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ARTICLE

Myelodysplastic Syndrome and Benzene Exposure Among Petroleum Workers: An International Pooled Analysis

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Background Benzene at high concentrations is known to cause acute myeloid leukemia (AML), but its relationship with other lymphohematopoietic (LH) cancers remains uncertain, particularly at low concentrations. In this pooled analysis, we examined the risk of five LH cancers relative to lower levels of benzene exposure in petroleum workers.

Methods We updated three nested case–control studies from Australia, Canada, and the United Kingdom with new incident LH cancers among petroleum distribution workers through December 31, 2006, and pooled 370 potential case subjects and 1587 matched LH cancer-free control subjects. Quantitative benzene exposure in parts per million (ppm) was blindly reconstructed using historical monitoring data, and exposure certainty was scored as high, medium, or low. Two hematopathologists assigned diagnoses and scored the certainty of diagnosis as high, medium, or low. Dose–response relationships were examined for five LH cancers, including the three most common leukemia cell-types (AML, chronic myeloid leukemia [CML], and chronic lymphoid leukemia [CLL]) and two myeloid tumors (myelodysplastic syndrome [MDS] and myeloproliferative disease [MPD]). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using conditional logistic regression, controlling for age, sex, and time period.

Results Cumulative benzene exposure showed a monotonic dose–response relationship with MDS (highest vs lowest tertile, >2.93 vs ≤0.348 ppm-years, OR = 4.33, 95% CI = 1.31 to 14.3). For peak benezene exposures (>3 ppm), the risk of MDS was increased in high and medium certainty diagnoses (peak exposure vs no peak exposure, OR = 6.32, 95% CI = 1.32 to 30.2) and in workers having the highest exposure certainty (peak exposure vs no peak exposure, OR = 5.74, 95% CI = 1.05 to 31.2). There was little evidence of dose–response relationships for AML, CLL, CML, or MPD.

Conclusions Relatively low-level exposure to benzene experienced by petroleum distribution workers was associated with an increased risk of MDS, but not AML, suggesting that MDS may be the more relevant health risk for lower exposures.

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Benzene is a well-known hematotoxin and leukemogen at a relatively high level of exposure (1–3). In 2009, the International Agency for Research on Cancer (IARC) reconfirmed that benzene causes the acute myeloid leukemia (AML) subtype in humans and also noted that benzene is likely to be related to other leukemia subtypes and lymphoid neoplasms (4). However, recent meta-analyses differ in their interpretation of whether previous literature suggests a consistent relationship between benzene and lymphoid neoplasms (5–8). A recent review using meta-regression to examine dose–response relationships suggests that benzene exposure less than 50 ppm-years results in a statistically significant elevated risk of all leukemias in aggregate (9). But few quantitative studies have examined risks between specific leukemia subtypes and exposure to lower concentrations of benzene (10). There is also sparse literature on specific myeloid tumors, such as myeloproliferative disorders (MPD) and myelodysplastic syndrome (MDS), which can precede and evolve into AML. Indeed, IARC (4) did not mention these myeloid tumors in their recent evaluation of benzene carcinogenicity.

Three nested case–control studies based on cohorts of petroleum distribution workers in Canada (11) and the United Kingdom (12), and based on petroleum distribution, refining, and upstream workers in Australia (13), are among the few studies that have examined specific subtypes of lymphohematopoietic (LH) cancer and benzene exposure. The Canadian study did not examine leukemia subtypes (at that time) and did not find consistent dose–response relationships for all leukemias, nor lymphoid tumors (11). The UK study reported a dose–response relationship for AML for categorical (but not continuous) exposure metrics (12). No other leukemia cell types showed suggestive relationships with benzene

exposure. The Australian study (13) reported a strong dose–response relationship for AML and a weaker, suggestive relationship for chronic lymphatic leukemia (CLL). No relationships were seen for other lymphoid tumors nor chronic myeloid leukemia (CML). All three studies were designed similarly and estimated benzene exposure using similar methods (14).

In this study, we updated each of the nested case–control studies (11–13) and pooled the resulting data in order to assess the risk of five specific LH subtypes—the three most common leukemia subtypes (AML, CML, and CLL) and two myeloid neoplasms (MDS and MPD)—relative to benzene exposure.

Methods

Study Population and Study Design

Three cohort studies that were the basis for each of the original nested case–control studies evaluated the following: mortality in the Canadian petroleum distribution workers from January 1, 1964, through December 31, 1983 (15); mortality and cancer incidence in the UK petroleum distribution workers from January 1, 1950, through December 31, 1989 (16); and mortality and cancer incidence in the Australian petroleum distribution, refining, and upstream workers from January 1, 1981, through December 31, 1996 (17). The Canadian and UK studies were both retrospective studies with a 1-year employment criterion for inclusion, and the Australian study was prospective with a 5-year employment criterion for inclusion. These studies were approved by ethics review boards at Statistics Canada (Canadian), the Office of National Statistics (UK), and the University of Adelaide (Australian).

The nested case–control studies were subsequently performed with the aim of estimating benzene exposure for specific LH cancer case subjects and matched control subjects from the same cohort (11–13). The Canadian study (11) was based on 31 case subjects with LH cancers, including 16 case subjects with leukemia from January 1, 1964, through December 31, 1983, and the UK study (12) included 90 case subjects with leukemia from January 1, 1950, through December 31, 1992 (other LH cancers were not studied in the UK population). Both studies matched four control subjects per case subject on age and sex and required control subjects to be LH cancer–free at the time of diagnosis in case subjects (ie, incidence density–based sampling method was used). The Australian study (13) was based on 79 case subjects with LH cancers, including 33 case subjects with leukemia from January 1, 1981, through December 31, 1999, and matched five control subjects per case subject on age and sex; incidence density–based sampling method was used to select the control subjects. The Canadian, UK, and Australian nested case–control studies were approved by ethics review boards at Statistics Canada, the Office of National Statistics, and Monash University, respectively.

We updated each nested case–control study to include new case subjects with LH cancers occurring through the most recent follow-up dates available (Canada: December, 1994; United Kingdom: December, 2005; Australia: December, 2006) (Figure 1) using the national mortality and cancer incidence registries in Canada, the United Kingdom, and Australia. Additionally, for the Australian study, self-reported LH cancers confirmed by medical documentation were included (n = 3 case subjects). All case subjects were male because of the paucity of females in the parent cohorts. For each new incident cancer, either five age-matched (Australian study) or four age- and company-matched (Canadian and UK studies) control subjects were selected from each cohort, consistent with each original study. Control subjects were selected with replacement from employees in the cohorts using incidence density–based sampling. Matched control subjects were free of LH cancer when the corresponding case subject was diagnosed. The pooled population included 370 case subjects and 1587 control subjects (Figure 1). Based upon cancer counts, biologic plausibility, and previous findings, five LH subtypes (n = 227 case subjects) were chosen for analyses reported herein: AML (n = 60 case subjects), CLL (n = 80 case subjects), CML (n = 28 case subjects), MDS (n = 29 case subjects), and MPD (n = 30 case subjects). The remaining 143 case subjects with other diagnoses included too few case subjects diagnosed with mixed myelodysplastic and myeloproliferative disease (including chronic myelomonocytic leukemia), acute leukemias of ambiguous lineage, acute lymphoid leukemia, and unspecified leukmias to be included in the statistical analysis, as well as case subjects with non-Hodgkin lymphoma and multiple myeloma, which were not included in the original UK study.

Consent and Approval

Ethical approval for the combined study and recruitment of new subjects was obtained from the relevant ethics committees. The study was approved by the following committees: Multicentre Research Ethics Committee (MREC) (United Kingdom), Office of National Statistics (United Kingdom), Monash University Human Research Ethics Committee (Australia), Australian Health and Welfare (AIHW) committee (Australia), University of Pittsburgh Institutional Review Board (United States), ExxonMobil Health Research Ethics Committee (United States), University of Saskatchewan Biomedical Research Ethics Board (Canada), and Veritas IRB (Canada). Cancer registry ethics committees within Australian states and territories and Canadian provinces also approved the study.

Diagnostic Classification

All available information for each case subject, including hospital records, histopathology reports, cancer registry data, physician notes and/or correspondence, and mortality registry data (including death certificates), was assembled, inspected for the first occurrence of a relevant diagnosis, and classified by two hematopathologists (including Dr Richard D. Irons), blinded to the exposure assessment. Documented secondary or treatment-related cancers were excluded (n = 3 case subjects). Of the 200 original case subjects (Figure 1), 18 were reclassified for this analysis with either a more specific (n = 7 case subjects) or a different (n = 11 case subjects) diagnosis. Eight of the latter 11 case subjects were reclassified from leukemia to a myeloid (MDS or MPD) disorder.

