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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

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Abstract

***Objectives*—To investigate the risk of leukaemia in workers in the petroleum distribution industry who were exposed to low levels of benzene.**

***Methods*—From the cohort of distribution workers, 91 cases were identified as having leukaemia on either a death certificate or on cancer registration. These cases were compared with controls (four per case) randomly selected from the cohort, who were from the same company as the respective case, matched for age, and alive and under follow up at the time of case occurrence. Work histories were collected for the cases and controls, together with information about the terminals at which they had worked, fuel compositions, and occupational hygiene measurements of benzene. These data were used to derive quantitative estimates of personal exposure to benzene. Odds ratios (OR) were calculated conditional on the matching, to identify those variables in the study which were associated with risk of leukaemia. Examination of the potential effects of confounding and other variables was carried out with conditional logistic regression. Analyses were carried out for all leukaemia and separately for acute lymphoblastic, chronic lymphocytic, acute myeloid and monocytic, and chronic myeloid leukaemias.**

***Results*—There was no significant increase in the overall risk of all leukaemias with higher cumulative exposure to benzene or with intensity of exposure, but risk was consistently doubled in subjects employed in the industry for > 10 years. Acute lymphoblastic leukaemia tended to occur in workers employed after 1950, who started work after the age of 30, worked for a short duration, and experienced low cumulative exposure with few peaks. The ORs did not increase with increasing cumulative exposure. The risk of chronic lymphocytic leukaemia seemed to be related most closely to duration of employment and the highest risk occurred in white collar workers with long service. These workers had only background levels of benzene exposure. There was no evidence of an association of risk with any exposure variables, and no evidence of an increasing risk with increasing cumulative exposure, mean intensity, or maximum intensity of exposure. The patterns of risk for acute myeloid and monocytic leukaemia were different from those of the lymphoid subgroups, in which duration of employment was the variable most closely related to risk. Risk was increased to an OR of 2·8 (95% confidence interval (95% CI) 0·8 to 9·4) for a cumulative exposure between 4·5 and 45 ppm-years compared with < 0·45 ppm-years. For mean intensity between 0·2 and 0·4 ppm an OR of 2·8 (95% CI 0·9 to 8·5) was found compared with < 0·02 ppm. Risk did not increase with cumulative exposure, maximum intensity, or mean intensity of exposure when treated as continuous variables. Cases of acute myeloid and monocytic leukaemia were more often classified as having peaked exposures than controls, and when variables characterising peaks, particularly daily and weekly peaks, were included in the analysis these tended to dominate the other exposure variables. However, because of the small numbers it is not possible to distinguish the relative influence of peaked and unpeaked exposures on risk of acute myeloid and monocytic leukaemia. There was no evidence of an increased risk of chronic myeloid leukaemia with increases in cumulative exposure, maximum intensity, mean intensity, and duration of employment, either as continuous or categorical variables. Analyses exploring the sensitivity of the results to the source and quality of the work histories showed similar patterns in general. However, no increases in ORs for categories of cumulative exposure were found for acute myeloid and monocytic leukaemia in the data set which included work histories obtained from personnel records still in existence, although numbers were reduced. Analyses excluding the last five and 10 years of exposure showed a tendency for ORs to reduce for chronic lymphocytic leukaemia and chronic myeloid leukaemia, and to increase for acute myeloid and monocytic leukaemia. Limitations of the study include uncertainties and gaps in the information collected, and small numbers in subcategories of exposure which can lead to wide CIs around the risk estimates and poor fit of the mathematical models.**

***Conclusions*—There is no evidence in this study of an association between exposure to benzene and lymphoid leukaemia, either acute or chronic. There is some suggestion of a relation between exposure**

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to benzene and myeloid leukaemia, in particular for acute myeloid and monocytic leukaemia. Peaked exposures seemed to be experienced for this disease. However, in view of the limitations of the study, doubt remains as to whether the risk of acute myeloid and monocytic leukaemia is increased by cumulative exposures of < 45 ppm-years. Further work is recommended to review the work histories and redefine their quality, to explore the discrepancies between results for categorical and continuous variables, and to develop ranges around the exposure estimates to enable further sensitivity analyses to be carried out.

