Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers

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Abstract

***Objective*—To evaluate the relation between mortality from lymphohaematopoietic cancer and long term, low level exposures to benzene among male petroleum distribution workers.**

***Methods*—This nested case control study identified all fatal cases of lymphohaematopoietic cancer among a previously studied cohort. Of the 29 cases, 14 had leukaemia, seven multiple myeloma, and eight non-Hodgkin's lymphoma. A four to one matching ratio was used to select a stratified sample of controls from the same cohort, controlling for year of birth and time at risk. Industrial hygienists estimated workplace exposures for benzene and total hydrocarbons, without knowledge of case or control status, for combinations of job, location, and era represented in all work histories. Average daily benzene concentrations ranged from 0·01 to 6·2 parts per million (ppm) for all jobs. Company medical records were used to abstract information on other potential confounders such as cigarette smoking, although the data were incomplete. Odds ratios (ORs) were calculated with conditional logistic regression techniques for several exposure variables.**

***Results*—Risks of leukaemia, non-Hodgkin's lymphoma, and multiple myeloma were not associated with increasing cumulative exposure to benzene or total hydrocarbons. For leukaemia, the logistic regression model predicted an OR of 1·002 ($P < 0·77$) for each ppm-y of exposure to benzene. Duration of exposure to benzene was more closely associated with risk of leukaemia than other exposure variables. It was not possible to completely control for other risk factors, although there was suggestive evidence that smoking and a family history of cancer may have played a part in the risk of leukaemia.**

***Conclusion*—This study did not show a relation between lymphohaematopoietic cancer and long term, low level exposures to benzene. The power of the study to detect low—such as twofold—risks was limited. Thus, further study on exposures to benzene in this concentration range are warranted.**

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Exposure to benzene undoubtedly causes leukaemia.[1] Contemporary debate focuses on whether low level exposures can cause leukaemia,[2–4] which leukaemic cell types can be ascribed to benzene,[5 6] and whether benzene can cause other lymphohaematopoietic malignancies such as multiple myeloma.[7–9]

The case reports of Aksoy *et al*[10–12] and Vigliani[13] strongly implied an excess occurrence of acute myeloid leukaemia (AML) for exposure to benzene which often exceeded 100 parts per million (ppm). Infante *et al*,[14] who studied rubber hydrochloride workers, was the first to suggest that concentrations < 35 ppm can result in excess risk of leukaemia. In updating the work of Infante *et al*, Rinsky *et al*[8] and Paxton *et al*[15] reported an increased risk of leukaemia for workers exposed to more than 40 ppm-y. Most risk predictions[2 6 16 17] for low level exposures are based on this cohort of rubber hydrochloride workers. This is due to the fact that work assignments were relatively well documented, there were few other exposures, and there are relatively few additional data on benzene[18 19] in workers exposed to lower concentrations.

Petroleum distribution workers are exposed to benzene while transferring gasoline and other petroleum products. Exposures are low relative to exposures in rubber hydrochloride,[8] shoe manufacturing,[10] and rotogravure[20 21] processes. Although petroleum distribution workers have been the subject of previous cohort studies,[22–25] no estimates of exposure to benzene were made. Thus, these studies could not relate leukaemia and other health outcomes to quantitative levels of exposure to benzene.

Findings from a full cohort[26] and a subcohort of petroleum distribution workers[23] were previously reported. These results indicated that mortality from multiple myeloma was 1·81 times higher than comparable Canadian national rates, and mortality from leukaemia was 1·35 times higher than national rates. Neither result was significant. However, the rate of leukaemia in a subgroup of tanker drivers was 3·35 times higher than the standard rate, and was significant. This study is a nested case control study within the original cohort of marketing and distribution workers.

The present study had a dual purpose. The first was to formulate and test a procedure to

generate quantitative exposure estimates for petroleum distribution workers. This objective is the subject of another report.[27] The second objective is to provide new data on the risk of leukaemia in benzene workers with chronic low level exposure to benzene. This paper reports on the second objective.

Methods

CASES

We identified cases from all workers in the cohort study[26] meeting the following criteria: (*a*) died with an underlying cause of death of either leukaemia (international classification of diseases eighth revision (ICD-8) codes 204 to 207 inclusive), multiple myeloma (ICD-8 code 203), or non-Hodgkin's lymphoma (ICD-8 codes 200 and 202·0, 202·1, 202·2, and 202·9); (*b*) ever worked in either the marketing or distribution, marine, or pipeline segments; and (*c*) died between 1964 and 1983, the study dates. Statistics Canada coded all death certificates for underlying cause of death. The criteria resulted in 31 cases of lymphohaematopoietic cancer (all men), including 16 leukaemias, seven multiple myelomas, and eight non-Hodgkin's lymphomas. We were unable to obtain reliable information on leukaemia cell types.