The pathologists scored the certainty (high, medium, or low) of the diagnosis, driven by the specificity of diagnostic terms in source records, documented diagnostic methods, the amount and type of source documentation, and agreement between source records. In general, complete specification of an LH cell type by appropriate diagnostic terms resulted in a medium score. If there

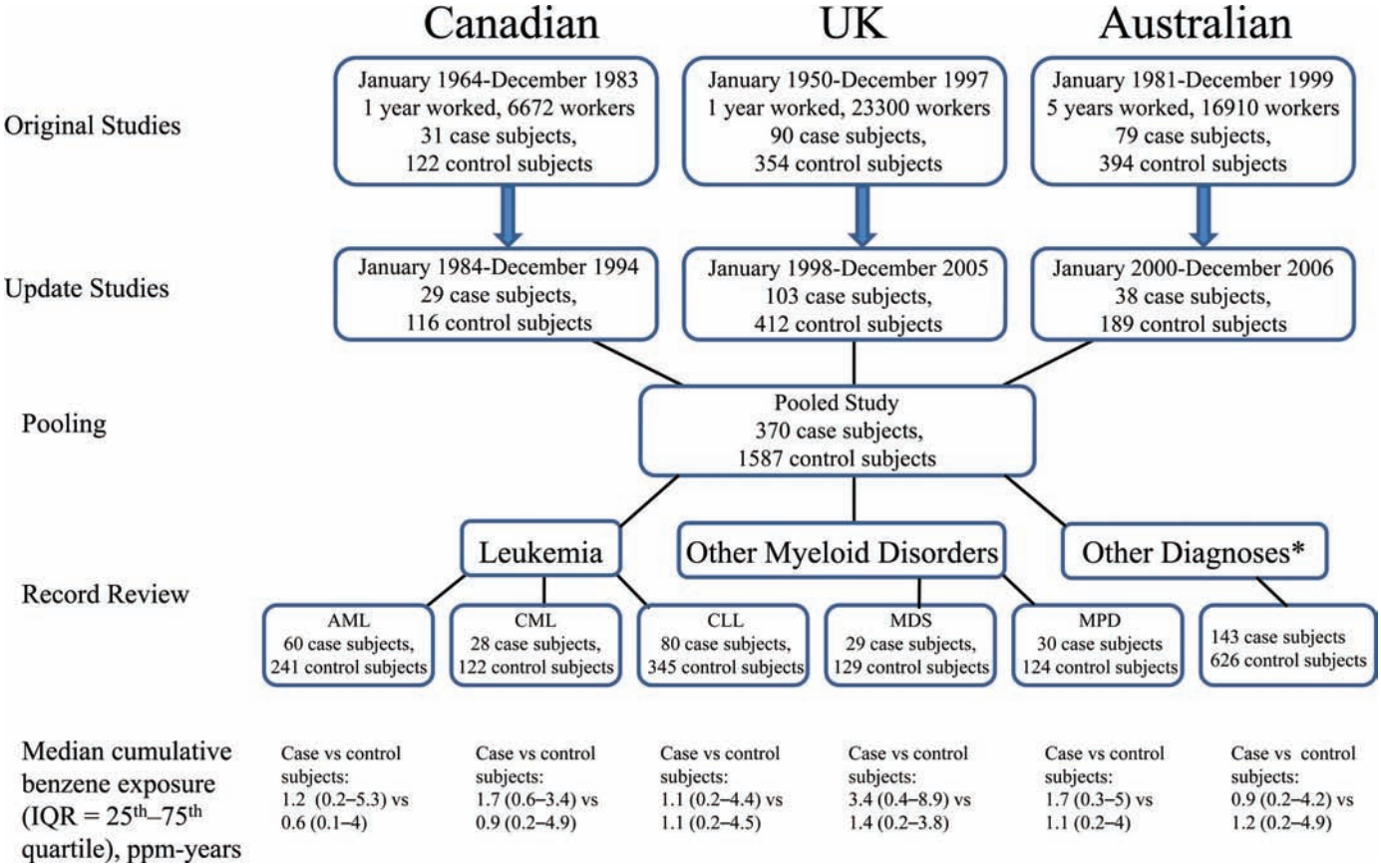


Figure 1. Process for pooling and updating three nested case–control studies in petroleum workers and resulting median cumulative exposure estimates for five lymphohematopoietic cancer subtypes. *These include diagnoses with too few case subjects for statistical analysis, plus non-Hodgkin lymphoma and multiple myeloma. AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; CLL = chronic lymphoid leukemia; CML = chronic myeloid leukemia; MPD = myeloproliferative disease; IQR = interquartile range.

was also more specific cytogenetic, immunophenotypic, or molecular information corroborating the specific diagnostic terms (eg, presence of the 9q22 translocation in CML), a high score was assigned. Disagreement between source records or the presence of ambiguous or nonspecific terms resulted in low certainty scores. Initially, the pathologists classified cancers according to both the International Classification of Diseases (ICD) and World Health Organization (WHO) (18) schemes, but because the results were similar, we report on the more recent WHO scheme.

Exposure Assessment

The three study populations were employed in the petroleum distribution sector, involving fuel transfer and storage in terminals, airports, product pipelines, and marine facilities. The Australian population additionally included refinery and upstream sectors. There were several diverse jobs present among the sectors, including tanker drivers, terminal operators, craft workers, drum fillers, mechanics, lab workers, gaugers, refuellers, fitters, and white collar workers. Benzene exposure was assessed by investigators who were blind to case–control status. Work histories consisting of job titles, locations, and effective dates were assembled from company records in the Canadian and UK studies for the entire follow-up period. For the Australian study, job history data was collected by trained interviewers for the entire cohort. These interviews were conducted in 1981–1983, 1986–1987, 1991–1993, and 1996–2000. The interview data was validated where possible against company records (10).

To facilitate the assignment of monitoring data to specific segments of a subject's work history, information was assembled on each study facility that included: 1) site technology and deployment dates, 2) fuel types handled, 3) gasoline source, 4) benzene content, and 5) engineering controls to reduce exposure. For each job or task, the average benzene exposure (base estimate [BE] in parts per million [ppm]) was derived from more than 5800 measurements collected at study facilities for specific exposed jobs and at both study and similar industrial facilities for jobs only exposed to background concentrations. Estimates of exposure intensity (workplace exposure estimates [WEs]) were calculated for work history entries by choosing the analogous BE or adjusting a BE for facility- or era-specific differences, including fuel transfer technology, benzene product content, and working environment variables (eg, temperature). Exposure assessment methodology has been detailed previously (19–21).

Six exposure metrics were derived to capture different aspects of benzene exposure: 1) cumulative exposure (ppm-years); 2) duration of employment (years); 3) average exposure intensity (ppm); 4) maximum exposure intensity (ppm) (ie, the highest job-specific full-shift WE); 5) peak exposure (at least 1-year employment in

jobs likely experiencing >3 ppm exposure for 15–60 minutes at least weekly); and 6) dermal exposure (the highest job-specific relative probability of skin contact for at least a year). Metrics were calculated over the entire work history as well as a 2–15-year exposure window for myeloid tumors, because recent exposures have been reported as more important in benzene-induced AML (22). Exposure estimates among the three studies were compared and refined to improve interstudy consistency (23).

A job exposure certainty score (high = 3, medium = 2, or low = 1) was allocated to each WE based upon: 1) the extent to which specific job duties were known, 2) knowledge of facility characteristics and technology, 3) knowledge of specific products handled, and 4) BE robustness for that job. The score was largely determined by the degree in which the first criterion was met. When all four criteria were met, a score of 3 was assigned. If one of the last three criteria were lacking, but job duties were reasonably certain, a score of 2 was usually assigned. If more than one of the last three criteria were lacking or job duties were not known with certainty, a score of 1 was assigned. Scores of 1 were more likely to be assigned to jobs held before 1960. An overall career exposure certainty score was calculated by weighting job-specific WEs by the number of years spent at each level of certainty.

Smoking data were collected from interview and workplace records, although this information was missing for 936 of the 1957 subjects (49%), mainly from the UK study. Thus, we performed limited analyses to control for the effect of smoking.

Statistical Methods

Conditional logistic regression was performed to assess the relationship between LH cancers relative to benzene exposure. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated relative to a background benzene concentration. Concentrations greater than the background level were categorized into tertiles, with cut-points based upon exposure distributions among control subjects. Background categories were not utilized for metrics that are not based on concentrations (eg, cumulative exposure, duration of exposure). For these metrics, the first teritile served as the baseline category. Global likelihood ratio χ^2 tests that assessed whether all ORs are consistent with a value of 1.0 (P_{global}) or whether ORs were consistent with a linear trend (using consecutive integer scores for P_{trend}) used one degree of freedom for ordinal exposure metrics.

We also used conditional logistic regression models with penalized regression smoothing splines (P-splines) to examine dose–response relationships. Models were fitted via the "coxph" function in R (24) as well as S-plus (25) software packages using matched risk sets (ie, matched case and control subjects) as strata. Degrees of freedom were determined by statistical fit and the biologic rationale of the dose–response relationship, and P_{spline} values (testing whether there was any dose–response relationship) from likelihood ratio tests were calculated. In another set of P-spline analyses, 0.001 was added to the exposure values and were $\log_2$-transformed to limit undue influence of extreme observations.

Subgroup analyses were conducted specific to study, facility type, and job. Heterogeneity of results by study was evaluated by assessing interaction terms (viz, study × exposure metric) using χ^2 tests ($P_{homogeneity}$). We focused on terminal workers and tanker drivers, as they are the groups most likely to be exposed to higher benzene concentrations. Sensitivity analyses were performed for diagnostic certainty (using only high and medium certain cancers) and exposure certainty (using only subjects with medium or high certainty as a weighted career average score) to mitigate possible effects of disease and exposure misclassification.

All statistical tests were two-sided, and *P*-values were considered statistically significant if they were .05 or less. Statistical analyses were done using SAS, version 9.2 (26) (SAS, Cary, NC).

Results

The number of case subjects and mean cumulative benzene exposures for the five LH subtypes and matched control subjects are shown in Figure 1. Benzene exposure was relatively low, with average cumulative exposure below 10 ppm-years derived from mean exposure intensities of 0.2–0.3 ppm and average durations of exposure close to 20 years. Median cumulative exposure was higher in MDS case subjects vs control subjects (median = 3.4 [interquartile range (IQR) = 0.4 to 8.9] ppm-years vs 1.4 [IQR = 0.2 to 3.8] ppm-years), but the same in CLL case subjects vs control subjects (median = 1.1 [IQR = 0.2 to 4.4] ppm-years vs 1.1 [IQR = 0.2 to 4.5] ppm-years). Average exposure certainty scores were the same in all case subjects combined and all control subjects combined (score = 2.2), but differed by study (Australian, score = 2.9; Canadian, score = 2.7; UK, score = 1.5). Approximately 74% of case subjects had a medium or high diagnostic certainty score, with CML and CLL outcomes having greater certainty than MPD and MDS (data not shown).