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In this paper we present the results of a nested case-control study, in which cases and controls were identified from a cohort of petroleum distribution workers, to investigate the risk of leukaemia associated with exposure to benzene. Quantitative benzene exposure was estimated for all cases and controls. The influence of possible confounding variables was explored and sensitivity analyses were carried out to assess the effects of possible misclassification of exposure.

There have been many studies reporting the carcinogenicity and haematotoxicity of benzene at high exposures, both in animal and epidemiological studies.[1 2] Benzene has been associated with leukopenia, thrombocytopenia, and aplastic anaemia[3–5]; the exposures responsible being generally well in excess of 25 ppm. The association of leukaemia with high exposures to benzene has also been reported, with acute myeloid leukaemia being most commonly described.[3 5–8] Evidence from human studies linking benzene to leukaemias other than acute myeloid is contadictory and inconsistent, with, for example, chronic lymphocytic leukaemia comprising only a small percentage (of the order of 2%) of the leukaemias found in these studies.[6 9–11]

Smokers are thought to be at an increased risk of leukaemia, in particular myeloid.[12] Cigarette smoke contains measurable quantities of benzene. Wallace[13] found smoking to be the single most important source of benzene exposure in a general population, with the average smoker (32 cigarettes a day) taking in about 1·8 mg benzene a day.

Recent interest has focused on the derivation of quantitative estimates of the dose-response relation between benzene exposure and leukaemia, with an emphasis on evaluating the risk at low exposures. Two studies examined the risk in chemical workers,[14–17] and several others have carried out risk assessments of workers exposed to benzene in the rubber hydrochloride (Pliofilm) manufacturing industry.[18–21] Most critiques of the risk assessment by Rinsky *et al*[18] have reassessed these projections, for example with different assumptions, exposure estimates, or mathematical models, and have not used new data.[22–24] All the current risk assessments have been based on very small numbers of leukaemia deaths—for example, 14 in the Pliofilm study—and have used extrapolation to assess risk at low concentrations of benzene—for example, < 5 parts per million (ppm).

These studies were carried out on chemical workers for whom benzene was the main solvent used. None of these risk assessments were based on employees in the petroleum industry, where daily exposures are generally well below 5 ppm, and for whom potential exposure is from a mixture of volatile organic compounds. Four recent cohort studies of oil distribution workers have reported mortalities. These are the Institute of Petroleum study in the United Kingdom,[25 26] the American Petroleum Institute study[27] in the United States, a Canadian study,[28] and the Australian Health Watch study.[29] Bisby[29] has also reported cancer incidence in the Australian study.

A finding common to all these studies is some excess of leukaemia and other cancers of the haematopoietic system. In the United Kingdom study, in which 23 300 men from four oil companies were followed up for nearly 40 years, the standardised mortality ratio (SMR) for the total population of the distribution centres for all leukaemias was 108 (95% confidence interval (95% CI) 83 to 140) and for acute myeloid leukaemia was 121 (95% CI 78 to 179). For those whose last job title was driver the corresponding figures were 125 (95% CI 83 to 181) and 155 (95% CI 82 to 265). The American study found an SMR of 89 (95% CI 59 to 129) for all leukaemias and an SMR of 151 for acute myeloid leukaemia (95% CI 80 to 257). The Canadian study found an SMR of 101 for all leukaemias (95% CI 40 to 208), and an SMR of 335 (95% CI 108 to 781) for all leukaemias in drivers. The Australian study found an SMR of 220 for all leukaemias (95% CI 70 to 500), and a standardised incidence ratio (deaths plus incidence) of 360 (95% CI 170 to 660).

The American, Canadian, and Australian studies have carried out nested case-control analyses of leukaemia and the other lymphatic cancers.[29–31] The American case-control study estimated exposure to total hydrocarbons only. The Canadian and Australian studies estimated exposure to both benzene and total hydrocarbons, but the Canadian study produced a quantitative estimate and the Australian simply ranked exposures. The American study found no increased risk or exposure-effect relation between exposure to total hydrocarbons and leukaemia. The Australian study found an increasing risk of lymphohaematopoietic cancer with increasing exposure to benzene. Schnatter *et al*, in the Canadian study,[30] found no dose response relation between all leukaemias and benzene intensities, which were primarily in the 0·1 and 1·0 ppm range. The strongest risk factors were smoking, a family history of cancer, and duration of employment.

