

The Relationship between Low-level Benzene Exposure and Leukemia in Canadian Petroleum Distribution Workers

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This study was conducted to evaluate the relationship between leukemia occurrence and long-term, low-level benzene exposures in petroleum distribution workers. Fourteen cases were identified among a previously studied cohort [Schnatter et al., *Environ Health Perspect* 101(Suppl 6):85–99 (1993)]. Four controls per case were selected from the same cohort, controlling for birth year and time at risk. Industrial hygienists estimated workplace exposures for benzene, without knowledge of case-control status. Average benzene concentrations ranged from 0.01 to 6.2 ppm. Company medical records were used to abstract information on other potential confounders such as cigarette smoking. Odds ratios were calculated for several exposure metrics. Conditional logistic regression modeling was used to control for potential confounders. The risk of leukemia was not associated with increasing cumulative exposure to benzene for these exposure levels. Duration of benzene exposure was more closely associated with leukemia risk than other exposure metrics, although results were not statistically significant. A family history of cancer and cigarette smoking were the two strongest risk factors for leukemia, with cumulative benzene exposure showing no additional risk when considered in the same models. This study is consistent with other data in that it was unable to demonstrate a relationship between leukemia and long-term, low-level benzene exposures. The power of the study was limited. Thus, further study on benzene exposures in this concentration range are warranted. — *Environ Health Perspect* 104(Suppl 6):1375–1379 (1996)

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Introduction

Benzene has been classified as a known human carcinogen (1). Most investigators (2–5) base risk predictions for occupational and environmental exposures on a cohort of rubber hydrochloride workers (6). However, this cohort was exposed to high concentrations of benzene, which sometimes exceeded time-weighted average

concentrations of 50 ppm (7,8). Petroleum distribution workers are exposed to benzene while transferring gasoline and other petroleum products. These exposure levels are generally less than 1 ppm on an 8-hr time-weighted average basis. Previous studies of these workers (9–12) have not examined leukemia risk by benzene exposure. The

aim of this article is to study this lower portion of the dose-response curve for benzene and leukemia.

Methods

We identified cases from all workers in a previously conducted cohort study (13) meeting the following criteria: *a*) died with an underlying cause of death of leukemia (*International Classification of Disease*, codes 204–207); *b*) ever worked in either the marketing/distribution, marine, or pipeline segments; and *c*) died between 1964 and 1983, the study end date. Statistics Canada coded all death certificates for underlying cause of death. The criteria resulted in 16 leukemias. We were unable to obtain reliable information on leukemia cell types for the cases. We selected four controls for each case from records in the same cohort. Controls were restricted to males, frequency matched by decade of birth, and were alive on or after the case's date of death. After excluding cases and controls with inadequate work histories, there were 14 leukemia cases and 55 controls.

The details of the exposure assessment strategy are described elsewhere (14). Briefly, work histories were abstracted from hard copy personnel records for each case and control and forwarded, without case/control status to industrial hygienists. The industrial hygienists derived workplace exposure estimates for benzene and total hydrocarbons for every job/location/era combination. The process started with site characterizations for the 89 study locations, including loading/unloading technology present at the sites, the types of materials handled, the typical tasks performed by workers, and typical environmental conditions such as average ambient temperatures. Surveys were available for some of the sites and were supplemented with data on similar operations from outside the company to derive "base exposure estimates" for job/location/era scenarios in the work histories. The industrial hygienists then applied adjustment factors, based on differences in environmental, operational, task, and worksite conditions. The values for the adjustment factors were estimated through physical-chemical first principles, or empirical data.

The validity of the estimating method was tested by comparing exposure estimates from the estimating procedure with results from industrial hygiene surveys carried out

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during the relevant time period. On average, estimates were within 22% of the measured data. This was considered reasonable agreement.

Eight-hour time-weighted average exposure intensity estimates were assigned to each line in every worker's job/location history. We subtracted absentee information from time at work, and then multiplied the intensity estimates by length of time in a job. These results were summed to arrive at a ppm-year estimate for every worker's career. Exposures for controls were only summed up to the corresponding case's date of death. We also lagged exposures by 5, 10, and 15 years (15). This strategy does not count exposures received 5, 10, or 15 years immediately prior to the case's date of death. The industrial hygienists also provided a ranked estimate for each line indicating the probability of dermal exposure to hydrocarbons. This was kept as a separate index from the estimated inhalation concentrations.