We analyzed LH subtype risks relative to different benzene exposure metrics by tertiles of exposure (Figure 2). The association of cumulative exposure with LH subtype increased monotonically for AML (0.348–2.93 vs ≤0.348 ppm-years [referent], OR = 1.04 [95% CI = 0.50 to 2.19]; ≥2.93 vs ≤0.348 ppm-years [referent], OR = 1.39 [95% CI = 0.68 to 2.85]; P_{global} = .62), MDS (0.348–2.93 vs ≤0.348 ppm-years [referent], OR = 1.73 [95% CI = 0.55 to 5.47]; ≥2.93 vs ≤0.348 ppm-years [referent], OR = 4.33 [95% CI = 1.31 to 14.3]; P_{global} =.03), and MPD (0.348–2.93 vs ≤0.348 ppm-years [referent], OR = 1.28 [95% CI = 0.47 to 3.48]; ≥2.93 vs ≤0.348 ppm-years [referent], OR = 1.79 [95% CI = 0.68 to 4.74]; P_{global} =.49) (Figure 2, A). The trend was statistically significant for MDS (P_{trend} = .01). Dose–response trends were weaker in tertile analyses of other exposure metrics (Figure 2, B–F), although MDS was the only outcome that showed consistent monotonic trends for all metrics (Figure 2, A–F). Peak exposures greater than 3 ppm showed an increased risk of MDS (ever peak exposure >3 ppm vs never peak exposure >3 ppm, OR = 2.48 [95% CI = 0.97 to 6.35]) (Figure 2, E) but were unremarkable for other LH cancer subtypes (Figure 2, E). When we restricted exposures to 2–15 years before diagnosis (recent exposures), the associations did not strengthen for AML, CML, and MDS (eg, third tertile cumulative exposure ≥2.93 ppm-years for all exposures vs recent exposures: for AML, OR = 1.39 [95% CI = 0.68 to 2.85] vs OR = 1.11 [95% CI = 0.37 to 3.34]; for CML, OR = 2.20 [95% CI = 0.63 to 7.68] vs OR = 1.70 [95% CI = 0.17 to 16.9]; and for MDS, OR = 4.33 [95% CI = 1.31 to 14.3] vs OR = 2.04 [95% CI = 0.40 to 10.3]). In contrast, recent exposures did strengthen the association between cumulative exposure and MPD (eg, third tertile cumulative exposure ≥2.93

ppm-years for all exposures vs recent exposures: OR = 1.79 [95% CI = 0.68 to 4.74] vs OR = 3.66 [95% CI = 0.81 to 16.6]), although dose–response relationships were generally not monotonic and results were less stable because of exclusion of a large fraction of the work history (data not shown).

The P-spline curves for the five LH subtypes showed monotonic dose–response relationships for MDS for all exposure metrics (Figure 3, A–D) and reached statistical significance for maximum exposure intensity (P_{spline} = .03) (Figure 3, C). No dose–response relationship was observed for CLL, except for a statistically significant association with duration of employment (P_{spline} = .03); the dose–response curve reached a plateau after 15 years (Figure 3, D). The dose–response curves for AML, CML, and MPD did not show a compelling relationship with benzene exposure (Figure 3, A–D), although the cumulative exposure metrics for AML and CML indicate a possible relationship (AML, P_{spline} = .14; CML, P_{spline} = .12) (Figure 3, A).

Because smoking has been associated with LH cancers, we attempted to adjust for its potential effect. For MDS, an ever or never smoker categorization was known for 15 of 29 MDS case subjects and 78 of 129 MDS control subjects. When P-spline analyses were analyzed with smoking as an additional independent variable, the dose–response relationship between benzene exposure and MDS was stronger in workers with known smoking histories compared with all workers (P_{spline} = .02 vs .07 for cumulative exposure; P_{spline} = .003 vs .07 for average exposure intensity; and P_{spline} = .004 vs .03 for maximum exposure intensity), suggesting that smoking is unlikely to be a confounder responsible for the association between MDS and benzene exposure.

We assessed dose–response relationships for peak exposure, dermal exposure, and for the highest cumulative exposure tertile for each of the three studies (Table 1). Patterns for average and maximum intensity of exposure and duration of exposure (data not shown) were similar to patterns for cumulative exposure. Dose–response relationships between studies were not statistically significantly heterogeneous for the six exposure metrics (eg, for MDS, $P_{homogeneity}$ = .18 for peak exposure, .16 for dermal exposure, .30 for cumulative exposure, .96 for maximum exposure

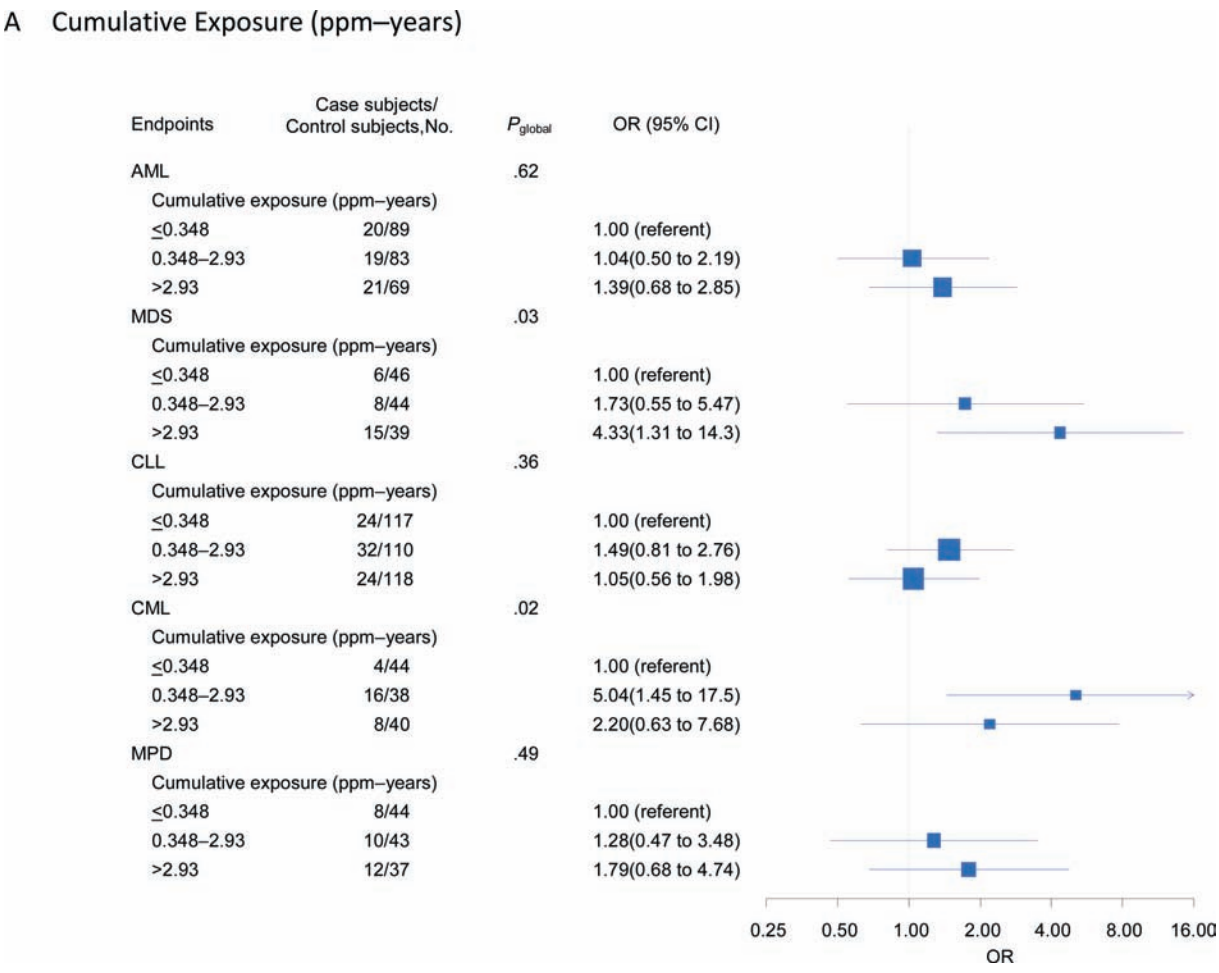
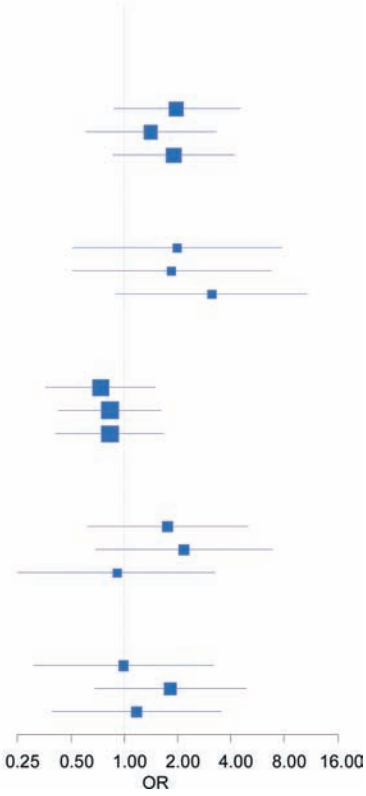


Figure 2. Funnel plots of dose–response relationships between five lymphohematopoietic (LH) cancer subtypes and six discrete benzene exposure metrics. Metrics were calculated over the entire work history as well as a 2–15-year exposure window for myeloid tumors AML, CML, MDS, and MPD. **A)** Association of cumulative exposure (ppm-years) with LH cancer subtype. **B)** Association of average exposure intensity (ppm) with LH cancer subtype. **C)** Association of maximum exposure intensity (ppm) with LH cancer subtype. **D)** Association of duration of employment (years) with LH cancer subtype. **E)** Association of peak exposure (at least weekly exposure to >3 ppm for 15–60 minutes) with LH cancer subtype. **F)** Association of dermal exposure (relative probability) with LH cancer subtype. AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; CLL = chronic lymphoid leukemia; CML = chronic myeloid leukemia; MPD = myeloproliferative disease.