CONTROLS

We selected four controls for each case from records in the same cohort. Controls were restricted to men, frequency matched by decade of birth, and were alive on or after the case's date of death. This resulted in 124 controls, bringing the total potential study population to 155.

ASSESSMENT OF EXPOSURE

Work histories were abstracted from hard copy personnel records for each case and control. The work histories were stripped of all case or control identifiers. A listing of all jobs, locations, and relevant time intervals from the pooled group of cases and controls was given to two industrial hygienists. The industrial hygienists derived workplace exposure estimates for benzene and total hydrocarbons for every combination of job, location, and era. The process is described briefly in this paper, and is detailed further elsewhere.[27]

The process started with site characteristics for the 89 study locations. The characteristics included the loading and unloading technology present at the sites over time, the types of materials handled, the typical tasks performed by workers, and typical environmental conditions such as average ambient temperatures. We interviewed retirees to obtain information on sites where records were not available.

The industrial hygienists used historical industrial hygiene surveys for some of the sites to specify "base estimates" applicable to certain scenarios of job, location, and era present in the work histories. The industrial hygienists then applied factors to adjust the base estimates for scenarios in which no past monitoring data were present. Values for the adjustment factors were derived from physical and chemical first principles—for example, Raoult's law—empirical data, or both. In some instances, in which technology or job tasks changed within the time covered by a work history entry, two (or more) estimates were provided to reflect the relevant changes related to exposure for different eras. The final product of the exposure assessment was an eight hour time weighted average estimate for benzene and total hydrocarbons specific for each job, location, and era.

The validity of the estimating method was tested against data from recent industrial hygiene surveys. This was done by comparing exposure estimates from the estimating procedure with results from industrial hygiene surveys carried out during the relevant period. On average, estimates were within 22% of the measured data, and the measured data were within 95% confidence intervals (95% CIs) placed on the exposure estimates.[27] This was judged as reasonable agreement.

We then applied the exposure estimates to each worker's job and 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-y 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 five, 10, and 15 years,[28] to account for the likely latency period and the potential irrelevance of exposures between diagnosis and death.

The industrial hygienists also added information on presumed dermal exposure to hydrocarbons. This was provided in a ranked manner, and kept as a separate index from the estimated inhalation concentrations. The final scheme consisted of a three level ranking indicating low, medium, and high potential for dermal contact to hydrocarbon fuels. We summed the number of years exposed to low, medium, and high dermal contact jobs for each worker, and also categorised each worker according to his highest potential for dermal contact.

Of the 155 workers, 30 (19%) had some missing work history, and 10 (6%) were missing more than half of their work history. We reviewed each of these 30 workers, and interpolated jobs in which a pattern—that is, all office work, consistent driver, or operator changes—could be assumed. We excluded all workers with > 60% of their work history missing and others in which the known work history showed no clear job progression patterns. After these exclusions, the study population consisted of 29 cases (14 leukaemias, seven multiple myelomas, and eight non-Hodgkin's lymphomas) and 115 controls. Thus, 93% of the population remained in the analysis.

POTENTIAL CONFOUNDERS

In an attempt to measure other factors which might affect the occurrence of leukaemia, multiple myeloma, or non-Hodgkin's lym-

Table 1 Comparison of attributes for lymphohaematopoietic cancer and controls

	Leukaemia		*Multiple myeloma*		*Non-Hodgkin's lymphoma*	
Characteristic	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Age (at case's death)	68·5	68·0	66·5	66·7	60·2	59·8
Age (at first exposure)	28·7	31·7	35·8	30·4	29·1	30·2
Exposure (y)	30·3	28·0	31·5	30·0	21·8	25·1

phoma, we abstracted company medical records. This information was kept separate from the work history information given to the industrial hygienists, so that diagnostic information possibly related to case or control status would not be discovered. This yielded some useful albeit incomplete information on smoking habits, hobbies, previous exposures, previous occupations, diagnostic radiation exposure, and family history of cancer.

STATISTICAL ANALYSES

The dependent variable in all analyses was case or control status. Cases were defined as one of the three lymphohaematopoietic cancer subtypes. The primary independent variable of interest is cumulative exposure to benzene measured in ppm-y. Other independent variables were: total hydrocarbon exposure (ppm-y), dermal exposure to benzene, intensity of exposure to benzene (mean ppm), whether the worker was ever exposed to a job ranked 0·5–1 ppm, or > 1 ppm, and a three levered ranking of socioeconomic status (job title groupings of managerial or professional, clerk or technician, and operators or drivers, etc). Potential confounders included age, smoking, family history of cancer, and the frequency of chest *x* ray films. Other potential confounders such as hobbies, previous occupations, and previous exposures, were not documented consistently in the medical records and could not be evaluated.

