studies. The remaining 185 studies were further reviewed, and studies with possible data on childhood leukemia and benzene exposure or a surrogate thereof were retained. This left 85 papers that were reviewed in detail. On the basis of the inclusion and exclusion criteria listed in the Appendix, 44 of these studies were excluded from our meta-analyses (Web Table 1). The remaining 41 studies were eligible for inclusion in the meta-analysis. Eight of these involved subjects who potentially overlapped with those in another included study and therefore were not included in the meta-analyses of all studies combined; however, they had data that could be used in subgroup analyses (Web Table 2). This left a total of 20 studies for the meta-analysis of all studies of occupational and household product exposure combined (Table 1), 12 studies for the meta-analysis of all traffic density and traffic-related pollution studies combined, and 3 studies for the meta-analysis of residential proximity to gas stations (Table 2).

Occupational and household product exposure studies

Of the studies in the meta-analysis of all studies of occupational and household product exposure, 8 were conducted in North America, 1 in South America, 7 in Europe, 3 in Asia, and 1 in Australia (Table 1). Most of the 17 occupational exposure studies assessed exposure using job records and job exposure matrices or direct questions about exposure to benzene ($n = 9$) (9, 31, 37–43), solvents ($n = 6$) (8, 44–48), petroleum chemicals ($n = 1$) (49), or work as a mechanic ($n = 1$) (50). The 3 studies of household product exposure assessed exposure to benzene (51), solvents (10), or petroleum products (11).

The summary relative risk for all 20 studies of occupational and household product exposure combined was 1.96 (95% confidence interval (CI): 1.53, 2.52; $P < 0.001$; $\chi^2 = 28.42$; P for heterogeneity = 0.08) (Table 3 and Figure 1A). Removing the study that included lymphomas (31) had little impact on results (summary relative risk (sRR) = 1.96; 95% CI: 1.51, 2.53). Sixteen of the 20 studies (80%) reported a relative risk estimate greater than 1.0, of which 8 (40%) were statistically significant. For the 6 studies that provided data on AML, the summary relative risk was 2.34 (95% CI: 1.72, 3.18; $P < 0.001$; $\chi^2 = 2.08$; P for heterogeneity = 0.84). All 6 reported a relative risk of 2.0 or higher (Figure 1B). In the 14 studies of occupational and household product use in which data on ALL were provided, the summary relative risk was 1.57 (95% CI: 1.21, 2.05; $\chi^2 = 24.73$; P for heterogeneity = 0.03).

Summary relative risks were higher in studies of maternal exposure (sRR = 1.96; 95% CI: 1.39, 2.78; $n = 13$) than in studies of paternal exposure (sRR = 1.23; 95% CI: 1.07, 1.41; $n = 14$). They were also higher in studies of exposure during gestation than in studies of other periods. In analyses by exposure metric, the summary relative risk was highest for

Table 1. Studies Included in the Overall Analysis of Occupational and Household Exposure to Benzene and Childhood Leukemia, 1987–2014