B Average Exposure Intensity (ppm)

Endpoints	Case subjects/ Control subjects,No.	P_{global}	OR (95% CI)
AML		.30	
Average exposure intensity(ppm)			
≤0.016	16/90		1.00 (referent)
0.016–0.081	15/46		1.97(0.87 to 4.50)
0.081–0.259	13/55		1.41(0.61 to 3.30)
>0.259	16/50		1.90(0.86 to 4.18)
MDS		.33	
Average exposure intensity(ppm)			
≤0.016	7/46		1.00 (referent)
0.016–0.081	5/21		1.99(0.51 to 7.76)
0.081–0.259	7/34		1.85(0.51 to 6.75)
>0.259	10/28		3.12(0.90 to 10.8)
CLL		.85	
Average exposure intensity(ppm)			
≤0.016	31/114		1.00 (referent)
0.016–0.081	15/76		0.74(0.36 to 1.50)
0.081–0.259	19/86		0.83(0.42 to 1.62)
>0.259	15/69		0.83(0.41 to 1.67)
CML		.43	
Average exposure intensity(ppm)			
≤0.016	7/42		1.00 (referent)
0.016–0.081	9/30		1.75(0.62 to 4.98)
0.081–0.259	8/24		2.17(0.69 to 6.88)
>0.259	4/26		0.91(0.25 to 3.28)
MPD		.63	
Average exposure intensity(ppm)			
≤0.016	9/45		1.00 (referent)
0.016–0.081	5/26		0.99(0.31 to 3.18)
0.081–0.259	10/27		1.82(0.68 to 4.88)
>0.259	6/26		1.17(0.39 to 3.52)



C Maximum Exposure Intensity (ppm)

Endpoints	Case subjects/ Control subjects,No.	P_{global}	OR (95% CI)
AML		.63	
Maximum exposure intensity(ppm)			
≤0.016	17/87		1.00 (referent)
0.016–0.118	13/47		1.49(0.65 to 3.37)
0.118–0.413	14/55		1.35(0.59 to 3.07)
>0.413	16/52		1.65(0.75 to 3.63)
MDS		.43	
Maximum exposure intensity(ppm)			
≤0.016	7/42		1.00 (referent)
0.016–0.118	5/27		1.46(0.35 to 6.02)
0.118–0.413	8/35		1.82(0.51 to 6.52)
>0.413	9/25		2.81(0.79 to 10.1)
CLL		.37	
Maximum exposure intensity(ppm)			
≤0.016	30/106		1.00 (referent)
0.016–0.118	14/86		0.55(0.26 to 1.18)
0.118–0.413	21/78		0.97(0.36 to 1.87)
>0.413	15/75		0.72(0.36 to 1.45)
CML		.26	
Maximum exposure intensity(ppm)			
≤0.016	8/42		1.00 (referent)
0.016–0.118	6/26		1.25(0.40 to 3.95)
0.118–0.413	11/28		2.12(0.77 to 5.82)
>0.413	3/26		0.59(0.15 to 2.37)
MPD		.67	
Maximum exposure intensity(ppm)			
≤0.016	9/42		1.00 (referent)
0.016–0.118	6/24		1.25(0.40 to 3.87)
0.118–0.413	10/30		1.70(0.61 to 4.75)
>0.413	5/28		0.85(0.28 to 2.61)

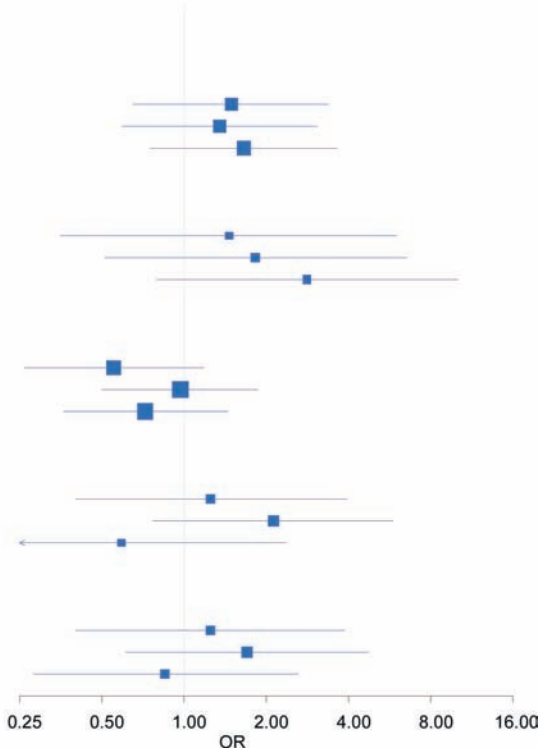
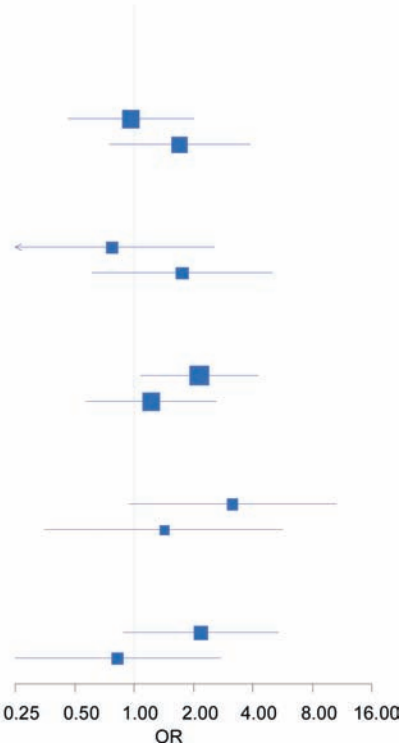


Figure 2. (continued)

D Duration of employment (years)

Endpoints	Case subjects/ Control subjects,No.	P_{global}	OR (95% CI)
AML		.33	
≤15.6	27/115		1.00 (referent)
15.6–28	16/77		0.96(0.46 to 2.01)
>28	17/49		1.70(0.75 to 3.87)
MDS		.25	
Duration of employment(years)			
≤15.6	7/35		1.00 (referent)
15.6–28	7/47		0.77(0.23 to 2.53)
>28	15/47		1.74(0.61 to 4.99)
CLL		.06	
Duration of employment(years)			
≤15.6	18/105		1.00 (referent)
15.6–28	36/115		2.14(1.08 to 4.24)
>28	26/125		1.22(0.57 to 2.60)
CML		.11	
Duration of employment(years)			
≤15.6	6/40		1.00 (referent)
15.6–28	14/38		3.13(0.93 to 10.6)
>28	8/44		1.42(0.35 to 5.67)
MPD		.09	
Duration of employment(years)			
≤15.6	9/50		1.00 (referent)
15.6–28	16/38		2.17(0.88 to 5.39)
>28	5/36		0.82(0.25 to 2.73)



E Peak exposure (> 3 ppm)

Endpoints	Case subjects/ Control subjects,No.	P_{global}	OR (95% CI)
AML		.19	
Peak exposure (> 3 ppm)			
None	25/124		1.00 (referent)
Yes	35/117		1.50(0.82 to 2.75)
MDS		.05	
Peak exposure (> 3 ppm)			
None	13/82		1.00 (referent)
Yes	16/47		2.48(0.97 to 6.35)
CLL		.14	
Peak exposure (> 3 ppm)			
None	50/187		1.00 (referent)
Yes	30/158		0.69(0.41 to 1.14)
CML		.11	
Peak exposure (> 3 ppm)			
None	17/63		1.00 (referent)
Yes	11/59		0.67(0.29 to 1.54)
MPD		.32	
Peak exposure (> 3 ppm)			
None	12/63		1.00 (referent)
Yes	18/61		1.47(0.68 to 3.19)

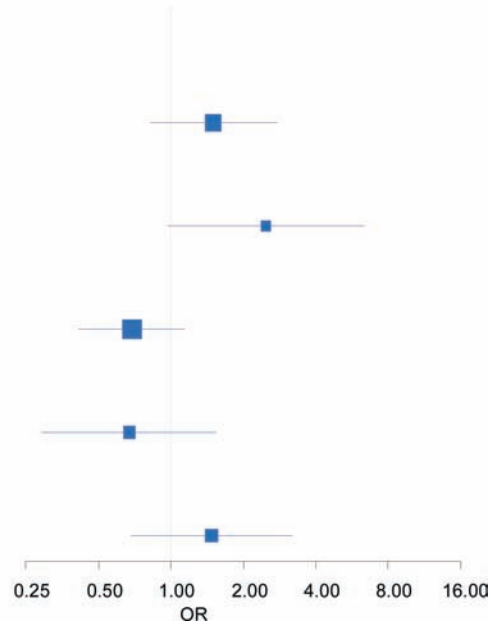


Figure 2. (continued)