Our paper presents the result of a nested case-control study from the United Kingdom cohort.

Method

The cases were men from the United Kingdom oil distribution cohort who (*a*) died before 1 January 1993 with a mention of leukaemia (either underlying or contributory cause) on the death certificate or, (*b*) had a cancer registration of leukaemia (international classification of diseases revision nine (ICD-9) codes 204–208). Altogether 91 cases were identified, 88 from death certificates with or without cancer registration and three from cancer registration alone. Of the 88 identified from death certificates, 75 had leukaemia as an underlying cause of death and 13 had leukaemia as a contributory cause of death. Cancer registrations were also received for 40 of the 88 deaths (cancer registrations were not available before 1971). In 11 of these there were differences between the diagnoses on the death certificates and cancer registration, in most cases the cancer registration was less specific—for example, "other leukaemia" rather than "acute leukaemia". The more specific diagnosis was adopted for analysis. Permission to contact histopathology departments to ask for histological confirmation of the diagnoses was received from the Office Population Censuses and Surveys (OPCS). Up to the present time confirmation of the diagnosis has been received for 38 of the cases, with no histology record available for a further 31. Histology reports have been received for nine of the 11 cases for whom differences were found between the diagnosis on the death certificate and on the cancer registration, all of them confirming the more specific diagnosis chosen from the death certificate for analysis. None of the histology reports for other cases resulted in a change of diagnosis for the study.

Four controls per case were selected as being both informative and efficient for the power of the study.[32] The controls were randomly selected from all men from the same oil company with a year of birth within three years either side of the date of birth of the case. So that the controls should be at risk of the disease at the time of case occurrence, the controls were selected from people alive and under follow up at the time of case occurrence (date of death for the cases identified from death certificates, and date of diagnosis for those identified from cancer registration only). Two controls were erroneously selected who were not under follow up on the relevant date. These have been excluded from the study. Also, during preparation for an external quality audit of the study, it was discovered that eight of the controls for the four cases from one company had been incorrectly matched for age. These controls have also been excluded from the analysis. This has resulted in one case, a patient with acute myeloid leukaemia, also being excluded from the analyses. After the discovery of this error the algorithm for selecting controls was rechecked and found to be correct. There was no evidence that this error occurred in other companies.

Six key areas were identified for which data had to be collected to provide quantitative exposure estimates, and to provide data on other variables which might potentially influence exposure. These related to: (*a*) work histories, (*b*) job descriptions, (*c*) terminal histories, (*d*) fuel compositions, (*e*) occupational hygiene measurements, and (*f*) possible confounding variables—such as smoking habits.

When the data were collected for the original distribution cohort only the last job title and location for those who had left and the current job title and location for those still working on 31 December 1975 were recorded. For the purpose of estimating exposure over the working life of each case and control a work history was required—that is, dates of starting and leaving each job, and the site. This was carried out blind to the subject's case or control status. The main source of information on work history in this study was company personnel records. However, their availability varied according to company record retention policies. For those study members for whom a personnel record could not be found or was incomplete, the information was obtained from a variety of sources including pension records, medical records, and interviews with retired or long service staff.

When a work history was incomplete, it was necessary to make certain assumptions or assign date values—for example, the mid-month or mid-year was used if days or months were unknown, and a date midway between known dates was taken if there were gaps in the dates for a change in either a job or location. When a work history was largely unavailable a typical work history was used. When assumptions were made these were flagged on the data base. As a measure of the quality of the work history, each study member was assigned a "job confidence" code of 1, 2, or 3, where code 1 indicated a complete work history, or one for which last job only was known, but the duration of employment was < 10 years, code 2 indicated a partially complete work history for which an assumption had been made, and code 3 indicated a poor work history, and was assigned when only the last job title was known, this was a supervisory or managerial post and the duration of employment was over 10 years.

None of the cases and only eight (2%) of the controls had job confidence score 3, the poor category. The partially complete classification was assigned to 21% of the work histories overall (26% cases, 19% controls).