First Author, Year (Reference No.)	RR	95% CI	Type of Leukemia	No. of Exposed Cases	Study Location	Study Years	Children's Ages, years	Exposure		
								Parent	Period	Exposure Assessed
<i>Studies of Occupational Exposures</i>										
Abadi-Korek et al., 2006 (8)	2.11	1.10, 4.20	ALL	112 ^a	Israel	1984–2002	0–19	Either	Overall	Solvents, based on detailed histories of parental occupations and exposures, every job held, and specific exposures
Buckley et al., 1989 (44)	2.0	1.2, 3.8	AML	57	United States and Canada	1980–1984	0–18	Father	Overall	Solvents, based on lifetime occupational history; 52 agents in 9 categories
Castro-Jiménez and Orozco-Vargas 2011 (9)	11.65	2.98, 45.59	ALL	85 ^a	Colombia	2000–2005	0–15	Both	Unknown	Benzene, based on occupations, JEM, and expert evaluation; conception to diagnosis
Cocco et al., 1996 (45)	1.5	0.3, 8.0	ALL	3	Italy	1980–1989	Unknown	Father	Unknown	Solvents, based on occupations, JEM, and expert evaluation
Feingold et al., 1992 (37)	1.6	0.5, 5.8	ALL	9	United States	1976–1983	0–14	Father	Periconception	Benzene, based on occupations and expert evaluation
Feychting et al., 2001 (38)	1.23	0.39, 3.85	Leukemia	3	Sweden	Children born 1976, 1977, 1981, 1982	0–14	Father	Preconception	Benzene, based on father's occupation in the census 1–2 years before the child's birth, JEM, and expert evaluation
Infante-Rivard et al., 1991 (46)	0.62	0.20, 1.91	ALL	6	Spain	1983–1985	0–15	Mother	Gestation	Solvents, based on occupation, specific substances during pregnancy, and expert evaluation
Infante-Rivard et al., 2005 (39)	1.47	0.25, 8.85	ALL	790 ^a	Canada	1980–2000	0–9, 0–14	Mother	Any or ever before birth	Benzene, based on occupations and specific exposures from 2 years before pregnancy to birth and on expert evaluation (highest exposure category)
Lowengart et al., 1987 (49)	1.00	0.33, 3.06	Leukemia	123 ^a	United States	1980–1984	0–10	Father	Overall	Petroleum chemicals, based on occupations and specific agents from 1 year before conception to 1 year before diagnosis
McKinney et al., 1991 (31)	4.00	0.30, 118	Leukemia and NHL	2	United Kingdom	1974–1988	0–14	Mother	Preconception	Benzene, based on occupations and specific questions about benzene
McKinney et al., 2008 (47)	2.0	0.7, 5.8	AML	256 ^a	United Kingdom	1991–1996	0–14	Mother	Gestation	Solvents, based on occupations and expert evaluation
Miligi et al., 2013 (43)	3.1	0.8, 12.4	Leukemia	6	Italy	1998–2001	0–10	Mother	Overall	Benzene, based on occupations, specific chemical exposures, and expert evaluation
Perez-Saldivar et al., 2008 (50)	2.81	0.48, 16.43	Leukemia (acute)	9	Mexico	1999–2000	0–15	Father	Preconception	Work as a mechanic, based on occupational history before conception
Reid et al., 2011 (40)	0.93	0.42, 2.09	ALL	9	Australia	2003–2006	0–14	Mother	Before birth	Benzene, based on occupations and expert evaluations
Shu et al., 1988 (41)	4.0	1.8, 9.3	AML	11	China	1974–1986	0–15	Mother	Gestation	Benzene, based on occupations and specific exposures

Table continues

Table 1. Continued

First Author, Year (Reference No.)	RR	95% CI	Type of Leukemia	No. of Exposed Cases	Study Location	Study Years	Children's Ages, years	Parent	Period	Exposure	
										Exposure Assessed	Exposure Assessed
Shu et al., 1999 (42)	0.7	0.3, 1.6	ALL	11	United States	1989–1993	0–15	Mother	Any	Benzene, based on occupations and specific exposures	
Smulevich et al., 1999 (48)	3.1	1.5, 6.3	Leukemia	20	Russia	1986–1988	0–14	Mother	Any	Solvents, based on occupations and job categories	
<i>Studies of Household Product Use</i>											
Kishi et al., 1993 (51)	2.73	1.21, 6.31	ALL	147 ^a	Japan	1980–1990	0–15	Mother	Gestation	Benzene, based on home exposures	
Scélo et al., 2009 (10)	2.23	1.01, 4.93	AML	100 ^a	United States	1995–2005	0–14	Family	Overall	Solvents, based on personal interviews on household use, from gestation to age 3 years (higher frequency category)	
Slater et al., 2011 (11)	2.33	1.30, 4.18	AML	29	United States and Canada	1996–2006	0–1	Mother	Any	Petroleum products, based on personal interview about household exposures 1 month before and during pregnancy	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; JEM, job exposure matrix; NHL, non-Hodgkin lymphoma; RR, relative risk estimate.

^a Total number of cases, including unexposed cases.

those studies in which maternal occupational exposure to benzene (sRR = 1.71; 95% CI: 0.91, 3.24; $n = 7$) or household product use (sRR = 1.67; 95% CI: 1.01, 2.78; $n = 6$) was assessed. In the 6 studies of maternal exposures (household or occupational) and AML, the summary relative risk was 2.31 (95% CI: 1.62, 3.28; P for heterogeneity = 0.77) (data not shown). Summary relative risks were also higher in studies in which there was adjustment for either direct measures of smoking (sRR = 1.94; 95% CI: 1.30, 2.90; $n = 8$) or an indicator of socioeconomic status (sRR = 1.94; 95% CI: 1.39, 2.71; $n = 13$).

Traffic-related and gas station studies

Nine of these studies were done in Europe (12, 52–59) and 4 in North America (60–63) (Table 2). Two of the gas station studies used the same study populations as a study in our traffic analyses (12, 55). Five of the traffic-related studies assessed relatively simple metrics of traffic density (12, 55, 58, 61, 62), and 7 used more complex exposure assessment models including California LINE Dispersion Model, version 4 (52–54, 56, 57, 60, 63).