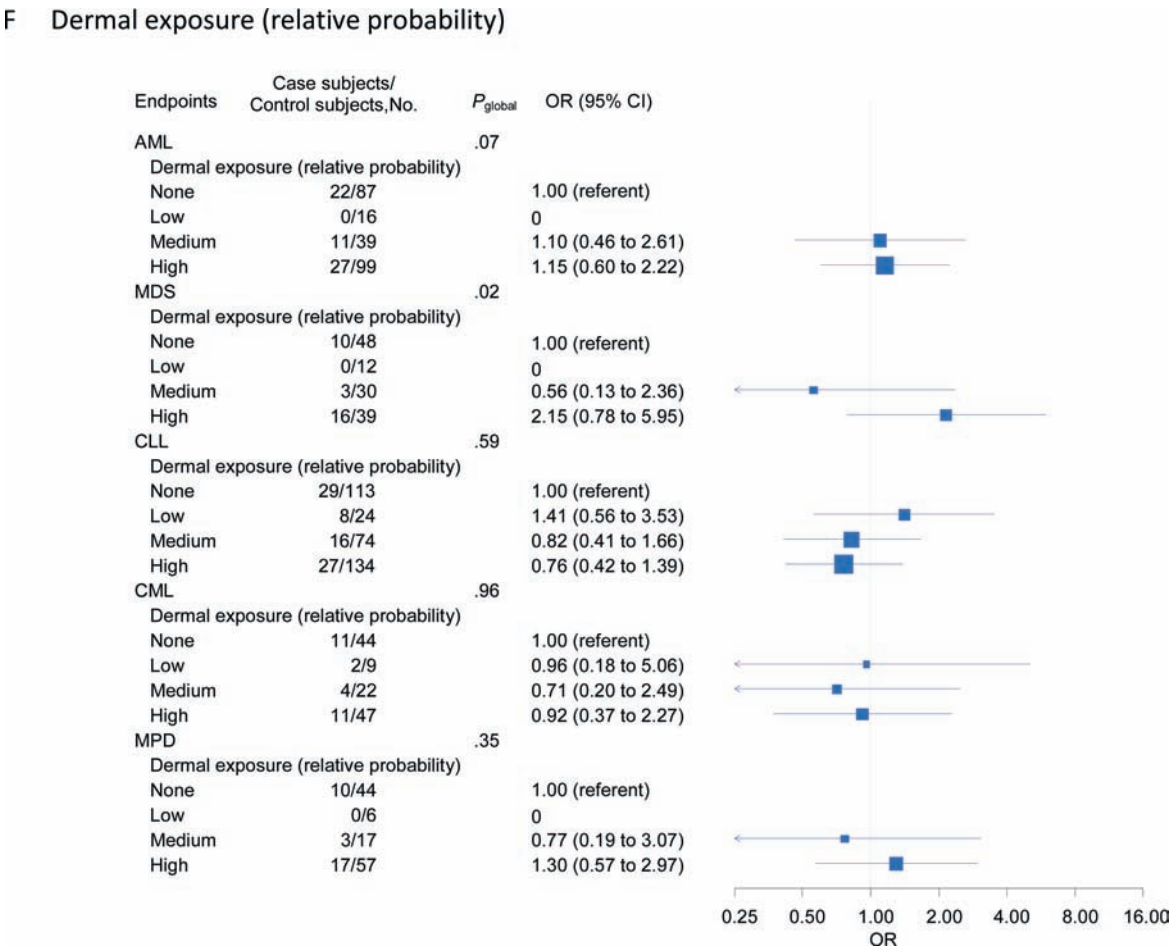


Figure 2. (continued)

intensity, .60 for average exposure intensity, and .92 for duration of exposure); thus data pooling was justified. However, some nonstatistically significant differences regarding dose–response relationships between studies (Table 1) were noted. Specifically, CLL was related to exposure more strongly in the Australian study (eg, third tertile cumulative exposure >2.93 vs ≤0.348 ppm-years [referent], OR = 5.2 [95% CI = 0.98 to 27.0]), and the relationship between peak exposure and MDS was less apparent in the UK study (ever peak exposure >3 ppm vs never peak exposure >3 ppm, OR = 0.80 [95% CI = 0.19 to 3.43]). However, MDS showed consistently increased associations for cumulative exposure in each study (third tertile cumulative exposure >2.93 vs ≤0.348 ppm-years [referent]: Australian study, OR = 3.6 [95% CI = 0.60 to 22]; Canadian study, OR = 3.0 [95% CI = 0.14 to 61]; UK study, OR = 3.4 [95% CI = 0.55 to 21]).

Facility and worker subgroup analyses indicated higher MDS risk at terminals (terminal facility type vs all other facility types, OR = 5.04 [95% CI 1.58 to 16.08]) and among tanker drivers employed for at least a year (ever tanker driver for 1 year vs never tanker driver for 1 year, OR = 2.16 [95% CI = 0.79 to 5.88]). There was also a higher risk of AML for tanker drivers (ever tanker driver for 1 year vs never tanker driver for 1 year, OR = 2.02 [95% CI = 1.08 to 3.78]), whereas refinery operators and craftsmen (primarily from the Australian study) showed a higher CLL risk (ever a refinery operator or craftsman for 1 year vs never a refinery operator or craftsman, OR = 2.26 [95% CI = 0.92 to 5.58]) (Table 2).

For AML, CML, CLL, and MPD, results for more certain case subjects (ie, medium and high diagnostic certainty) and exposures (ie, career weighted average exposure certainty score ≥2) were generally similar vs results for all workers but with wider confidence intervals (data not shown). However, the relationship between MDS and benzene exposure strengthened (ie, a steeper slope and lower *P*-value were obtained in the dose–reponse curve, despite being based upon only 51% of subjects) for all subjects vs subjects with more certain diagnoses: for cumulative exposure, P_{spline} = .07 vs P_{spline} = .02; for average exposure, P_{spline} = .07 vs P_{spline} = .03; and for maximum exposure, P_{spline} = .03 vs P_{spline} = .02) (Figure 4, A–C). Workers having more certain exposures, which accounted for 75% of subjects, showed a higher risk of MDS (ie, a steeper slope in the dose–response curve) for maximum exposure vs all workers, but this result was not statistically significant (P_{spline} = .063) (Figure 4, C), whereas other metrics (Figure 4, A, B, and D) showed a similar risk of MDS vs all workers.

When we examined sensitivity results for medium or high certainty diagnoses and jobs with weighted exposure certainty scores of 2 or more, worker subgroups showed some clear patterns despite being based on fewer study subjects. The risk of MDS was statistically significant among tanker drivers (ever a tanker driver

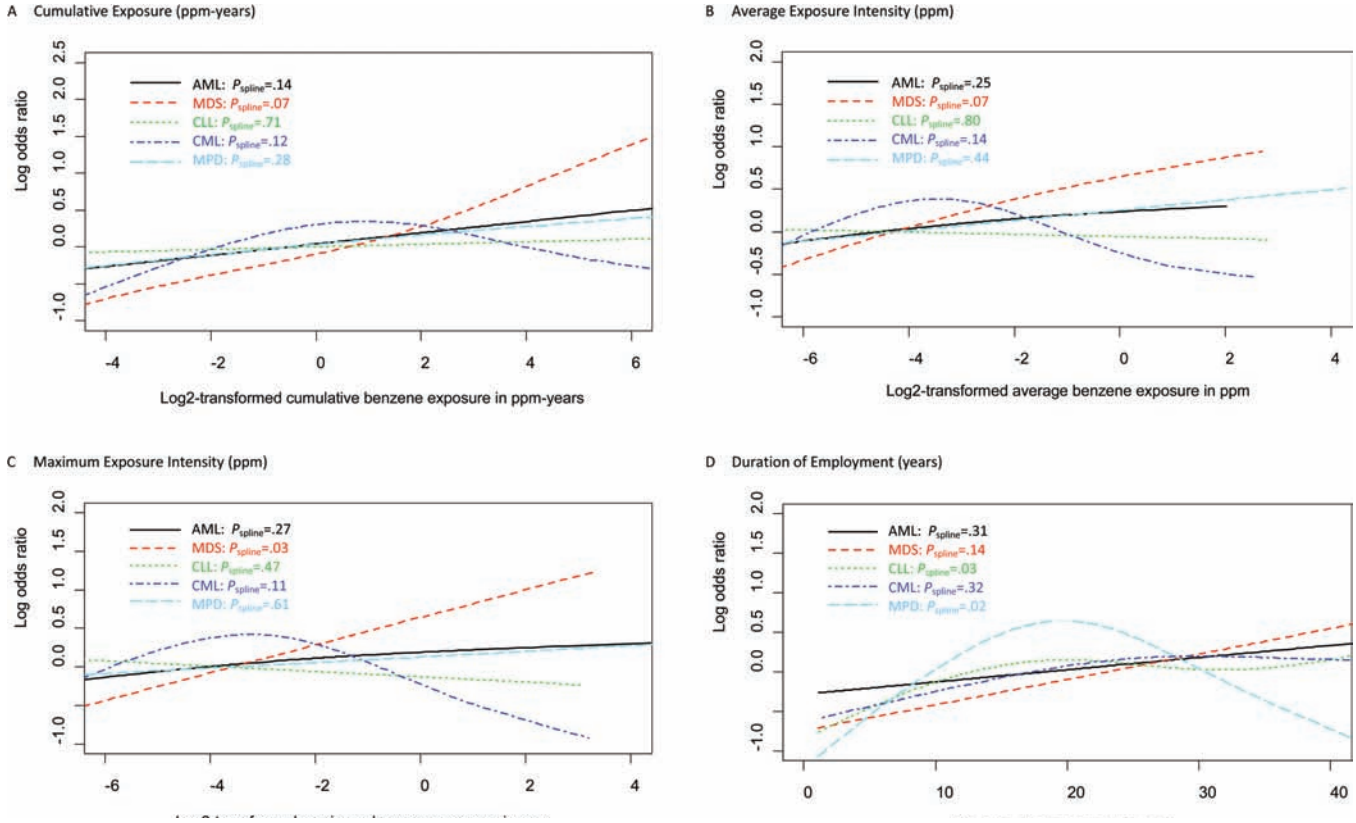


Figure 3. Penalized regression smoothing spline (P-spline) functions showing log odds ratio of risk of lymphohematopoietic (LH) cancer subtypes and specific benzene exposure metrics. We used conditional logistic regression models with P-splines to examine dose–response relationships. P_{spline} *P*-values (testing whether there was any dose–response relationship) were calculated using two-sided likelihood ratio tests. **A)** Association of cumulative exposure (ppm-years) with LH cancer subtype. **B)** Association of average exposure intensity (ppm) with LH cancer subtype. **C)** Association of maximum exposure intensity (ppm) with LH cancer subtype. **D)** Association of duration of employment (years) with LH cancer subtype.