Altogether 315 terminals were identified from the work histories, over 95% of which were closed by the time of data collection. A detailed proforma was developed for collecting information on the terminals over the complete period of the terminal's existence. Data collected included, for broad periods, approximate numbers of staff, the range of products stored, sources and methods of supply, storage capability, distribution practices for products

handled at the terminal, information on working practices for different tasks carried out around the terminal, and use of protective equipment by all staff. All terminals still open were visited to obtain these data. Retired and long service employees were interviewed about closed sites. Other sources of information included site plans, booklets, photographs, company magazines, and other material available from company libraries, and property and engineering departments. A major source of archive material on all aspects of the oil industry was the British Petroleum (BP) Archive held at Warwick University.

Data on other variables which might influence risk of leukaemia—such as smoking habits and jobs held before work in the oil industry—were also sought. Information on smoking was occasionally available from medical records and information on previous jobs was available from some personnel records. To gain information on the terminals retired or long service employees were interviewed and they were also asked if they could recall the smoking habits of relevant study members. However, the resulting data on smoking was sparse.

Data collection for fuel compositions and occupational hygiene measurements, and the method of developing quantitative exposure estimates relating to the work histories of each study member is described in detail in a separate paper,[33] and is therefore only briefly given here. The method used for this study was an extension of that developed for the Canadian case-control study.[30] A representative set of benzene measurements (referred to as base estimates), which were also well characterised—that is, had values for factors considered to affect exposure—was assembled for different tasks in the distribution centres. The base estimate exposure measurements (ppm) were time weighted to eight hours (8-hour TWA). These base estimates were then adjusted to take account of changes in factors which were considered to affect exposure to give a workplace estimate. The six adjustment factors used were job activity (to adjust for known differences in tasks from those covered in the base estimate), number of loads handled per day, loading technology (in particular to adjust for differences between top splash and top submerged loading), percentage of benzene in the fuel, product mix (to adjust for handling products other than gasolines—such as diesel—during the same work), and air temperature.

For some terminals the data on individual employees were insufficient to indicate whether drivers were assigned to road tankers carrying black oils—such as, heating oils—or white oils—such as motor gasolines, (black oils do not contain benzene). Two workplace estimates were derived when this arose, and a probability based on the product mix at the terminal was assigned. The workplace estimates were derived for each line of a work history, the base estimate being multiplied by the six modifying factors. The adjusted estimate for each job and site for each line was multiplied by the time spent for that job, and these were then summed over each study member's complete work history to give a cumulative exposure (ppm-years).

Exposures were further classified qualitatively into 12 categories according to whether they were likely to have occurred in intermittent peaks, defined by frequency (daily, weekly, or monthly), intensity (1–3 ppm, > 3 ppm), and duration (1–15 minutes, 15–60 minutes). The potential for skin exposure to benzene was estimated, for each job in the work history, as none, low, medium, or high.

As well as cumulative exposure (ppm-years; both categorised into discrete ranges and as a continuous variable), mean intensity (mean 8-hour TWA, (ppm); cumulative exposure divided by duration of employment), maximum intensity (maximum 8-hour TWA, (ppm); highest intensity for any job in the work history), and years of employment have been analysed. Cumulative exposure was analysed in (*a*) quintiles, primarily to check assumptions of linearity, and (*b*) in four categories which represented a working lifetime of 45 years (< 0·45, 0·45–4·49, 4·5–4·99, ⩾ 45 ppm-years). To aid comparison of results between different subgroups the cumulative exposure quintiles for all leukaemias (< 0·26, 0·26–0·59, 0·60–1·64, 1·65–4·78, ⩾ 4·79) have been used for all analyses, assuming the most probable exposure to white oil or black oil when this uncertainty arose. The categorisations for maximum and mean intensities of exposure and duration of employment were chosen by examining the distribution of these variables for the whole study sample before separating them into cases and controls.

The end date for the cases was taken as the date of diagnosis when this was available or date of death otherwise. Exposures for controls were summed to the end date of the corresponding case. Lagged exposures of five and 10 years were also analysed excluding exposures received five and 10 years immediately before the end date.

Potential confounding or effect modifying variables considered were smoking, employment status at end date, socioeconomic status based on the job title of longest duration, age, and date started work, ever had a previous job, and ever had a previous job as a driver.