Potential confounders were abstracted from company medical records, and included information on smoking habits, hobbies, previous exposures and occupations, diagnostic radiation exposure, and family history of cancer. The dependent variable in all analyses was case/control status. The primary independent variable of interest is cumulative benzene exposure measured in ppm-years. Other exposure characterizations, such as dermal exposure and average intensity of exposure during the entire work history, were also analyzed. We also categorized cumulative exposure in various ways to guard against a cutpoint effect (16). We examined results according to the following schemes using the distribution of exposures in the controls:

- the quartile distribution
- the tertile distribution
- four categories split at the median, 75th, and 90th percentiles
- ppm-years split at 0.45, 4.5, and 45 ppm-years (the category boundaries correspond to 0.01, 0.1 ppm, and 1 ppm for 45 years)
- ppm-years split at 0.9, 9.9, and 99 ppm-years (the category midpoints correspond to 0.01, 0.1, and 1.0 ppm for 45 years).

Results

The mean ages (at first exposure and last follow up) and number of years exposed, are displayed in Table 1 for leukemia cases and controls. On average, the leukemia cases were three years younger than controls.

Table 1. Comparison of attributes for leukemia cases and controls.

Characteristic	Cases	Controls
Age, at case's death	68.5	68.0
Age, at first exposure	28.7	31.7
Years exposed	30.3	28.0

Table 2. Leukemia risk by potential confounders.

	No. exposed cases	Odds ratio	95% CI
Socioeconomic job type			
Managerial/professional	4	1.00	—
Clerk/technician	4	0.34	0.03–3.10
Operator/driver	6	0.41	0.07–2.33
Smoking status			
Never	0	1.00	—
Ever	7	∞	—
Familial cancer			
No	8	1.00	—
Yes	5	2.51	0.51–13.3
No. chest X-rays			
0–9	7	1.00	—
10–14	3	1.41	0.18–11.2
15–19	2	0.75	0.01–18.8
20+	1	1.73	0.02–156

CI, confidence interval.

Cases were also exposed for a similar number of years as controls.

Table 2 displays matched odds ratios (ORs) for the 14 leukemia cases and 55 controls according to potentially confounding variables. The two strongest risk factors are a family history of cancer (OR = 2.51), and smoking (OR = ∞), although both have wide or noncalculable confidence intervals. The number of chest X-rays documented in medical records is not strongly related to leukemia risk, while the risk of leukemia is highest in managerial and professional job designations.

Table 3 shows the risk of leukemia according to cumulative exposure to benzene. None of the categorizations shows a monotonic trend for leukemia risk by cumulative exposure, although there are a small number of cases and controls in each category. For cumulative benzene exposure, the highest leukemia risks are observed in the second quartile (OR = 5.06) and middle tertile (OR = 4.37), but the ORs decrease in the highest quartiles and tertile.

When examining the highest exposure categories in Table 3, cumulative benzene exposures greater than 5.5, 8, 20, 45, and 99.9 (up to 220 ppm-years) result in ORs of 0.92, 2.11, 0.96, 1.47, and 1.03, respectively. All five of the categorizations suggest risks consistent with unity for the highest

Table 3. Leukemia risk by cumulative exposure to benzene.

Benzene exposure, ppm-years	No. exposed cases	Odds ratio	95% CI
0–0.17 ^a	2	1.00	—
0.18–0.49	8	5.06	0.34–295
0.50–7.9	1	0.88	0.01–18.2
8.0–219.8	3	2.11	0.10–138
0–0.22 ^b	3	1.00	—
0.23–5.49	8	4.37	0.72–48.6
5.50–219.8	3	0.92	0.10–11.2
0–0.49 ^c	10	1.00	—
0.50–7.99	1	0.22	0–1.82
8.0–19.99	1	0.42	0.01–3.95
20.0–219.8	2	0.96	0.09–6.81
0–0.45 ^d	10	1.00	—
>0.45–4.5	1	0.43	0.01–4.05
>4.5–45	1	0.16	0–1.32
>45	2	1.47	0.16–13.1
0–0.90 ^d	10	1.00	—
>0.90–9.9	2	0.43	0.04–2.36
>9.9–99.9	1	0.48	0.01–4.55
>99.9	1	1.03	0.02–20.3

^aCategorized according to quartiles. ^bCategorized according to tertiles. ^cCategorized according to median, 75th, and 90th percentiles. ^dCategorized according to regulatory considerations.