Table 1. Associations between four LH cancer subtypes and specific benzene exposure metrics by study*

LH cancer subtype	Study	Benzene exposure metric, OR (95% CI)				
		Peak vs no peak exposure	High vs no dermal exposure	Cumulative exposure, third vs first tertile	Cumulative exposure, all tertiles	
					P_{global}†	P_{trend}‡
AML	Australian	2.28 (0.53 to 9.81)	0.92 (0.20 to 4.29)	4.13 (0.36 to 47.4)	.47	.25
	Canadian	0.64 (0.18 to 2.24)	0.79 (0.22 to 2.78)	0.38 (0.09 to 1.65)	.30	.17
	UK	1.84 (0.84 to 4.03)	1.48 (0.62 to 3.54)	1.99 (0.79 to 4.98)	.33	.14
MDS	Australian	4.66 (1.10 to 19.7)	3.45 (0.59 to 20.2)	3.64 (0.60 to 22.1)	.06	.06
	Canadian	5.17 (0.49 to 54.2)	5.17 (0.49 to 54.2)	2.95 (0.14 to 60.8)	.08	.21
	UK	0.80 (0.19 to 3.43)	1.04 (0.19 to 5.55)	3.38 (0.55 to 20.8)	.37	.18
CLL	Australian	0.65 (0.26 to 1.66)	1.33 (0.42 to 4.23)	5.15 (0.98 to 27.0)	.07	.24
	Canadian	0.63 (0.14 to 2.94)	0.65 (0.14 to 2.99)	0.52 (0.09 to 2.92)	.73	.47
	UK	0.71 (0.37 to 1.38)	0.62 (0.27 to 1.43)	0.65 (0.27 to 1.60)	.24	.40
CML	Australian	0.34 (0.07 to 1.67)	0.56 (0.12 to 2.57)	0.45 (0.04 to 5.19)	.03	.70
	Canadian§	NC	NC	NC	NC	NC
	UK	0.49 (0.15 to 1.61)	0.51 (0.13 to 2.0)	1.67 (0.25 to 11.3)	.15	.71

* Petroleum workers were pooled from three nested case–control studies (11, 12, 13). Peak exposure was defined as at least 1 year employment in jobs likely experiencing greater than 3 ppm exposure for 15–60 minutes at least weekly; referents are workers without such jobs (ie, no peak exposure). High dermal exposure was defined as the highest job-specific relative probability of skin contact with benzene for at least a year; referents are workers assigned only to jobs with no probability of skin contact with benzene or jobs with any skin contact for less than a year. Cumulative exposure was derived from estimates of benzene concentration for a job multiplied by the number of years at that job, summed over all jobs held. Third tertile cumulative exposure was defined as greater than 2.93 ppm-years; referents are first tertile cumulative exposure of 0.348 or less ppm-years. Study-specific comparisons were not made for MPD because 25 of the 30 case subjects were in the UK study. Associations were analyzed using a conditional logistic regression model with referents matched on age, sex, and alive at the time of case subject diagnosis. OR = odds ratio; CI = confidence interval; LH = lymphohematopoietic; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; CLL = chronic lymphoid leukemia; CML = chronic myeloid leukemia; NC = no convergence.

† *P*-values were calculated using two-sided Breslow-Day χ^2 test.

‡ *P*-values were calculated using two-sided likelihood ratio χ^2 test for linear trend.

§ No convergence because of small sample size (n = 4 case subjects).

Table 2. Associations between the risk of five endpoints and worker subgroup*

	Petroleum facility type, OR (95% CI)		Job for at least 1 year, OR (95% CI)	
LH cancer subtype	**Terminal vs other facility**	**Refinery vs other facility**	**Ever tanker driver vs other workers**	**Ever refinery operator vs other workers**
AML	0.63 (0.27 to 1.47)	1.04 (0.24 to 4.56)	2.02 (1.08 to 3.78)	1.97 (0.38 to 10.2)
MDS	5.04 (1.58 to 16.1)	0.08 (0.01 to 0.66)	2.16 (0.79 to 5.88)	0.17 (0.02 to 1.42)
CLL	0.74 (0.38 to 1.46)	1.99 (0.87 to 4.57)	0.64 (0.36 to 1.14)	2.26 (0.92 to 5.58)
CML	0.74 (0.23 to 2.20)	1.57 (0.44 to 5.66)	1.26 (0.51 to 3.11)	0.70 (0.13 to 3.67)
MPD	1.24 (0.34 to 4.61)	1.41 (0.19 to 10.3)	1.38 (0.60 to 3.21)	4.00 (0.10 to 17.3)

* Associations were analyzed using a conditional logistic regression model with referents matched on age, sex, and alive at the time of case subject diagnosis. Terminal workers were employed in terminals for most or all of their career and compared to workers employed at other facility types. Refinery workers were employed in refineries for most or all of their career and compared to workers employed at other facility types. Ever tanker drivers were employed as tanker drivers for at least 1 y and compared to all other workers. Ever refinery operators were employed as refinery operators or craftsmen for at least 1 y and compared to all other workers. OR = odds ratio; CI = confidence interval; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; CLL = chronic lymphoid leukemia; CML = chronic myeloid leukemia; MPD = myeloproliferative disease.

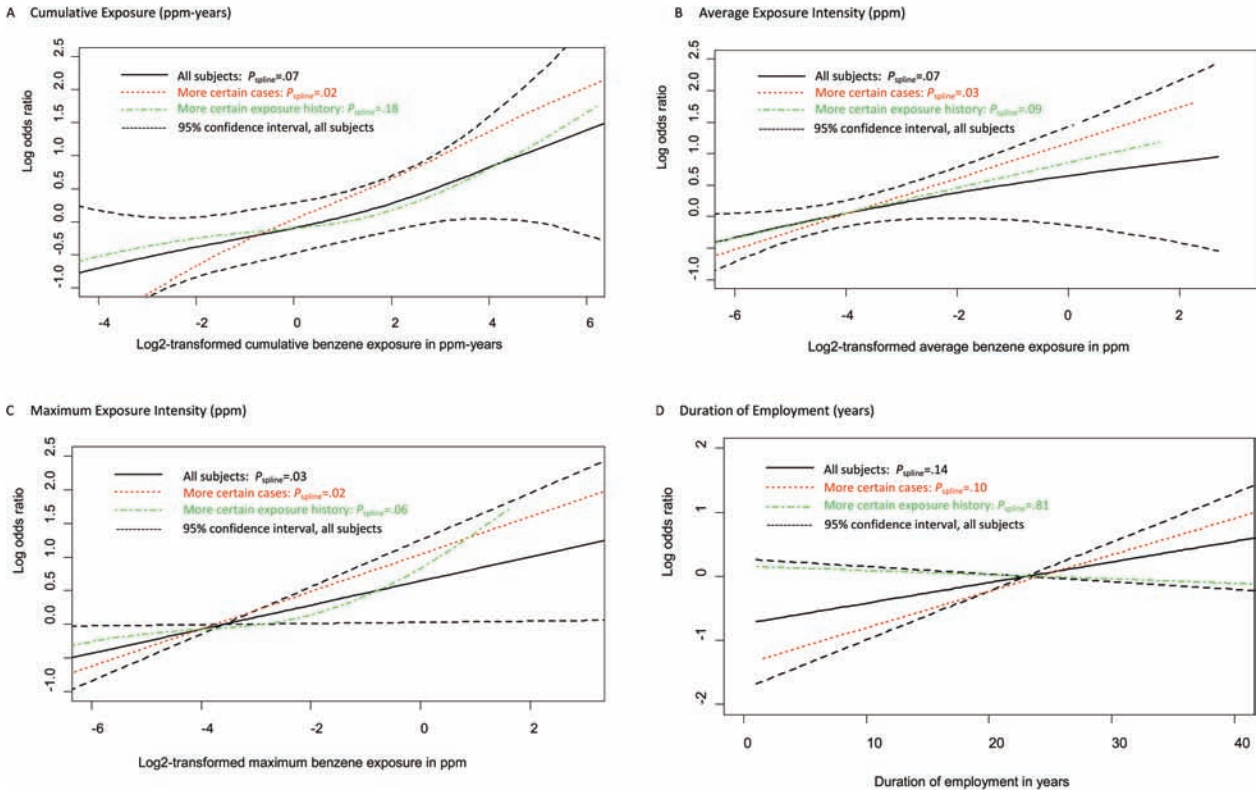


Figure 4. Penalized regression smoothing spline (P-spline) functions showing log odds ratio of risk of myelodysplastic syndrome (MDS) and specific benzene exposure metrics for more certain cases and more certain exposure history. We defined more certain case subjects as those with diagnostic certainty scores of 2 or higher, and more certain exposure history as subjects whose weighted career certainty score was 2 or higher. Here 95% confidence intervals around P-spline functions are displayed for all case and control subjects. **A)** Association of cumulative exposure (ppm-years) with MDS. **B)** Association of average exposure intensity (ppm) with MDS. **C)** Association of maximum exposure intensity (ppm) with MDS. **D)** Association of duration of employment (years) with MDS.

for more than 1 year vs never a tanker driver for more than 1 year, OR = 7.2 [95% CI = 1.37 to 37.4]). Also, jobs with peak exposure showed a statistically significant risk for more certain case subjects (peak exposure vs no peak exposure, OR = 6.32 [95% CI = 1.32 to 30.2]) and more certain exposure histories, OR = 5.74 [95% CI = 1.05 to 31.2]. Similar patterns of MDS risk were found among workers with more certain exposure histories (Table 3).