The highest potential skin contact in the work history was used to characterise dermal exposure. Two variables which characterised peak exposure were derived—namely, the number of years exposed to the peak—and ever experiencing the peak for more than one year. This was compared with those never experiencing any of the 12 peaks and who also had the lowest working lifetime cumulative exposure category (< 0·45 ppm-years). Although these derived variables attempt to characterise the nature of peaked exposure, the results for these variables proved difficult to interpret and should be treated circumspectly.

The data were put into the Paradox database. Data manipulation and exploratory analysis was carried out with the statistical package SAS. The epidemiological package EGRET was used for case-control analyses.

Table 1 Numbers of leukaemias by subtype

Lymphoid:	
Acute	7
Chronic	31
Other	1
Total	39
Myeloid:	
Acute	31
Chronic	11
Other	2
Total	44
Monocytic:	
Acute	1
Chronic	1
Other	1
Total	3
Other:	
Acute	3
Other	2
Total	5
Total leukaemia	91

The main comparison variable in all analyses was case-control status. Odds ratios (ORs) (the odds, or risk, of disease in higher *v* lowest exposure groups) were calculated, conditional on the matching, to identify those variables in the study which were associated with risk for leukaemia. Investigation of the potential effects of other variables and adjustment of the ORs to take into account confounding variables has been carried out with conditional logistic regression. The ORs have been estimated for exposure variables which were treated as categorical variables and, if the categorical analysis suggested that this was appropriate, as continuous variables to aid comparison with other case-control studies.[30 31] The method of conditional logistic regression assumes an exponential relation between the disease risk and other continuous variables, such as exposure. However, a linear model is often used for the assessment of cancer risk with epidemiological data, and was the preferred model mentioned by the United States Occupational Safety and Health Administration (OSHA) in their ruling on occupational exposure to benzene.[34] The first approach of categorising continuous variables facilitated the estimation of ORs for each level of exposure without constraint to any specific pattern.[35]

The effect of important potential biases, such as potential misclassification of exposures where product mix was uncertain (exposure to black oils which do not contain benzene, or to white oils which do), and sensitivity to quality and source of the work histories was examined in separate analyses, to assess the effect of the uncertainties on the results.

Separate analyses were carried out for all leukaemias, and for four leukaemia groups: (*a*) acute lymphoblastic leukaemia, (*b*) chronic lymphocytic leukaemia, (*c*) acute myeloid and acute monocytic leukaemia, and (*d*) chronic myeloid leukaemia. Numbers of cases were too small to carry out separate analyses for other leukaemia subtypes.

Previous studies have generally been too small to enable such separate analyses to be carried out, and hence, have analysed all leukaemias together. However, a recent paper by Wong[36] has shown the importance of taking specificity of this disease into consideration in causation analysis. Others have also recognised the distinct aetiology, pathogenesis, treatment and prevention of these four different groups of leukaemia.[37 38]

Table 2 Characteristics of the study sample

Variable	*Cases n (%)*	*Controls n (%)*	*Total n (%)*
Age at 1st exposure (y):			
< 25	36 (40)	137 (39)	173 (39)
25–34	33 (37)	125 (35)	158 (36)
⩾ 35	21 (23)	92 (26)	113 (25)
Mean age of 1st exposure	28·7	28·3	28·4
Date of hire:			
Before 1930	22 (24)	98 (28)	120 (27)
1930–39	20 (22)	71 (20)	91 (20)
1940–49	15 (17)	68 (19)	83 (19)
1950–59	18 (20)	66 (19)	84 (19)
After 1960	15 (17)	51 (14)	66 (15)
Years of employment:			
< 10	14 (16)	95 (27)	109 (25)
10–19	24 (27)	76 (21)	100 (22)
20–29	22 (24)	84 (24)	106 (24)
30–39	21 (23)	65 (18)	86 (19)
⩾ 40	9 (10)	34 (10)	43 (10)
Mean duration of employment	23·4	20·8	21·4
Highest potential skin exposure:			
None	28 (31)	97 (27)	125 (28)
Low	8 (9)	25 (7)	33 (7)
Medium	35 (39)	154 (44)	189 (43)
High	19 (21)	78 (22)	97 (22)
Cumulative exposure (ppm-y):			
< 1	44 (49)	183 (52)	227 (51)
1–4	27 (30)	105 (30)	132 (29)
5–9	11 (12)	40 (11)	51 (12)
⩾10	8 (9)	26 (7)	34 (8)
Mean cumulative exposure	5·6	4·4	4·6
Mean intensity (ppm):			
<0·02	32 (36)	114 (32)	146 (33)
0·02–0·19	33 (37)	163 (46)	196 (44)
0·2–0·39	19 (21)	45 (13)	64 (14)
⩾0·4	6 (7)	32 (9)	38 (9)
Mean of mean intensity (ppm)	0·20	0·22	0·21
Maximum intensity (ppm):			
< 0·02	31 (35)	104 (29)	135 (30)
0·02–0·19	30 (33)	131 (37)	161 (36)
0·2–0·39	9 (10)	43 (12)	52 (12)
⩾0·4	20 (22)	76 (22)	96 (22)
Mean maximum intensity (ppm)	0·39	0·41	0·40
Longest job:			
Professional or managerial	4 (4)	8 (2)	12 (3)
Clerical	12 (13)	38 (110)	50 (11)
Skilled	63 (69)	274 (76)	330 (74)
Unskilled	11 (12)	41 (12)	52 (12)
Smoking:			
Non-smoker	5 (5)	18 (5)	23 (5)
Smoker	6 (7)	24 (7)	30 (7)
Not known	79 (88)	312 (88)	391 (88)