Table 4. Leukemia risk by alternate benzene exposure metrics.

	No. exposed cases	Odds ratio	95% CI
Benzene intensity, mean ppm			
0–0.01	9	1.00	—
>0.01–0.19	2	0.88	0.08–6.47
0.20–0.49	1	0.19	0–1.55
0.50–6.16	2	0.96	0.09–6.81
Maximum benzene intensity, ppm			
<0.5	10	1.00	—
0.5–0.99	0	0	0–7.57
1.0+	4	1.02	0.21–4.26
Maximum probability of dermal exposure			
Low	8	1.00	—
Medium	4	0.61	0.12–2.51
High	2	0.47	0.04–2.86

exposure group, although the confidence intervals are extremely wide.

Leukemia risk according to other exposure metrics is shown in Table 4. Risk did not increase in a consistent way for the mean intensity over a worker's career, for workers ever exposed between 0.5 and 1 ppm or over 1 ppm, nor by a worker's highest ranked probability of dermal exposure.

ORs and *p*-values for coefficients in the logistic models were very similar when

exposures were lagged for 0, 5, 10, or 15 years. Therefore, we will report results only for no lag period.

Cumulative benzene exposure did not show a strong relationship with leukemia when regressed separately (OR = 1.002/ppm-year, $p = 0.77$). The p -value for the score statistic ($p = 0.76$) indicates that this model does not fit the data well (Table 4, model 1). We also added into the model separate terms for an employee's mean exposure intensity and total exposure duration. This maneuver produced a noninterpretable result; exposure intensity (OR = 2.27/ppm) and duration (OR = 1.07/year) showed a positive relationship, yet the OR for cumulative exposure fell below 1.0 (Table 5). A model with only exposure duration showed a coefficient of 1.06/year exposed with a 95% confidence interval of 0.99 to 1.14 (Table 5, model 4) and resulted in a reasonable overall model p -value ($p = 0.10$). Thus, for these data, the simple measure of exposure duration was most closely associated with leukemia, while cumulative benzene exposure and mean intensity of benzene exposure did not explain leukemia risk.

Next we examined whether exposure above a certain level was related to leukemia risk, by using the number of years worked above either 0.5 or 1 ppm as independent variables. Neither of these variables explained leukemia risk adequately nor fit the data well (Table 5, models 5,6). The coefficient for years above 0.5 ppm (1.02) was slightly greater than the coefficient for years above 1 ppm (1.00).

The number of years spent in jobs ranked as having a low, medium, or high probability of dermal exposure was explored in one model. The risks were higher (and closer to significance) for a year spent in a low-probability job (OR = 1.06/year, $p = 0.14$) versus a high probability job (OR = 1.02/year, $p = 0.76$).

Since the Mantel-Haenszel analyses showed that leukemia risk did not increase for increasing categories of cumulative exposure, we constructed models with square terms for duration and intensity of exposure. This allows for nonexponential increases in risk per unit exposure. For all combinations of duration and intensity of exposure, and the squares of these variables, a model with only duration of exposure squared fit the data best ($p = 0.05$). The OR for this model (1.001/year²) was not quite statistically significant ($p = 0.07$).

Since both cigarette smoking and a family history of cancer were related to leukemia

Table 5. Conditional logistic regression modeling results for leukemia and benzene exposure.