Models of MDS risk that simultaneously included peak exposure and other exposure metrics suggested that peak exposure was the more robust metric, which means for highly certain case subjects, the *P*-values for the cumulative exposure term increased when including peak exposure in the model, yet the *P*-value for peak exposure remained statistically significant and unchanged when including cumulative exposure in the model. We also examined spline models to assess whether a threshold of exposure could be identified for cumulative, average, and maximum exposure. Initial models with unrestricted degrees of freedom suggested a potential threshold at 0.99 ppm maximum exposure, but this value was not confirmed when the degrees of freedom were restricted to more biologically justified values (eg, values that are not prone to

Table 3. Sensitivity analyses on associations between risk of five endpoints vs job and peak exposure*

LH cancer subtype	High disease certainty, OR (95% CI)			High exposure certainty, OR (95% CI)		
	Ever refinery worker vs referent	Ever tanker driver vs referent	Peak vs referent	Ever refinery worker vs referent	Ever tanker driver vs referent	Peak vs referent
AML	1.97(0.38 to 10.18)	1.66 (0.86 to 3.19)	1.27 (0.66 to 2.43)	1.29 (0.20 to 8.49)	2.12 (0.31 to 14.5)	5.10 (0.87 to 30.0)
MDS	0	7.17 (1.37 to 37.4)	6.32 (1.32 to 30.2)	0.25 (0.03 to 2.14)	20.1 (2.36 to 170)	5.74 (1.05 to 31.2)
CLL	2.26 (0.92 to 5.58)	0.65 (0.36 to 1.19)	0.69 (0.41 to 1.16)	1.73 (0.57 to 5.27)	0.44 (0.05 to 3.60)	2.31 (0.61 to 8.78)
CML	0.70 (0.13 to 3.67)	1.46 (0.58 to 3.64)	0.73 (0.32 to 1.71)	1.04 (0.18 to 5.88)	0.69 (0.07 to 6.42)	0.64 (0.13 to 3.26)
MPD	4.00 (0.36 to 44.1)	1.90 (0.62 to 5.81)	2.41 (0.87 to 6.68)	5.40 (0.47 to 62.1)	1.63 (0.08 to 34.6)	2.00 (0.17 to 23.9)

* Associations were analyzed using a conditional logistic regression model with referents matched on age, sex, and alive at the time of case subject diagnosis. High disease certainty refers to case subjects rated as moderate or high diagnostic certainty. High exposure certainty refers to workers who held jobs in which exposure certainty was rated as 3 (the highest level of certainty). Ever refinery worker refers to employment in a refinery for at least a year; referents were those not working in refineries for at least a year; ever tanker driver refers to employment as a tanker driver for at least a year; referents were those not working as a tanker driver for at least a year. Peak refers to workers employed in jobs experiencing peak exposure (>3 ppm for 15–60 minutes at least weekly) for at least a year; referents were all other workers not experiencing peak exposure. OR = odds ratio; CI = confidence interval; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; CLL = chronic lymphoid leukemia; CML = chronic myeloid leukemia; MPD = myeloproliferative disease.

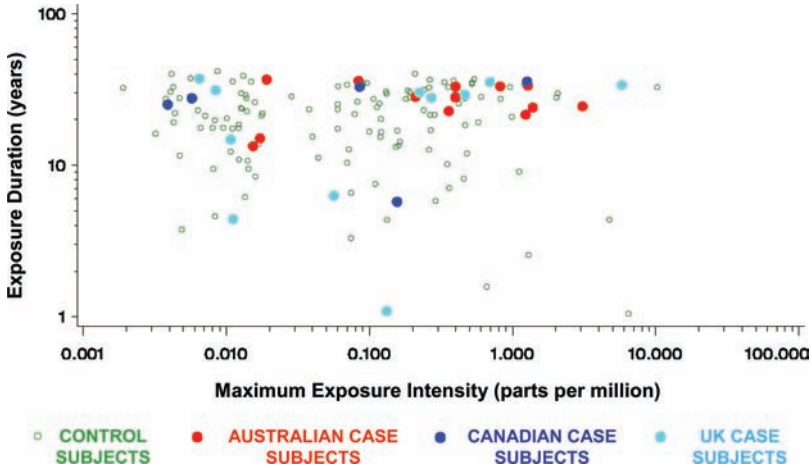


Figure 5. Plot of MDS case subjects and control subjects by maximum exposure intensity (ppm) and duration of employment (years).

overfitting the data). A simple plot of MDS case subject vs control subject exposures seemed to indicate an over-representation of case subjects (beyond the percentage predicted by the baseline matching ratio) starting at approximately 0.7 ppm maximum exposure (Figure 5).

Discussion

In this pooled analysis among petroleum workers from Canada, the United Kingdom, and Australia who were exposed to low levels of benzene, we found statistically significant dose–response relationships between MDS and more than one benzene exposure metric, but similar findings with AML were not observed. Because AML is the LH cancer subtype most frequently linked to benzene, and 8-hour-shift average benzene exposure concentrations in our study were largely under 1 ppm, our findings deserve careful scrutiny.

Exposure and disease misclassification and the effects of unmeasured confounders are inherent in retrospective case–control studies. Although the study strengths noted below likely mitigated these effects, some limitations remained. We were unable to account for infrequent and individualized exposure events, such as spills, nonroutine maintenance activities, or compromised work practices, which may have led to exposure underestimation in individual study subjects. Such underestimation could lead to estimating effects at lower concentrations but should not result in bias because it is likely that such effects applied similarly to case subjects and matched control subjects. Smoking has been related to AML and MDS, although smoking data was incomplete in our study. Among workers with known smoking histories, the MDS–benzene relationship did not weaken, suggesting that smoking is not likely to be a positive confounder. Chemicals reported to be associated with LH cancer (eg, butadiene, styrene, ethylene oxide) are not present in these operations, whereas other coexposures in this setting (eg, toluene, aliphatic hydrocarbons) have not been linked to LH cancers. Other potential confounders (eg, radiation exposure, genetic susceptibility) were not assessed, and although the prevalence of these exposures and traits are unlikely to have markedly different distributions among case subjects and matched workplace control subjects, we cannot exclude the possibility of effect modification, especially because of genetic predisposition (27).

The major strengths of this study are: 1) an enhanced ascertainment of disease subtype diagnoses via assembly of source records and use of hematopathologic expertise; 2) extensive exposure validation to ensure comparability across the three studies (23); 3) use of sensitivity analyses based on more certain diagnostic and

exposure assessments to limit disease and exposure misclassification; and 4) its size, which allowed analysis of etiologically distinct LH cancer subgroups.

Recognition of MDS as a hematopoietic malignancy was slow to evolve; it was formally classified as a distinct disease by the French American British working group in 1982 (28) and by the ICD in 1999 (29). MDS became reportable in many cancer registries in 1999, and in 2001, the WHO outlined more specific diagnostic and classification criteria (18). Increases in its incidence (30) are almost certainly related to improved diagnosis and reporting. The definitive existing diagnostic criteria for MDS requires histopathologic examination of the bone marrow, a procedure not widely employed until modern biopsy techniques were introduced in the 1970s (31). Consequently, subjects with MDS were likely grouped with or misclassified as aplastic anemia, myeloproliferative diseases, or other leukemias in the early literature (30,32,33). Because two of the parent cohorts in our study extend back to the 1960s, other MDS case subjects may have been missed while diagnostic practices were evolving. Indeed, the record review employed in this study identified five such cases. Missing case subjects could result in a bias in a cohort study but would likely simply result in a loss of power in this nested case–control study, because case subjects were matched to control subjects within the relevant cohort in this pooled study, and both populations were assessed for previous benzene exposure blinded to disease status.

There are few studies on MDS risk following benzene exposure, and we are not aware of others using the nested case–control design, with its attendant advantages for exposure assessment (10). A recent study from Shanghai demonstrated a strong association for MDS subtypes in individuals with high (>20 ppm) benzene exposure (34,35). Another study (3) reported a statistically significant association between benzene and combined AML/MDS for higher (ie, a mean of 22.5 ppm amongst study subjects) exposure. Although the relationship between MDS and peak exposures >3 ppm was the most robust relationship observed, some analyses are also consistent with MDS effects for long-term exposure to lower levels (eg, maximum shift average exposures of >0.7–1 ppm).

Previous findings on the association of benzene exposure and AML (36) have been the driver for reducing benzene exposure in occupational settings (37) and ambient air (38). Indeed, the original Australian study (13) reported a strong relationship with AML, but this was not replicated in the pooled data, partly because of the absence of a relationship for updated case subjects and partly because of reclassification of some AML case subjects to MDS. The latter is not without precedent (32) and is likely the result of changing diagnostic practices and documentation over time.

At least two possible interpretations are consistent with the present data. First, MDS is the most relevant outcome for benzene exposure, and previous studies relying on vital records in eras when MDS was not yet defined could have reported AML or aplastic anemia excesses, rather than the true excess of MDS. The relatively strong excess of MDS and modest excess of AML found in the Shanghai study (34,35,39) support this interpretation as does the fact that 10%–30% of cases of MDS progress to AML. Thus, an association between benzene and AML may have been detected historically when diagnostic criteria for MDS were absent.