Conditional odds ratios (ORs: the odds of exposure in cases relative to controls) were calculated over all matched sets for each type of lymphohaematopoietic cancer with the Mantel-Haenszel technique.[29] This method was chosen because the estimates are not affected by zero cell entries and give a consistent estimate of the ORs common to all matched sets.[30] The EGRET software package[31] was used for calculations. This package uses the algorithm defined in Mehta *et al*[32] to compute exact CIs for the conditional OR.

Table 2 Risk of leukaemia by potential confounders

	Exposed cases (n)	*OR (95% CI)*
Socioeconomic job type:		
Managerial or professional	4	1·00 —
Clerk or technician	4	0·34 (0·03 to 3·10)
Operator or driver	6	0·41 (0·07 to 2·33)
Smoking status:		
Never	0	1·00 —
Ever	7	∞ —
Familial cancer:		
No	8	1·00 —
Yes	5	2·51 (0·51 to 13·3)
Chest *x* ray films (n):		
0–9	7	1·00 —
10–14	3	1·41 (0·18 to 11·2)
15–19	2	0·75 (0·01 to 18·8)
⩾ 20	1	1·73 (0·02 to 156)

We categorised cumulative exposure in various ways to guard against a cut off point effect.[33] We examined results according to the following schemes with the distribution of exposures in the controls: (*a*) the quartile distribution, (*b*) the tertile distribution, (*c*) four categories split at the median, 75th, and 90th percentiles, (*d*) ppm-y split at 0·45, 4·5, and 45 ppm-y (the category boundaries correspond to 0·01, 0·1, and 1 ppm for 45 years), (*e*) ppm-y split at 0·9, 9·9, and 99 ppm-y (the category midpoints correspond to 0·01, 0·1, and 1·0 ppm for 45 years).

We also examined exposure continuously with a logistic regression model.

Additional models incorporated the potential confounders previously discussed which, when included, either changed the sign of the coefficient of the exposure variable, or increased or decreased the coefficient of the exposure variable by > 25%. The few cases prevented detailed analyses for multiple myeloma and non-Hodgkin's lymphoma. For each model, P values for the score statistic (indicating the goodness of fit of the overall model), as well as the Wald statistic (indicating the significance of each variable in the model), were calculated.

Results

Table 1 shows the mean ages (at first exposure and last follow up) and number of years exposed for each lymphohaematopoietic cancer subtype and corresponding controls. As expected, the matched design resulted in cases and controls of comparable ages. On average, the leukaemia cases were three years younger, but cases of multiple myeloma were five years older than their corresponding controls at date of first exposure. Cases were exposed for a similar number of years to the controls; the largest difference was for the cases of non-Hodgkin's lymphoma, who were exposed for about 3·3 years less than their controls.

LEUKAEMIA

Table 2 shows matched ORs for the 14 cases of leukaemia 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 non-calculable CIs. Smoking status was unknown for seven of 14 (50%) cases, and 15 of 55 (27%) controls, thus limiting the conclusions that can be drawn from these data. Of the seven cases who were known smokers, six smoked cigarettes and one smoked pipes and cigars. The number of chest *x* ray films documented in medical records is not strongly related to risk of leukaemia, which is highest in managerial and professional jobs.

Table 3 shows the risk of leukaemia according to cumulative exposure to total hydrocarbons and benzene with no lag and a five year lag. None of the categories show a monotonic trend for risk of leukaemia by cumulative exposure, although there are few cases in each

Table 3 Risk of leukaemia by cumulative exposure (ppm-y) to benzene and total hydrocarbons

	No lag		*Five year lag*	
Exposure	*n*	*OR (95% CI)*	*n*	*OR (95% CI)*
Total hydrocarbons (by quartiles):				
0·0–11·6	4	1·00 —	5	1·00 —
11·7–29·9	5	1·00 (0·07 to 14·8)	5	1·53 (0·17 to 19·16)
30·0–549	3	1·22 (0·09 to 11·6)	2	0·76 (0·05 to 7·92)
550–6721	2	0·55 (0·04 to 5·44)	2	0·50 (0·04 to 4·10)
Benzene (by quartiles):				
0·0–0·17	2	1·00 —	3	1·00 —
0·18–0·49	8	5·06 (0·34 to 295)	7	NC (0·33 to NC)
0·50–7·9	1	0·88 (0·01 to 18·2)	1	1·09 (0·02 to 23·9)
8·0–219·8	3	2·11 (0·10 to 138)	3	1·81 (0·17 to 25·7)
Benzene (by tertiles):				
0·0–0·22	3	1·00 —	4	1·00 —
0·23–5·49	8	4·37 (0·72 to 48·6)	7	2·15 (0·42 to 15·00)
5·50–219·8	3	0·92 (0·10 to 11·2)	3	0·86 (0·10 to 7·34)
Benzene (by median, 75th, and 90th percentiles):				
0·0–0·49	10	1·00 —	10	1·00 —
0·50–7·99	1	0·22 (0·0 to 1·82)	1	0·21 (0·0 to 1·71)
8·0–19·99	1	0·42 (0·01 to 3·95)	1	0·53 (0·01 to 5·80)
20·0–219·8	2	0·96 (0·09 to 6·81)	2	0·96 (0·09 to 6·81)
Benzene (by regulatory standards):				
0·0–0·45	10	1·00 —	10	1·00 —
> 0·45–4·5	1	0·43 (0·01 to 4·05)	1	0·43 (0·01 to 4·05)
> 4·5–45	1	0·16 (0·0 to 1·32)	1	0·16 (0·0 to 1·32)
> 45	2	1·47 (0·16 to 13·1)	2	1·47 (0·16 to 13·1)
Benzene (by regulatory standards):				
0·0–0·90	10	1·00 —	10	1·00 —
> 0·90–9·9	2	0·43 (0·04 to 2·36)	1	0·40 (0·04 to 2·19)
> 9·9–99·9	1	0·48 (0·01 to 4·55)	1	0·48 (0·01 to 4·55)
> 99·9	1	1·03 (0·02 to 20·3)	2	1·03 (0·02 to 20·3)