In the meta-analysis of all traffic-related studies combined, the summary relative risk was 1.48 (95% CI: 1.10, 1.99; $n = 12$; $P = 0.005$; $\chi^2 = 27.49$; P for heterogeneity = 0.004) (Table 4). The summary relative risk was higher for studies of ALL (2.07; 95% CI: 1.34, 3.20; $P = 0.001$) than for studies of AML (1.49; 95% CI: 1.07, 2.08; $P = 0.01$). In analyses by exposure metric, the highest summary relative risks were seen in studies that used more detailed metrics of traffic-related pollution (1.70; 95% CI: 1.16, 2.49; $n = 7$; $P = 0.003$). The summary relative risk was also higher in studies in which exposure at diagnosis was assessed (sRR = 1.46; 95% CI: 1.03, 2.08) than in those in which exposure at birth was assessed (sRR = 0.92; 95% CI: 0.73, 1.17). It was also higher in US studies (sRR = 2.02) than in the European studies (sRR = 1.35). The summary relative risks in the 3 studies of residential proximity to gas stations were above 1.0, but they were not statistically significant.

Publication bias

No evidence of publication bias was seen in the meta-analysis of all studies of occupational or household product exposures, whether in the funnel plot (Figure 2A), when using the test by Egger et al. (36) (bias coefficient = -0.075 ; $P = 0.93$), or when using Begg and Mazumdar's test (35) ($P = 0.97$). Possible evidence of publication bias is seen in the funnel plot of the traffic-related studies using more detailed models (Figure 2B) (i.e., a lack of studies in lower left corner), although the number of studies is small. No indication of bias was seen using the test by Egger et al. (bias coefficient = 0.61; $P = 0.69$) or Begg and Mazumdar's test ($P = 0.88$), and removing the largest study (53) resulted in a pattern less consistent with publication bias (Web Figure 4).

DISCUSSION

Overall, the present meta-analysis provides new evidence that benzene exposure might be associated with a higher risk

Table 2. Studies Included in the Overall Analysis of Traffic Density, Traffic-Related Air Pollution Models, or Gas Station Residential Proximity and Childhood Leukemia, 1999–2014

First Author, Year (Reference No.)	RR	95% CI	Type of Leukemia	No. of Exposed Cases	Study Location	Years	Child Age, Years	Exposure	
								Period	Exposure Assessed or Model Used
<i>Studies of Traffic Density or Traffic-Related Air Pollution Models</i>									
Amigou et al., 2011 (52)	3.1	0.8, 11.6	AML	3	France	2003–2004	0–14	At diagnosis	Composite (density, proximity, and nitrogen dioxide)
Badaloni et al., 2013 (53)	1.30	0.79, 2.12	Leukemia	74	Italy	1998–2001	0–10	Lifetime (never moved)	Land-use regression models (nitrogen dioxide)
Crosignani et al., 2004 (54)	4.31	1.47, 12.62	Leukemia	7	Italy	1978–1997	0–14	At diagnosis	California LINE Source Dispersion Model, version 4
Harrison et al., 1999 (55)	1.16	0.74, 1.72	Leukemia	24	United Kingdom	1990–1994	0–15	At diagnosis	Traffic density
Heck et al., 2014 (60)	1.94	0.89, 4.19	AML	66	United States	1990–2007	0–5	Birth	Air monitoring data for benzene (per IQR)
Langholz et al., 2002 (61)	1.4	0.7, 3.0	Leukemia	46	United States	1978–1984	0–10	Residence of longest duration	Traffic density
Pearson et al., 2000 (62)	8.28	2.09, 32.8	Leukemia	8	United States	1976–1983	0–14	At diagnosis	Traffic density (distance-weighted)
Raaschou-Nielsen et al., 2001 (56)	0.4	0.1, 1.6	Leukemia	870 ^a	Denmark	1968–1991	0–14	Childhood (all residences)	Operational Street Pollution Model (benzene)
Steffen et al., 2004 (12)	1.1	0.8, 1.6	Leukemia	155	France	1995–1999	0–14	Childhood (all residences)	Traffic density (heavy traffic roads)
Vinceti et al., 2012 (57)	1.92	0.64, 5.78	AML	19	Italy	1998–2009	0–14	At diagnosis	California LINE Source Dispersion Model, version 4 (per 1 µg/m ³ benzene)
Visser et al., 2004 (58)	4.9	1.6, 11.4	ALL	5	Netherlands	1989–1997	0–14	At diagnosis	Traffic density (traffic intensity score)
Whitworth et al., 2008 (63)	2.02	1.03, 3.96	AML	31	United States	1995–2004	0–19	At diagnosis	Assessment System for Pollution Exposure Nationwide
<i>Studies of Residential Proximity to Gas Stations</i>									
Brosselin et al., 2009 (59)	1.1	0.5, 2.5	AML	7	France	2003–2004	0–18	Any	Residential proximity to garages or gas stations based on personal interviews; all residences from pregnancy to diagnosis
Harrison et al., 1999 (55)	1.48	0.65, 2.93	Leukemia	8	United Kingdom	1990–1994	0–15	At diagnosis	Living within 100 m of a gas station
Steffen et al., 2004 (12)	7.7	1.7, 34.3	AML	4	France	1995–1999	0–14	Childhood	Proximity to repair garages or gas stations, based on interviews about residential history from conception to diagnosis

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; IQR, interquartile range; RR, relative risk.