Second, benzene may cause MDS at lower exposures, although higher concentrations are needed to develop AML. Epigenetic mechanisms have been implicated in the MDS pathogenesis (40,41), and some studies from China suggest that immune-mediated inflammation is an early developmental step in benzene-induced MDS (34,42,43). Because MDS is prevalent in the elderly, the disease could remain relatively low grade for years and progress to full-blown MDS in conjunction with age-related decreases in immune competency. In contrast, higher benzene concentrations (2,39) that occur temporally close to diagnosis (3,22) may be required for AML. Our data did not confirm that exposures occurring within 15 years of diagnosis are more strongly related to AML (or MDS and CML); the lower exposures among these workers may have a different temporal effect on disease outcomes vs higher exposures. Whether AML is an independent effect or a possible outcome in benzene-induced MDS (or both) remains unresolved. Further studies are needed to clarify the relationship between lower benzene exposures and temporal relationships with LH cancer outcomes, including AML, MDS, and MPD.

Although our study showed little relationship between benzene exposure and CLL, other studies of populations with benzene exposure have found effects. Elevated CLL mortality in pre-1950 workers was identified in one of two refinery populations (44), and IARC (4) noted other similar results. Because refineries represent a more complex exposure environment vs distribution terminals, coexposures other than benzene may be a factor in CLL etiology.

Although the myeloid neoplasms that we examined are distinct diseases, they share common biologic features. Thus, future studies of benzene and LH cancers should review all available diagnostic information relating to disease progression. Future studies based solely on death certificates should be discouraged.

Because MDS incidence is increasing as diagnosis and classification of the disease becomes more common, observational epidemiology is now possible in large populations such as ours. Although it is difficult to ascribe precise concentrations of benzene to MDS, our results likely represent a real association with MDS at lower levels than previously reported. Future benzene studies should include MDS as an outcome and seek to measure benzene exposure, smoking, and individual susceptibility factors as precisely as possible.

References

1. Schnatter AR, Kerzic PJ, Zhou Y, et al. Peripheral blood effects in benzene-exposed workers. *Chem Biol Interact.* 2010;184:174–181.
2. Crump KS. Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates. *J Toxicol Environ Health*. 1994;42(2):219–242.
3. Hayes RB, Yin SN, Dosemeci M, et al. Benzene and the dose-related incidence of hematologic neoplasms in China. Chinese Academy of Preventive Medicine–National Cancer Institute Benzene Study Group. *J Natl Cancer Inst*. 1997;89(14):1065–1071.
4. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals: Vol. 100F-Evaluation*. International Agency for Research on Cancer; 2010. http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php. Accessed September 20, 2012.
5. Bergsagel DE, Wong O, Bergsagel PL, et al. Benzene and multiple myeloma: appraisal of the scientific evidence. *Blood*. 1999;94(4):1174–1182.
6. Steinmaus C, Smith AH, Jones RM, Smith MT. Meta-analysis of benzene exposure and non-Hodgkin lymphoma: biases could mask an important association. *Occup Environ Med*. 2008;65(6):371–378.

7. Kane EV, Newton R. Benzene and the risk of non-Hodgkin lymphoma: a review and meta-analysis of the literature. *Cancer Epidemiol*. 2010;34(1):7–12.
8. Alexander DD, Wagner ME. Benzene exposure and non-Hodgkin lymphoma: a meta-analysis of epidemiologic studies. *J Occup Environ Med*. 2010;52(2):169–189.
9. Vlaanderen J, Portengen L, Rothman N, Lan Q, Kromhout H, Vermeulen R. Flexible meta-regression to assess the shape of the benzene-leukemia exposure-response curve. *Environ Health Perspect*. 2010;118(4):526–532.
10. Schnatter AR, Rosamilia K, Wojcik NC. Review of the literature on benzene exposure and leukemia subtypes. *Chem Biol Interact*. 2005;153-154:9–21.
11. Schnatter AR, Armstrong TW, Nicolich MJ, et al. Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occup Environ Med*. 1996;53(11):773–781.
12. Rushton L, Romaniuk H. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med*. 1997;54(3):152–166.
13. Glass DC, Gray CN, Jolley DJ, et al. Leukemia risk associated with low-level benzene exposure. *Epidemiology*. 2003;14(5):569–577.
14. Miller BG, Fransman W, Heederik D, Hurley JF, Kromhout H, Fitzsimons E. A review of the data quality and comparability of case-control studies of low-level exposure to benzene in the petroleum industry. *Int Arch Occup Environ Health*. 2010;83(1):69–76.
15. Schnatter AR, Katz AM, Nicolich MJ, Thériault G. A retrospective mortality study among Canadian petroleum marketing and distribution workers. *Environ Health Perspect*. 1993;101(6 suppl):85–99.
16. Rushton L. A 39-year follow-up of the U.K. oil refinery and distribution center studies: results for kidney cancer and leukemia. *Environ Health Perspect*. 1993;101(6 suppl):77–84.
17. Gun RT, Pratt NL, Griffith EC, Adams GG, Bisby JA, Robinson KL. Update of a prospective study of mortality and cancer incidence in the Australian petroleum industry. *Occup Environ Med*. 2004;61(2):150–156.
18. Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon: IARC Press; 2001.
19. Armstrong TW, Pearlman ED, Schnatter AR, Bowes SM III, Murray N, Nicolich MJ. Retrospective benzene and total hydrocarbon exposure assessment for a petroleum marketing and distribution worker epidemiology study. *Am Ind Hyg Assoc J*. 1996;57(4):333–343.
20. Lewis SJ, Bell GM, Cordingley N, Pearlman ED, Rushton L. Retrospective estimation of exposure to benzene in a leukaemia case-control study of petroleum marketing and distribution workers in the United Kingdom. *Occup Environ Med*. 1997;54(3):167–175.
21. Glass DC, Adams GG, Manuell RW, Bisby JA. Retrospective exposure assessment for benzene in the Australian petroleum industry. *Ann Occup Hyg*. 2000;44(4):301–320.
22. Richardson DB. Temporal variation in the association between benzene and leukemia mortality. *Environ Health Perspect*. 2008;116(3):370–374.
23. Glass DC, Armstrong TW, Pearlman ED, Verma DK, Schnatter AR, Rushton L. Ensuring comparability of benzene exposure estimates across three nested case-control studies in the petroleum industry in support of a pooled epidemiological analysis. *Chem Biol Interact*. 2010;184(1-2):101–111.
24. R Foundation for Statistical Computing. A language and environment for statistical computing; 2008. http://www.R-project.org. Accessed May 1, 2010.
25. Insightful Corporation. *S-PLUS 8 for Windows User's Guide*. Insightful Corporation: Seattle, WA; 2007.
26. SAS Institute Inc. *SAS/STAT 9.2 User's Guide*. Cary, NC: SAS Institute Inc; 2008.
27. Hahn CN, Chong CE, Carmichael CL, et al. Heritable GATA2 mutations associated with familial myelodysplastic syndrome and acute myeloid leukemia. *Nat Genet*. 2011;43(10):1012–1017.
28. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol*. 1982;51(2):189–199.
29. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory committee meeting, Airlie House, Virginia, November 1997. *J Clin Oncol*. 1999;17(12):3835–3849.
30. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: incidence and survival in the United States. *Cancer*. 2007;109(8):1536–1542.
31. Jamshidi K, Swaim WR. Bone marrow biopsy with unaltered architecture: a new biopsy device. *J Lab Clin Med*. 1971;77(2):335–342.
32. Iwanaga M, Hsu WL, Soda M, et al. Risk of myelodysplastic syndromes in people exposed to ionizing radiation: a retrospective cohort study of Nagasaki atomic bomb survivors. *J Clin Oncol*. 2011;29(4):428–434.
33. Honda Y, Delzell E, Cole P. An updated study of mortality among workers at a petroleum manufacturing plant. *J Occup Environ Med*. 1995;37(2):194–200.
34. Irons RD, Gross SA, Le A, et al. Integrating WHO 2001–2008 criteria for the diagnosis of myelodysplastic syndrome (MDS): a case-case analysis of benzene exposure. *Chem Biol Interact*. 2010;184(1-2):30–38.
35. Lv L, Lin G, Gao X, et al. Case-control study of risk factors of myelodysplastic syndromes according to World Health Organization classification in a Chinese population. *Am J Hematol*. 2011;86(2):163–169.
36. Rinsky RA, Smith AB, Hornung R, et al. Benzene and leukemia. An epidemiologic risk assessment. *N Engl J Med*. 1987;316(17):1044–1050.
37. *ACGIH TLV Documentation Benzene*. Cincinnati, OH: American Conference of Governmental Industrial Hygienists; 2001.
38. The WHO European Centre for Environment and Health. *WHO Guidelines for Indoor Air Quality: Selected Pollutants*. Bonn: World Health Organization; 2010.
39. Wong O, Harris F, Armstrong TW, Hua F. A hospital-based case-control study of non-Hodgkin lymphoid neoplasms in Shanghai: analysis of environmental and occupational risk factors by subtypes of the WHO classification. *Chem Biol Interact*. 2010;184(1-2):129–146.
40. Leone G, Voso MT, Teofili L, Lübbert M. Inhibitors of DNA methylation in the treatment of hematological malignancies and MDS. *Clin Immunol*. 2003;109(1):89–102.
41. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*. 2006;106(8):1794–1803.
42. Irons RD, Lv L, Gross SA, et al. Chronic exposure to benzene results in a unique form of dysplasia. *Leuk Res*. 2005;29(12):1371–1380.
43. Song Y, Du X, Hao F, et al. Immunosuppressive therapy of cyclosporin A for severe benzene-induced haematopoietic disorders and a 6-month follow-up. *Chem Biol Interact*. 2010;186(1):96–102.
44. Huebner WW, Wojcik NC, Rosamilia K, Jorgensen G, Milano CA. Mortality updates (1970–1997) of two refinery/petrochemical plant cohorts at Baton Rouge, Louisiana, and Baytown, Texas. *J Occup Environ Med*. 2004;46(12):1229–1245.

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