Model	Model p -value ^a	Variable	Odds ratio	95% Lower limit	95% Upper limit	Variable p -value ^b
1	0.76	Cumulative benzene exposure	1.002	0.989	1.015	0.77
2	0.28	Cumulative benzene exposure	0.980	0.933	1.030	0.43
		Mean intensity	2.271	0.426	12.098	0.34
		Duration	1.069	0.990	1.155	0.09
3	0.50	Intensity	1.171	0.729	1.880	0.51
4	0.10	Duration	1.061	0.985	1.144	0.12
5	0.70	Years at 0.5+ ppm	1.015	0.940	1.095	0.71
6	0.93	Years at 1.0+ ppm	1.004	0.921	1.094	0.93
7	0.38	Years at low dermal	1.061	0.984	1.144	0.14
		Years at medium dermal	1.054	0.954	1.164	0.30
		Years at high dermal	1.022	0.895	1.167	0.75

^aBased on score statistic. ^bBased on Wald chi-square statistic.

Table 6. Conditional logistic modeling results for leukemia for cases and controls with known values for potential confounders.

Model	Model p -value ^a	Variable	Odds ratio	95% Lower limit	95% Upper limit	Variable p -value ^b
1	0.11	Family history of cancer	5.53	0.54	56.6	0.15
2	0.02	Family history of cancer	14.0	1.04	188.0	0.05
		Ever smoked cigarettes	8.89	0.66	119.0	0.10
3	0.06	Family history of cancer	11.5	0.83	160.0	0.07
		Ever smoked cigarettes	6.93	0.48	100.0	0.16
		Cumulative benzene exposure	0.97	0.82	1.15	0.72
4	0.06	Family history of cancer	11.2	0.81	119.0	0.07
		Ever smoked cigarettes	7.99	0.55	115.0	0.13
		Intensity	0.34	0	26.5	0.63
5	0.03	Family history of cancer	18.8	1.33	265.0	0.05
		Ever smoked cigarettes	15.1	0.61	376.0	0.12
		Duration	1.08	0.95	1.22	0.25
6	0.04	Family history of cancer	16.5	1.11	244.0	0.04
		Ever smoked cigarettes	13.0	0.37	455.0	0.16
		Duration	0.82	0.43	1.57	0.55
		Duration squared	1.01	0.99	1.02	0.49

^aBased on score statistic. ^bBased on Wald chi-square statistic.

in the Mantel-Haenszel analyses, we constructed a series of models among cases and controls for which we had known values for these variables. We then added cumulative exposure, exposure intensity, and years exposed to these models. Since these models are performed on a different set of cases and controls, the results should not be compared to those in Table 5. Table 6 shows results from the model with only the potential confounders (an employee's family history of cancer and whether he ever smoked cigarettes). This model produced high but unstable ORs (OR = 14.0 and 8.9, respectively) for each variable. The score statistic indicated that the model fit was statistically significant ($p = 0.02$). Next, we added different combinations of cumulative benzene exposure, mean intensity of benzene exposure, duration of exposure, and the

square of the latter two variables. None of the expanded models resulted in a better fit to the data, as measured by the score statistic. Adding cumulative benzene exposure to this model resulted in an OR for benzene of 0.97/ppm-year, and reduced the score test significance from 0.02 to 0.06 (Table 6). Only when duration of exposure squared was added did the model again achieve statistical significance (score test p -value = 0.04). All of these models resulted in ORs for cumulative benzene exposure and mean benzene intensity of less than 1.0, and ORs for duration of exposure of greater than 1.0, but none of the exposure variables were statistically significant ($p > 0.25$).

Thus, these results show that a family history of cancer and cigarette smoking are the two strongest risk factors in these data. Cumulative benzene exposure did not

explain any incremental risk in leukemia when added to a model with these two risk factors.

Discussion

In general, this study did not find evidence that low-level exposure to benzene increased the risk of leukemia. However, the interpretation of this study must take into account its limited size. If benzene exposure caused a 2-fold increase in risk for the >45 ppm-year category, this study would have a 16% chance of detecting this at a 20% exposure rate and a 5% significance level. For 80% power, 90 cases would be needed. Despite the study's small size, it is useful to focus on the pattern of results, with emphasis on the magnitude of the risk estimates, rather than their precision.

We did not find a dose-response relationship between leukemia cases and any of five classifications of cumulative benzene exposure. Alternate exposure metrics, including average exposure intensity, years of exposure above 0.5 or 1 ppm, or a ranked estimate of dermal exposure also did not show a dose-response pattern. Duration of exposure produced the best goodness of fit statistic among the models with only exposure variables, but was not statistically significant. These results are most consistent with insufficient power to detect a small effect, or a lack of effect for low benzene exposures (primarily between 0.1 and 1.0 ppm).