^a Total number of cases, including unexposed cases.

Table 3. Results of the Meta-Analyses of Studies of Childhood Leukemia and Parental and Early Childhood Exposure to Benzene in Occupational and Household Products, 1987–2014

Group and Subgroup	No. of Studies	Fixed Effects		Shore-Adjusted ^a	Random Effects ^a		Heterogeneity		
		sRR	95% CI	95% CI	sRR	95% CI	χ^2	P Value	
Outcome									
All studies combined	20	1.96	1.60, 2.41	1.53, 2.52	1.94	1.48, 2.53	28.42	0.08	
AML only	6	2.34	1.72, 3.18	NA	NA	NA	2.08	0.84	
ALL only	14	1.57	1.30, 1.90	1.21, 2.05	1.63	1.21, 2.21	24.73	0.03	
Parent									
Mother	13	1.96	1.52, 2.55	1.39, 2.78	1.94	1.34, 2.80	21.55	0.04	
Father	14	1.23	1.08, 1.39	1.07, 1.41	1.27	1.08, 1.50	16.23	0.24	
Exposure metric									
Maternal occupational exposure									
Benzene	7	1.71	1.14, 2.58	0.91, 3.24	1.94	0.97, 3.91	14.51	0.02	
Solvents	7	1.17	0.94, 1.46	0.84, 1.63	1.25	0.87, 1.80	13.66	0.03	
Paternal occupational exposure									
Benzene	6	1.18	1.00, 1.41	0.94, 1.50	1.27	0.89, 1.80	9.43	0.09	
Solvents	9	1.18	1.00, 1.39	NA	NA	NA	6.65	0.57	
Household product use ^b	6	1.67	1.24, 2.26	1.01, 2.78	1.88	1.10, 3.21	14.16	0.01	
Adjustments ^c									
Smoking	8	1.94	1.43, 2.64	1.30, 2.90	1.94	1.27, 2.97	11.97	0.10	
Socioeconomic status	13	1.94	1.50, 2.51	1.39, 2.71	1.95	1.37, 2.71	20.44	0.06	
Time of exposure									
Preconception									
Maternal	6	1.32	0.92, 1.89	0.84, 2.08	1.38	0.83, 2.27	7.98	0.16	
Paternal	8	1.31	1.11, 1.54	NA	NA	NA	6.64	0.47	
Periconception									
Maternal	3	1.29	0.97, 1.71	NA	NA	NA	1.26	0.53	
Paternal	4	1.13	0.94, 1.37	NA	NA	NA	1.53	0.67	
Gestation (maternal exposure)	9	2.06	1.51, 2.81	1.41, 3.02	1.93	1.29, 2.88	12.12	0.15	
Postnatal	6	1.51	0.99, 2.30	NA	NA	NA	3.95	0.56	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; NA, not applicable; sRR, summary relative risk.

^a The Shore-adjusted and random-effects models were used if the χ^2 statistic was greater than the degrees of freedom (the number of studies minus 1).

^b Includes benzene, aromatic hydrocarbon, solvent, and petroleum product use.

^c Includes adjusted results and results from studies in which the authors stated that the adjustments had little or no impact on the results.

of childhood leukemia. Summary relative risks greater than 1.0 were seen for several different potential metrics of benzene exposure, including maternal occupational exposure, household use of benzene-related products, and traffic-related air pollution. **This evidence was particularly strong and heterogeneity was particularly low for studies of AML.** In our analysis of occupational and household product studies, all 6 AML studies had relative risk estimates greater than 2.0. In our analysis of the traffic-related pollution studies, all 4 AML studies reported relative risk estimates greater than 1.9. Overall, the low *P* values, confidence intervals that excluded 1.0, and large proportion of individual relative risk

estimates greater than 1.0 all provide evidence that our major findings are not due to chance. In addition, the finding of higher relative risks in studies of more direct or detailed indicators of exposure (e.g., exposure to benzene vs. solvents and detailed traffic models vs. simple traffic density models) and the positive results in studies that included adjustment for smoking and socioeconomic status also support the validity of these findings. Our finding of a higher summary relative risk for AML than for ALL is consistent with previous findings in adults (64), which helps support the biologic plausibility of our results. Although benzene exposures in children are likely lower than those in occupationally exposed adults,