NC = Not calculable.

category. For cumulative exposure to benzene, the highest risks of leukaemia are found in the second quartile (OR 5·06) and middle tertile (OR 4·37) with no lag, but the ORs decrease in the highest quartiles and tertile. The cumulative exposure to benzene with a five year lag is not calculable in the 0·18–0·49 exposure category, but is likely to be higher than in the other categories, again resulting in a non-monotonic response.

Table 3 shows the highest exposure categories of cumulative exposure to benzene, > 5·5, 8, 20, 45, and 99·9 (up to 220 ppm-y) which result in ORs of 0·92, 2·11, 0·96, 1·47, and 1·03, respectively for no lag and 0·86, 1·81, 0·96, 1·47, and 1·03, respectively, for the five year lag. All five of the categories suggest risks consistent with unity for the highest exposure group, although the confidence intervals are extremely wide.

Table 4 shows the risk of leukaemia according to other exposure variables. Risk did not increase in a consistent way for the mean intensity over a worker's career, for workers ever exposed to 0·5–1 ppm or over 1 ppm, nor by a worker's highest ranked probability of dermal exposure.

Cumulative exposure to benzene did not show a strong relation with leukaemia when regressed separately (OR 1·002/ppm-y, $P < 0·77$). The P value for the score statistic ($P < 0·76$) indicates that this model does not fit the data well (table 5, model 1). We also added separate terms into this model for an employee's mean intensity of exposure and total duration of exposure. This manoeuvre produced a non-interpretable result; exposure intensity (OR 2·27/ppm) and duration (OR 1·07/year) showed a positive relation, yet the OR for cumulative exposure fell below 1·0 (table 5). A model with only duration of exposure showed a coefficient of 1·06/year exposed with a 95% CI 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 duration of exposure was most closely associated with leukaemia, whereas cumulative exposure to benzene and mean intensity of exposure to benzene did not explain risk of leukaemia.

Next we examined whether exposure above a certain level was related to risk of leukaemia,

Table 4 Risk of leukaemia by alternative benzene exposure variables

	No lag		*Five year lag*	
	n	*OR (95% CI)*	*n*	*OR (95% CI)*
Intensity of benzene (mean ppm):				
0·0–0·01	9	1·00 —	10	1·00 —
> 0·01–0·19	2	0·88 (0·08 to 6·47)	1	0·39 (0·01 to 4·14)
0·20–0·49	1	0·19 (0·0 to 1·55)	1	0·18 (0·00 to 1·39)
0·50–6·16	2	0·96 (0·09 to 6·81)	2	0·96 (0·09 to 6·81)
Maximum intensity of benzene (ppm):				
< 0·5	10	1·00 —	10	1·00 —
0·5–0·99	0	0·0 (0·0 to 7·57)	0	1·00 (0·0 to 7·57)
⩾ 1·0	4	1·02 (0·21 to 4·26)	4	1·02 (0·21 to 4·26)
Maximum rank of dermal exposure:				
Low	8	1·00 —		
Medium	4	0·61 (0·12 to 2·51)		
High	2	0·47 (0·04 to 2·86)		

Table 5 Conditional logistic regression modelling results for leukaemia and exposure to benzene

Model number	*Model P value**	*Variable*	*OR (95% CI)*	*Variable P value†*
1	0·76	Cumulative exposure to benzene	1·002 (0·989 to 1·015)	0·77
2	0·28	Cumulative exposure to benzene	0·980 (0·933 to 1·030)	0·43
		Intensity (mean)	2·271 (0·426 to 12·098)	0·34
		Duration	1·069 (0·990 to 1·155)	0·09
3	0·50	Intensity	1·171 (0·729 to 1·880)	0·51
4	0·10	Duration	1·061 (0·985 to 1·144)	0·12
5	0·70	Years at ⩾ 0·5 ppm	1·015 (0·940 to 1·095)	0·71
6	0·93	Years at ⩾ 1·0 ppm	1·004 (0·921 to 1·094)	0·93
7	0·38	Years at low dermal	1·061 (0·984 to 1·144)	0·14
		Years at medium dermal	1·054 (0·954 to 1·164)	0·30
		Years at high dermal	1·022 (0·895 to 1·167)	0·75

*Based on score statistic.
†Based on Wald χ^2 statistic.