The strongest risk factors were non-occupational (smoking and a family history of cancer). However, these data were not present for all workers in the study, and need to be interpreted cautiously. Despite incomplete information, this study does raise a question on the relevancy of tobacco use on the occurrence of leukemia. Siegel et al. (17) suggested that smoking increases the risk of myeloid leukemia by 50%. The limited amount of smoking information, and the incomplete records prevented the assessment of interaction between benzene and smoking. Future studies of low-dose benzene exposures should also attempt to measure smoking

habits to shed further light on the meaning of these preliminary results.

We also found that a family history of cancer was a significant predictor of leukemia risk. However, since our records came from pre-employment physicals, supplemented by notes from periodic physical exams, the findings must be interpreted with caution. Leukemia has been related to a positive family history of other cancers, but not consistently. Tajima (18) found a raised incidence of T-cell leukemia in persons with a family history of any cancer, which was stronger in those with a family history of hematopoietic malignancies. Our measure of family history included any cancers in parents, siblings, and children. Only two of the cancers were leukemia.

The fact that duration of exposure was more strongly related to leukemia occurrence than either exposure intensity or cumulative exposure could indicate that long-term exposure, regardless of the concentration, can result in leukemia. Another interpretation is that this is the best exposure metric because it is measured with the most precision. However, this would imply that the considerable effort to classify intensity of exposure actually resulted in severe misclassification, even between the highest and lowest intensity designations. We regard this as highly unlikely, partly due to the exposure assessment validation exercise (14). Finally, one could regard the finding as the chance result of examining many different exposure metrics, and that it has no biological significance.

Subpopulations represented in previous studies may have been exposed to similar benzene exposure levels to those present in the current study. The following risks pertain to levels up to 83 ppm-years, or about 2 ppm for 40 years. Wong (19) reported slight deficits in SMRs of 0.97 (0–14.9 ppm-years), and 0.78 (15–59.9 ppm-years). Bond et al. (20) reported an SMR of 1.67 for workers exposed to less than 42 ppm-years, but found no cases in those exposed between 42 and 83 ppm-years. Finally, Paxton et al. (6), reported SMRs of 1.33 in workers exposed to 5 or fewer

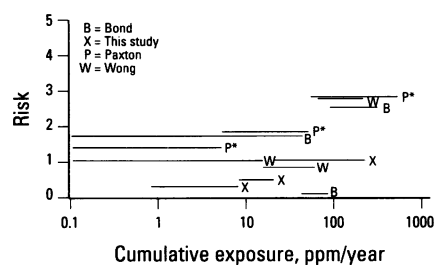


Figure 1. Leukemia risk by cumulative benzene exposure, four studies. Asterisk (*) indicates risk at 11.9.

ppm-years, and 1.79 in workers exposed between 5 and 50 ppm-years. The present study, along with these other studies, suggests that risks under about 50 ppm-years are either small or nonexistent. However, these data cannot be used to rule out a risk at these levels, since the risk estimates are based on relatively few workers.

The relevant studies are summarized in Figure 1. The figure shows that for exposures under approximately 100 ppm-years, the risks for total leukemia reported in four studies are approximately evenly distributed around 1.0.

For higher exposures (generally above 60 ppm-years), higher risks have been documented. Paxton et al. (6) reported SMRs of 2.80 for exposures from 50 to 500 ppm-years, Wong (19) reported an SMR of 2.76 for 60 ppm-years or greater, and Bond et al. (20) reported an SMR of 2.50 for 83+ ppm-years. Thus, one could argue that exposures in this range produce a 2- to 3-fold risk of leukemia (Figure 1).

Previous epidemiologic studies in which benzene exposure has been quantified have been limited by the small number of leukemia cases observed. The most-studied worker cohort now consists of 15 leukemia cases, including one female case (6). Other cohorts had only 5 (20) and 6 (19) cases of leukemia. Thus, the 14 leukemia cases represented in this study is a significant contribution, especially for exposures below 50 ppm-years. At the very least, this study can be used to provide a check on risk predictions for lower levels of benzene exposure.

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