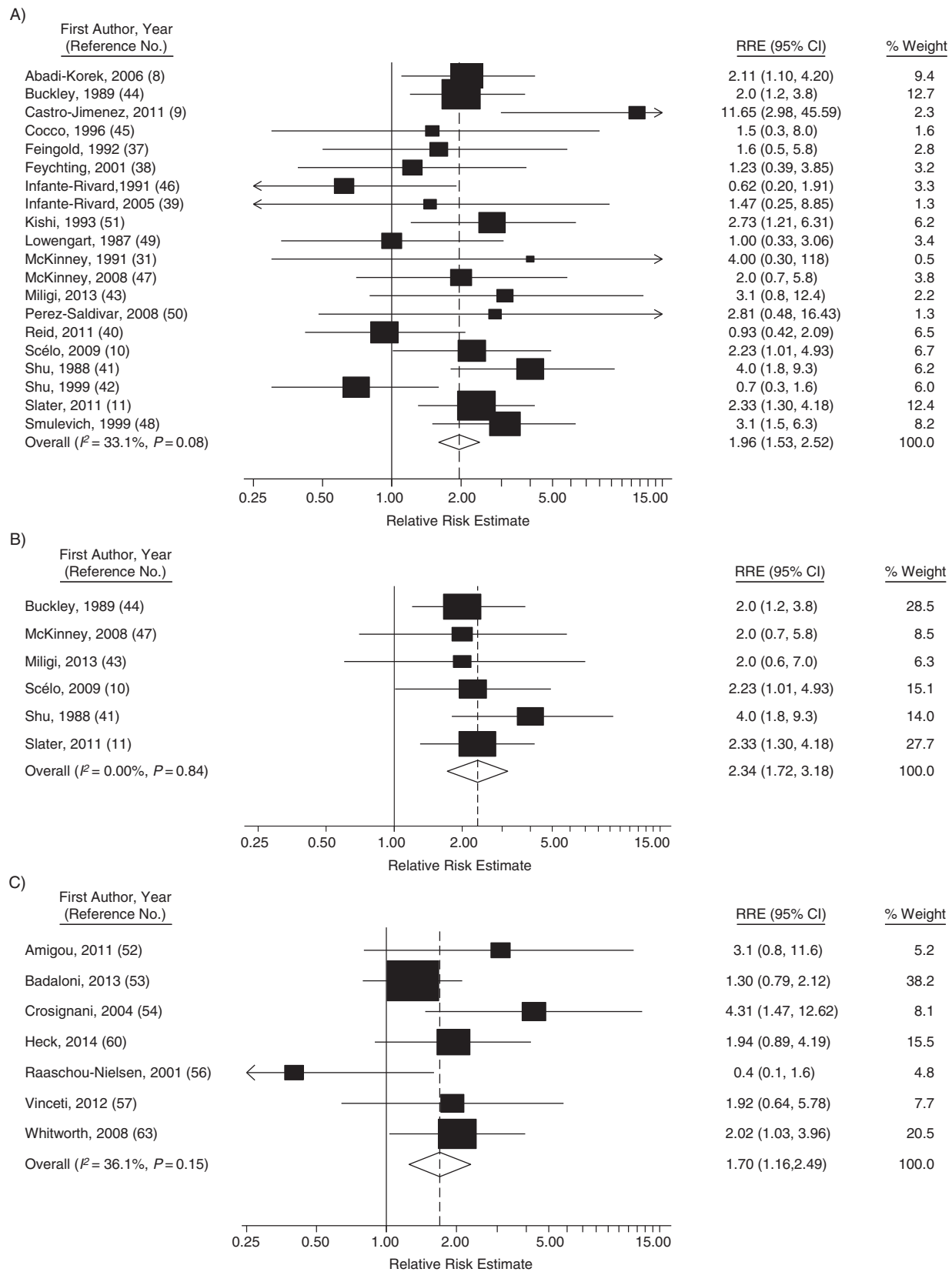


Figure 1. Forest plots of studies included in the meta-analyses of benzene and childhood leukemia, 1987–2014. A) All studies of occupational or household product use; B) studies of acute myeloid leukemia and occupational or household product use; and C) studies of more detailed traffic-related pollution models. CI, confidence interval; RRE, relative risk estimate.