Table 6 Conditional logistic modelling results for leukaemia for cases and controls with known values for potential confounders

Model number	*Model P value**	*Variable*	*OR (95% CI)*	*Variable P value†*
1	0·11	Family history of cancer	5·53 (0·54 to 56·6)	0·15
2	0·02	Family history of cancer	14·0 (1·04 to 188·0)	0·05
		Ever smoked cigarettes	8·89 (0·66 to 119·0)	0·10
3	0·06	Family history of cancer	11·5 (0·83 to 160·0)	0·07
		Ever smoked cigarettes	6·93 (0·48 to 100·0)	0·16
		Cumulative benzene exposure	0·97 (0·82 to 1·15)	0·72
4	0·06	Family history of cancer	11·2 (0·81 to 119·0)	0·07
		Ever smoked cigarettes	7·99 (0·55 to 115·0)	0·13
		Intensity	0·34 (0·0 to 26·5)	0·63
5	0·03	Family history of cancer	18·8 (1·33 to 265·0)	0·05
		Ever smoked cigarettes	15·1 (0·61 to 376·0)	0·12
		Duration	1·08 (0·95 to 1·22)	0·25

*Based on score statistic.
†Based on Wald χ^2 statistic.

Table 7 Multiple myeloma risk by potential confounders

	n	*OR (95% CI)*
Socioeconomic job type:		
Managerial or professional	0	1·00 —
Clerk or technician	3	∞ —
Operator or driver	4	∞ —
Smoking status:		
Never	0	1·00 —
Ever	4	∞ —
Familial cancer:		
No	5	1·00 —
Yes	1	0·51 (0·01 to 7·81)
Chest *x* ray films (n):*		
0–9	2	1·00 —
10–14	3	1·67 (0·14 to 25·6)
15–19	1	0·68 (0·01 to 16·2)
⩾ 20	0	0·0 (0·0 to 11·0)

*Conditional ORs not calculable, unconditional ORs shown.

with the number of years worked at an intensity of ⩾ 1 ppm and the number of years worked > 0·5 or 1 ppm as independent variables. Neither of these variables explained the risk of leukaemia adequately, nor did they fit the data well (table 5, models 5 and 6). The coefficient for years > 0·5 ppm (1·02) was slightly greater than the coefficient for years > 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/y, P < 0·14) than a high probability job (OR 1·02/y, P < 0·75).

As both cigarette smoking and a family history of cancer were related to leukaemia in the Mantel-Haenszel analyses, we constructed a series of models among cases and controls who had known values for these variables. We then added cumulative exposure, intensity of exposure, and years exposed to these models. As these models are performed on a different set of cases and controls, the results should not be compared with those in table 5. Table 6 shows results with only the potential confounders (an employee's family history of cancer and whether he ever smoked cigarettes) in the model, as well as models which added exposure to benzene. Adding any form of exposure to benzene did not improve the model, nor was the exposure variable significant. Given that there were some missing data on the confounders, especially smoking status, the results cannot be interpreted strongly. However, there was a suggestion that a family history of cancer and cigarette smoking may be relevant risk factors for leukaemia in these workers.

The original cohort study reported a standardised mortality ratio (SMR) for leukaemia of 3·35 based on five cases who were ever employed as tanker drivers.[23] As discussed in the original report, however, that study was based on computerised work histories,