Table 4. Results of the Meta-Analyses of Studies of Childhood Leukemia and Traffic Density, Traffic-Related Air Pollution Models, or Gas Station Residential Proximity, 1999–2014

Group and Subgroup	No. of Studies	Fixed Effects		Shore-Adjusted ^a	Random Effects ^a		Heterogeneity		
		sRR	95% CI	95% CI	sRR	95% CI	χ^2	P Value	
Outcome									
All studies combined	12	1.48	1.23, 1.78	1.10, 1.99	1.80	1.29, 2.52	27.49	<0.01	
AML only	4	2.07	1.34, 3.20	NA	NA	NA	0.40	0.94	
ALL only	7	1.49	1.20, 1.84	1.07, 2.08	1.79	1.21, 2.65	14.96	0.02	
Exposure metric									
Traffic density	11	0.97	0.88, 1.07	0.82, 1.15	1.25	0.96, 1.62	29.92	<0.01	
Traffic density (excluding Heck et al. (85)) ^b	10	1.17	0.99, 1.40	0.89, 1.55	1.38	0.96, 1.62	23.26	0.01	
Traffic pollution models (e.g., CALINE4) ^c	7	1.70	1.25, 2.30	1.16, 2.49	1.77	1.17, 2.68	9.38	0.15	
Adjustments ^d									
Socioeconomic status	9	1.49	1.19, 1.86	1.07, 2.08	1.77	1.20, 2.62	18.05	0.02	
Area									
Europe	8	1.35	1.09, 1.68	0.95, 1.93	1.65	1.09, 2.52	19.51	0.01	
United States	4	2.02	1.35, 3.00	1.20, 3.38	2.13	1.25, 3.64	5.02	0.17	
Time of exposure									
Birth or gestation only	4	0.92	0.75, 1.14	0.73, 1.17	0.94	0.73, 1.22	3.93	0.27	
Postnatal (any)	13	1.36	1.15, 1.60	1.05, 1.76	1.59	1.19, 2.13	29.19	<0.01	
At diagnosis only	9	1.46	1.19, 1.80	1.03, 2.08	1.94	1.30, 2.91	22.91	<0.01	
Residential proximity to gas stations	3	1.59	0.95, 2.67	0.70, 3.62	1.88	0.78, 4.55	5.08	0.08	

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CALINE4, California LINE Source Dispersion Model, version 4; CI, confidence interval; NA, not applicable; sRR, summary relative risk.

^a The Shore-adjusted and random-effects models were used if the χ^2 statistic was greater than the degrees of freedom (the number of studies minus 1).

^b Heck et al. (85) contributed 69% of the total weight in the traffic-density analysis.

^c Includes studies with more detailed modeling of traffic pollution or ambient air levels of benzene.

^d Includes adjusted results and results from studies in which the authors stated that the adjustments had little or no impact on results. Few of these studies were adjusted for tobacco smoking.

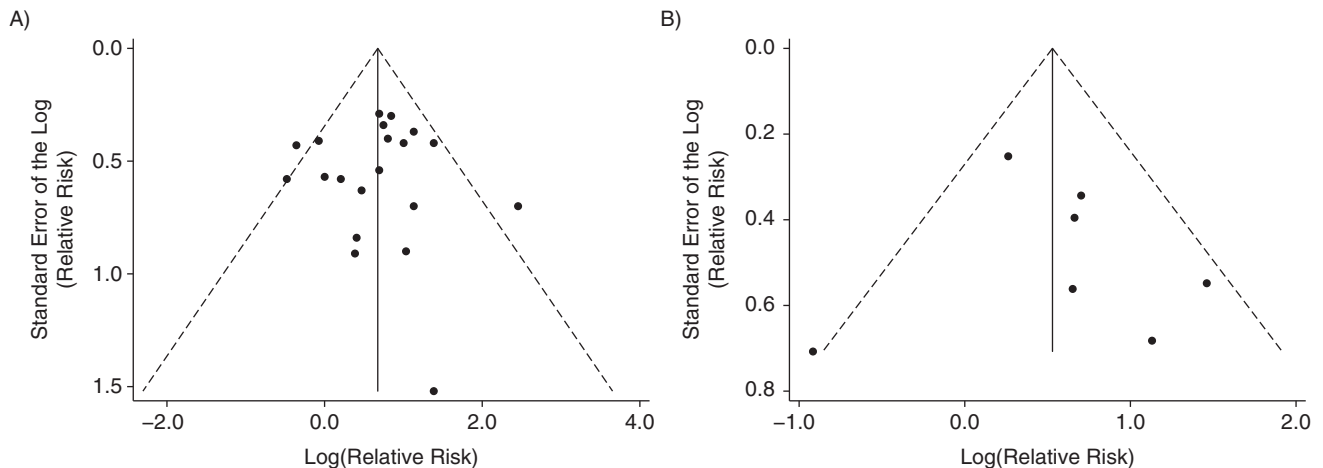


Figure 2. Funnel plots of studies included in the meta-analyses of benzene and childhood leukemia, 1987–2014. A) Studies of occupational or household product use; and B) studies of more detailed traffic-related pollution models. Funnel plots are graphical representations of the logarithm of each study's relative risk estimate versus the standard error of the logarithm of each study's relative risk estimate. The dotted lines are pseudo 95% confidence intervals.

there are a variety of reasons that children or fetuses might be particularly susceptible to these exposures, including their undeveloped detoxification or excretion pathways or their markedly higher intakes or inhalation rates per body weight compared with adults (65). These factors and others could explain why children might be affected at lower benzene levels than adults.

Mechanistic studies further support our findings. The higher summary relative risk for maternal versus paternal exposure and the higher summary relative risk for gestational exposure are consistent with a greater association in the fetal period. For childhood ALL and AML, it has been shown that the disease is usually initiated in utero: The leukemic translocations and other genetic changes have been shown to be present in blood spots collected at birth (66–68). Because the genotoxic action of benzene metabolites induces multiple genetic abnormalities, it seems probable that benzene exposure could initiate both AML and ALL in utero by causing the chromosomal rearrangements and mutations that are on the causal pathway to these malignancies in fetal hematopoietic stem cells. This hypothesis is supported by human and animal studies that show the following: 1) benzene and its metabolites cross the placenta into the fetuses of exposed humans and mice (69–71); 2) low levels of benzene exposure alter the growth of myeloid and erythroid progenitor cells in fetal tissue in mice (70) and decrease CD4 and CD8 T-cell counts in neonatal beef calves (72); 3) in utero benzene exposure increases the frequency of micronuclei and DNA recombination events in hematopoietic tissue of fetal and postnatal mice (70, 71, 73, 74); and 4) benzene exposure causes oxidative stress and disrupts hematopoietic cell signaling pathways in the fetal blood progenitor cells of exposed mice (70, 75). Taken together, these data strongly suggest that benzene can initiate childhood leukemia in utero and that early life exposures might cause the leukemic clone to proliferate further.

Most of the studies used here were adjusted or matched for age and sex. The higher summary relative risks in our analyses of studies that included adjustment for smoking or socioeconomic status suggest that these factors did not cause the positive associations seen in our meta-analysis. Overadjustment related to socioeconomic status is possible, although the summary relative risk changed minimally when only studies adjusted for socioeconomic status were examined. Other factors, such as radiation, genetics, and viral infections, have also been linked to childhood leukemia (15). However, we found no clear evidence that these factors were sufficiently prevalent or strongly related to benzene exposure in the studies we reviewed to have caused major confounding. Benzene exposure might be highly correlated with other toxic agents, including other solvents or common air pollutants (63). For this reason, our findings might not represent the effects of benzene and could be due to these other factors. For example, air pollution can contain a number of carcinogenic agents, including diesel exhaust and polycyclic aromatic hydrocarbons. Less research has been done on these other agents than on benzene, so the possibility that some other agent is responsible for some or all of the associations we identified cannot be ruled out. However, benzene seems the most plausible agent because it, and not these other agents, has been clearly linked to leukemia in exposed adults (1). The strong

links between benzene and leukemia in adults, the data on biologic plausibility presented in previous studies, and the fact that we identified elevated summary relative risks for a variety of different potential benzene exposure metrics combine to support the hypothesis that benzene is responsible for the associations identified here.

None of the studies included in this meta-analysis involved personal prospective measurements of benzene exposure. Most of the occupational studies used self-reports of job histories and expert evaluations or self-reports of specific exposures. Self-reported job histories have been shown to correlate reasonably well with company, pension, or union records (76). Results of some studies have also shown fairly good agreement between self-reported exposures and industrial hygiene measurements, employer reports, and expert evaluations (77, 78), although results varied widely across studies (76). For traffic-related exposure studies, Raaschou-Nielsen et al. (79) reported a correlation of 0.55 for the association between traffic density and weekly average benzene air concentrations, which rose to 0.68 when more complex models that included street configuration and meteorological data were used. In other studies, investigators have reported somewhat similar correlations for yearly mean and yearly median benzene concentrations (57, 80). It is important to note that because in all of the included studies exposure was assessed similarly in cases and controls, most exposure misclassification likely biased results towards finding no association. Our use of studies that included different exposure metrics might have caused some bias. However, some metrics are likely to be better indicators of true exposure than others, and including less accurate metrics would most likely bias results towards the null. That we found a lower summary relative risk in studies in which all solvents were assessed together than in those in which only benzene was assessed and that we found a lower summary relative risk in studies of simple traffic density than in those that included more detailed metrics of traffic pollution might be evidence of this bias. This might also explain why we saw a higher summary relative risk for gestational exposures in our analysis of studies of occupational and household product exposure (sRR = 1.91) than in our analysis of exposures at birth in the traffic studies (sRR = 0.92). Because most studies of traffic exposure at birth were based on the residence listed on the birth certificate and studies have shown that many women change residences during pregnancy (9%–32%) (81), exposure misclassification in these studies might have caused some bias towards the null.