Table 8 Risk of multiple myeloma by exposure to benzene and total hydrocarbons

	No lag		*Five year lag*	
Exposures	*n*	*OR (95% CI)*	*n*	*OR (95% CI)*
Total hydrocarbons:*				
0·0–11·6	0	1·00 —	0	1·00 —
11·7–29·9	3	1·00 —	3	1·00 —
30·0–549	1	0·78 (0·01 to 15·6)	1	1·41 (0·02 to 118)
550–6721	3	0·79 (0·09 to 6·86)	3	0·86 (0·10 to 7·48)
Benzene (ppm-y):				
0·0–0·49	3	1·00 —	3	1·00 —
0·50–7·99	1	0·39 (0·01 to 5·66)	1	0·52 (0·01 to 12·06)
8·00–19·99	1	0·60 (0·01 to 7·83)	1	0·65 (0·01 to 8·72)
20·0–219·8	2	1·22 (0·07 to 20·0)	2	1·35 (0·08 to 23·04)
Benzene (ppm-y):				
0·0–0·90	3	1·00 —	3	1·00 —
> 0·90–9·9	1	0·44 (0·01 to 11·2)	1	0·44 (0·01 to 11·2)
> 9·9–99·9	3	1·44 (0·16 to 12·2)	3	1·44 (0·16 to 12·2)
> 99·9	0	0·0 NC	0	0·0 NC
Intensity of benzene (mean ppm):				
0·0–0·01	2	1·00 —	2	1·00 —
> 0·01 to 0·19	2	1·00 (0·07 to 14·8)	2	1·00 (0·07 to 14·8)
0·20–0·49	1	1·00 (0·01 to 78·5)	1	1·00 (0·01 to 78·5)
0·50–6·16	2	0·91 (0·06 to 14·0)	2	0·91 (0·06 to 14·0)
Maximum intensity of benzene (ppm):				
< 0·5	3	1·00 —	3	1·00 —
0·5–0·99	0	0·0 (0·0 to 117)	0	0·0 (0·0 to 117)
⩾ 1·0	4	1·81 (0·27 to 13·7)	4	1·81 (0·27 to 13·7)

*ORs for first two quartiles are combined.
NC = Not calculable.

Table 9 Risk of non-Hodgkin's lymphoma by potential confounders

	n	OR (95% CI)
Socioeconomic job type:		
Managerial or professional	1	1·00 —
Clerk or technician	4	4·47 (0·26 to 358)
Operator or driver	3	0·79 (0·03 to 57·0)
Smoking status:		
Never	0	1·00 —
Ever	6	∞ —
Familial cancer:		
No	8	1·00 —
Yes	0	0 (0·0 to 2·78)
Chest *x* ray films (n):		
0–9	5	1·00 —
10–14	1	0·63 (0·01 to 6·90)
15–19	2	0·85 (0·01 to 19·7)
⩾ 20	0	0·0 (0·0 to 117)

whereas the present study was based on more complete hard copy records. When drivers were defined from these more complete records, five leukaemia cases and 10 controls were classified as drivers. The crude OR for tanker drivers is 2·50, reasonably close to the original SMR of 3·35. A logistic model restricted to tanker drivers who were cases and their corresponding controls produced an OR of 1·092 ($P < 0·36$) for cumulative exposure to benzene.

MULTIPLE MYELOMA

Table 7 shows the risk of multiple myeloma by potentially confounding variables. By contrast with the leukaemia results, no cases of multiple myeloma worked as managers or professionals for most of their career. Again, all cases for which smoking information was available did smoke, although there were three cases (43%) and seven controls (25%) with unknown smoking history. Neither a family history of cancer nor a greater number of chest *x* ray films was related to occurrence of multiple myeloma in these data.

Table 8 shows the risk of multiple myeloma by various exposure variables and no lag, or a five year lag. For brevity, we have not shown all the cumulative exposure schemes, although these results were similar. None of the exposure category schemes suggest a strong relation with multiple myeloma. Four of the seven cases worked in a job with > 1 ppm exposure, for an OR of 1·81, although the 95% CI shows that the result is imprecise.

The few cases of multiple myeloma prevented an accurate characterisation of risk through logistic modelling. However, the number of years spent in a job ranked at ⩾ 1·0 ppm suggested an OR of 1·10/year exposed, although the result did not reach significance ($P < 0·20$). The model could not adequately incorporate smoking, as all cases with information on smoking available smoked.

NON-HODGKIN'S LYMPHOMA

Table 9 shows the risk of non-Hodgkin's lymphoma by potential confounders. Half of the cases were employed as clerks or technicians; this produced a relatively high but unstable OR of 4·47. Again, all of the cases with known histories of smoking smoked, although information on smoking was not recorded for two cases (25%) and seven controls (22%). No cases reported a family history of cancer, and most of the cases had fewer than 10 chest *x* ray films documented in their medical records.

The exposure of cases of non-Hodgkin's lymphoma to benzene and total hydrocarbons was similar to that of their matched controls (table 10). A relatively high but imprecise OR of 5·85 was found for workers exposed to 0·5–1 ppm benzene at some point in their work history. However, only one case was exposed to > 1 ppm, resulting in an OR of 0·54.

Again, there were too few cases of non-Hodgkin's lymphoma to accurately characterise risk through logistic modelling. Like cases of multiple myeloma, all cases of non-Hodgkin's lymphoma for whom smoking history was known did smoke, so a model could not adequately incorporate the effect of smoking on risk of non-Hodgkin's lymphoma.