There was some suggestion of publication bias in the funnel plot of studies that included more detailed assessments of traffic-related air pollution (Figure 2B). However, closer inspection suggests that this might be due to the largest study (Badaloni et al. (53)) rather than publication bias, which typically affects smaller studies. In that study, the authors reported an odds ratio of 1.30 (95% CI: 0.97, 2.12) and used land-use regression models to estimate nitrogen dioxide exposure. Although residences before diagnosis were assessed, data from the traffic pollution models were obtained 4–7 years after case diagnosis (53). Although publication bias cannot be entirely excluded, the fact that this large study affected the interpretation of the funnel plot highlights the possibility that the funnel plot asymmetry might be due to other factors.

In several of the studies used in the present meta-analysis, benzene exposure was assessed based on self-reports, and thus the studies were susceptible to recall bias. This bias could cause false associations if the parents of case children were more likely to recall past exposures than were parents of controls. Our finding of an elevated summary relative risk for studies of benzene but not for studies of all solvents (Table 3) provides some evidence that this was generally not the case. Using retrospectively collected information about occupations and self-reported exposure to solvents and other agents, the authors of a large case-control study of parental occupation and childhood cancer found some evidence of this type of bias. However, the results suggested that its magnitude was small (i.e., causing relative risks between 1.1 and 1.2), and the authors concluded that “. . . it is unlikely that recall bias can entirely explain associations in the order of 1.5–2.0” (82, p. 715). In another comprehensive review of recall bias, the authors also concluded that this issue was unlikely to cause major bias in occupational studies (76).

Our results generally agree with those from several previous meta-analyses (29, 83, 84). For example, in a meta-analysis of 8 studies of traffic density published up to July 2011, Boothe et al. (83) reported a summary odds ratio for leukemia of 1.53 (95% CI: 1.12, 2.10) for postnatal exposures. This is similar to the summary relative risk of 1.46 (95% CI: 1.03, 2.08) that we reported for a collection of studies that included studies of traffic density, studies of more complex traffic pollution models, 4 studies published since 2011, and findings by leukemia subtype. In a meta-analysis, Zhou et al. (84) reported a pooled odds ratio for ALL and solvents of 1.25 (95% CI: 1.09, 1.45), but they did not evaluate AML or specific data on benzene.

In conclusion, although confounding, recall bias, and publication bias are possible, the overall findings of the present meta-analysis provide evidence that exposure to benzene is associated with childhood leukemia. Both laboratory research and epidemiologic findings in adults support the associations found here. Our findings suggest that future studies on this issue should examine specific subtypes of leukemia, include maternal exposures during gestation, and involve exposure assessment methods that focus more directly on benzene. Occupational and environmental exposure to benzene is widespread, and leukemia is the most common type of cancer in children. Our findings could help guide future research and policies that could eventually help reduce the worldwide burden of this cancer.

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F.M.C.-W. sits on the advisory board of the Filipino American Coalition for Environmental Solidarity. M.T.S. has received consulting and expert testimony fees from law firms representing both plaintiffs and defendants in cases involving exposure to benzene. Other authors have no potential conflicts of interest.

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APPENDIX

Inclusion and Exclusion Criteria for Studies in the Meta-Analysis of Benzene and Childhood Cancer, 1987–2014

Inclusion Criteria

- Was epidemiologic in nature and assessed childhood leukemia (younger than 20 years of age) and benzene exposure

- Assessed occupational or home benzene exposure or a surrogate of benzene exposure, including aromatic hydrocarbon use, solvent use, petroleum product use, residential proximity to gas stations or automotive repair facilities, work in an automotive repair shop or gas station, residential traffic density, and modeled residential ambient traffic pollution or air benzene concentrations
- Was published in a peer-reviewed journal
- Provided a relative risk estimate and variance estimate for leukemia incidence or the data to estimate them
- For studies with overlapping populations, 1 result was selected based on the following factors in the following order: most appropriate exposure metric, leukemia type, higher exposure category, type of parental exposure, exposure period, largest number of cases, or statistical adjustment (details in Web Figures 1 and 2 and in the Methods section).

Exclusion Criteria

- Assessed exposure only after a cancer diagnosis
- Did not report relative risk or variance estimates or the data to calculate them
- Reported on only leukemia mortality
- Included smoking as the sole benzene source
- Was published only in a government or industry report or as an abstract
- Was conducted in populations with another potential major risk factor for leukemia (e.g., Down syndrome or residence near power lines)
- Involved broad occupational categories (e.g., drivers or painters) or unclear exposure situations (e.g., residential proximity to a petrochemical plant or hazardous air pollution scores)