Table 10 Risk of non-Hodgkin's lymphoma by exposure to benzene and total hydrocarbons

	No lag		Five year lag	
Exposures	*n*	*OR (95% CI)*	*n*	*OR (95% CI)*
Total hydrocarbons (ppm-y):				
0·0–11·6	3	1·00 —	3	1·00 —
11·7–29·9	2	1·73 (0·02 to 137)	2	1·73 (0·02 to 137)
30·0–549	2	0·0 (0·0 to 5·27)	2	0·52 (0·01 to 12·1)
550–6721	1	1·22 (0·01 to 137)	1	1·22 (0·01 to 137)
Benzene (ppm-y):				
0·0–0·49	4	1·00 —	4	1·00 —
0·50–7·99	3	1·21 (0·16 to 8·07)	3	1·44 (0·17 to 12·0)
8·00–19·99	1	1·14 (0·02 to 22·1)	1	1·14 (0·02 to 22·1)
20·0–219·8	0	0·0 (0·0 to 27·6)	0	0·0 NC
Benzene (ppm-y):				
0·0–0·90	6	1·00 —	6	1·00 —
> 0·90–9·9	1	0·30 (0·01 to 3·28)	1	0·33 (0·01 to 4·14)
> 9·9–99·9	1	0·85 (0·01 to 19·7)	1	0·85 (0·01 to 19·7)
> 99·9	0	0·0 NC	0	0·0 NC
Intensity of benzene (mean ppm):				
0·0–0·01	4	1·00 —	4	1·00 —
> 0·01 to 0·19	2	1·25 (0·10 to 11·3)	2	1·87 (0·13 to 26·9)
0·20–0·49	2	0·97 (0·08 to 7·58)	2	0·93 (0·08 to 7·19)
0·50–6·16	0	0·0 (0·0 to 10·7)	0	0·0 (0·0 to 10·7)
Maximum intensity of benzene (ppm):				
< 0·5	5	1·00 —	5	1·00 —
0·5–0·99	2	5·85 (0·30 to 354)	2	5·85 (0·30 to 354)
⩾ 1·0	1	0·54 (0·01 to 5·94)	1	0·54 (0·01 to 5·94)

NC = Not calculable.

Discussion

This study was conducted to follow up a previously reported excess of leukaemia in tanker drivers[23] and provide new risk information for lower exposure to benzene. There is little direct information on common exposure to predominantly < 1 ppm benzene in modern occupational environments. However, some models predict that excess cases of cancer will occur at these concentrations.[4]

For the three lymphohaematopoietic cancer types studied, we did not find a dose response relation for any of five different classifications of cumulative exposure to benzene, with lag periods of 0, 5, 10, and 15 years. Alternate exposure variables, including average exposure intensity, years of exposure at > 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 statistical goodness of fit among the models with only exposure variables. These results are most consistent with insufficient power to detect a small effect, or a lack of effect for low exposure to benzene (mainly 0·1–1·0 ppm).

For leukaemia, there was some suggestion that non-occupational risk factors (smoking and a family history of cancer) may be important. However, these data were not present for all workers in the study, and need to be interpreted cautiously.

The fact that duration of exposure was more strongly related to occurrence of leukaemia than either intensity of exposure or cumulative exposure can be interpreted in several ways. One interpretation is that prolonged exposure, resulting in repeated insults to stem cells, can finally either trigger or progress neoplastic changes, regardless of exposure intensity. There are few data to support or refute this view, as it would require study of multiple populations exposed to low doses and long durations. Another interpretation is that duration of exposure is easy to classify based on employment records, although intensity of exposure is more difficult. Thus, the surrogate for duration of exposure might be relatively good. However, this would imply that there is no additional value in the intensity estimates, which is doubtful. Specifically, Armstrong *et al* reported that estimates of exposure intensity differed from measured values by about 20% in this study population.[27] If this were the true level of misclassification in intensity estimates, it is likely that moderate cumulative exposure relations should still be obvious. Finally, the finding could be regarded as the chance result of examining many different exposure variables, and having no biological relevance.

For most logistic models, the P value for the score statistic indicates a model fit which is not significant. This is consistent with the lack of an exposure effect at these levels, the small study size, or a possible violation of model assumptions. A logistic model assumes that risk increases exponentially per unit of exposure, and that the independent variables are not collinear. Some of the models clearly violate the assumption that independent variables are not collinear—for example, models with cumulative exposure and duration of exposure entered simultaneously—although one could argue that the model is fairly robust to violations in this assumption. Probably more importantly, the categorical results do not suggest an exponential (or even monotonic) increase in risk, and this may explain the relatively poor fits obtained through the logistic models.

The original cohort[23] reported an SMR for leukaemia of 3·35 in tanker drivers. The present study, which used more complete work histories, confirmed that tanker drivers were more prevalent in the case series. When a logistic model restricted to cases of tanker drivers and their matched controls was run, an OR of 1·09 was found for cumulative exposure to benzene. As expected, this OR is higher than the comparable OR of 1·002 for all cases and controls, as tanker drivers were one of the more highly exposed job titles in this study. However, other jobs—such as loaders, warehousemen, and plantmen—were also relatively highly exposed, and were more prevalent in controls than cases. This argues that either the pattern of exposure to benzene in tanker drivers results in a unique risk, or that factors other than exposure to benzene were associated with the original finding.

Subpopulations represented in other studies may have been exposed to similar benzene concentrations as those in our study. The following risks pertain to concentrations < 83 ppm-y, or about 2 ppm for 40 years. Wong[18] reported slight deficits in SMRs of 0·97 (0–14·9 ppm-y), and 0·78 (15–59·9 ppm-y). Bond *et al*[19] reported an SMR of 1·67 for workers exposed to < 42 ppm-y, but found no cases in those exposed between 42 and 83 ppm-y. Finally, Paxton *et al*[15] reported SMRs of 1·33 in workers exposed to ⩽ 5 ppm-y, and 1·79 in workers exposed to 5–50 ppm-y. The present study, along with these other studies, suggests that risks are either small or non-existent for < 50 ppm-y. However, these data cannot be used to rule out a risk at these concentrations, as the risk estimates are based on relatively few workers.

For higher exposures (generally > 60 ppm-y), higher risks have been documented. Paxton *et al*[15] reported SMRs of 2·80 for exposures of 50–500 ppm-y, Wong[18] reported an SMR of 2·76 for ⩾ 60 ppm-y, and Bond *et al*[19] reported an SMR of 2·50 for > 83 ppm-y. Thus, it could be argued that exposures in this range produce a two to threefold risk of leukaemia. The present study is not inconsistent with these results, as ORs of 1·47 are found for exposures > 45 ppm-y, and 1·03 for exposures > 99·9 ppm-y. Although these ORs are somewhat lower than the SMRs previously reported, the CIs include the previously reported results. Although cumulative exposures are similar, differences in the intensity and duration components of cumulative exposure may have an impact on the various risk estimates.

With a background lifetime incidence of 0·007 for leukaemia and the results from the unlagged cumulative exposure model, these

data suggest that an exposure of 1 ppm over a working career results in 0·6 excess deaths/1000 workers. This result is similar to the "preferred analysis" of 0·5 excess deaths found by Brett *et al.*[16] Crump presented various models that predict 0·02–5 excess deaths/1000 workers.[6]

Previous epidemiological studies in which exposure to benzene has been measured have been limited by the few observed cases of leukaemia. The most studied worker cohort now consists of 15 cases of leukaemia, including one woman.[15] Other cohorts had only five and six cases of leukaemia.[19 18] Thus, the 14 cases of leukaemia represented in this study is a significant contribution, especially for exposures < 50 ppm-y. The nested case control approach would seem to be the most practical design for future study of this question in cohorts already assembled, as exposure estimation is by far the most time and resource intensive task involved. Thus, one of the strengths of this study is that it provides the most study material for a given resource investment.

This study attempted to measure the influence of potential confounding variables—such as radiation exposure, previous occupational and recreational exposures, tobacco use, and a history of familial cancer. This effort was not totally successful, due to the lack of historical information recorded in the company medical records. The effect of unknown smoking histories can be investigated in these data. For leukaemia, the seven cases (50%) and 15 controls (27%) who lacked data on smoking were randomly assigned to smokers and non-smokers. When the simulated values for smoking were combined with the known histories on smoking, 128 possible values for the crude OR for smoking resulted. The median value of this OR was 2·0, and 75% of the estimated ORs were > 1·0. Thus, despite incomplete information, this study indicates the possibility of the relevance of smoking on leukaemia and other lymphohaematopoietic cancer. For leukaemia, the suggestion is supported by several recent studies,[35–37] although one recent study did not find an association.[38] Evidence is also mounting that smoking increases the risk of non-Hodgkin's lymphoma.[39–42] The evidence for a relation between multiple myeloma and smoking is much weaker, due to the large, negative study in American veterans.[43]

There was also a suggestion that a family history of cancer could be a risk factor for leukaemia. However, unlike smoking histories, this measure came primarily from pre-employment physical examinations. Thus, the findings must be interpreted with caution. Leukaemia has been related to a positive family history of other cancers, but not consistently. Tajima[44] found an increased incidence of T cell leukaemia in people with a family history of any cancer, which was stronger in those with a family history of haematopoietic malignancies. Our measure of family history included any cancers in parents, siblings, and children, and only two of the cancers were leukaemia. One study has reported that with a family history of any cancer[45] a significant risk ratio of 2·5 for multiple myeloma exists but our study did not replicate these findings.

The interpretation of this study is hindered by its size. For example, if exposure to benzene caused a twofold increase in risk for (say) the > 45 ppm-y category, this study would have only a 16% chance of detecting this at a 20% exposure rate and a 5% significance level. For 80% power, 90 cases would be needed. We did not regard this as grounds for dismissing this study, simply because we think that few single studies ever provide definitive evidence of a risk or lack of risk. The question must be viewed as a long term one, and we think that this study is an initial step in assessing the extent of risks for longer term lower exposure to benzene.

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