Results

The following sections present many ORs, many with wide confidence intervals (CIs) due to small numbers. Relatively few hypotheses were postulated for this study, although the main focus is the evaluation of the possible relation between acute myeloid leukaemia and cumulative exposure to benzene. In general, therefore, the ORs have not been used in formal testing of hypotheses, in particular as this can lead to problems of multiplicity (multiple testing) and hence difficulties in interpretation. Emphasis has been placed on exploration of patterns and magnitude of risk, with sensitivity analyses where appropriate.

Table 1 gives the number of leukaemias by leukaemia subtype. Five leukaemias were "other leukaemias", three being acute and two not specified as to type or whether acute or chronic. The 13 leukaemias identified as a contributory cause of death were eight chronic lymphocytic leukaemias, three chronic myeloid leukaemias, one other myeloid leukaemia and one other lymphoid leukaemia. The underlying causes of death for these 13 leukaemias were heart disease (six), stroke (two), pneumonia (two), cancer of the pancreas (one), chronic obstructive airway disease (one), and hyperplasia of the prostate (one). All the acute leukaemias identified from death certificates were the underlying cause on the certificate. The three cases identified only from cancer registration data were one case each of acute myeloid leukaemia, chronic lymphocytic leukaemia, and unspecified leukaemia. The remaining results presented in

this paper exclude the 10 controls which were incorrectly selected, and one corresponding matched case.

Table 2 summarises some of the characteristics of the study sample.

The distribution of age at first exposure was similar for cases and controls, range (12·6 to 57) as was date of hire from 1909 to 1970. Mean duration of employment was slightly higher for cases than controls, with a larger percentage of controls working for < 10 years. Cases and controls for whom the longest job was unskilled had a much shorter mean duration of employment (15·5 years for cases, 11·7 years for controls) than the overall study sample.

The distribution of the highest potential skin contact was similar in cases and controls, with slightly higher proportions of controls in the medium and high contact groups.

The distribution of cumulative exposure was similar for cases and controls. Cumulative exposures ranged from close to 0 to > 200 ppm-years, although 81% were < 5 ppm-years. The upper tail of the distribution was distorted by 15 subjects who were known to have worked previously for a company which marketed benzene enriched products, and hence had greater exposures to benzene. Only one of these was a case. There was a larger proportion of cases than controls with a mean intensity of exposure between 0·2 and 0·4 ppm. The distribution of maximum intensity of exposure was similar for cases and controls.

Just under a third of the study sample had never experienced a peak at all, with proportionately more cases than controls in this group. More cases experienced daily or weekly peaks than controls.

To provide a measure of socioeconomic status, study members were classified according to the job that they held longest within their work history—that is, as professional or managerial, clerical or office workers, skilled manual (driver, operator, or supervisor), unskilled. There were proportionately more cases than controls in the professional and clerical groups.

The distribution of smokers and non-smokers was the same for cases and controls but information on smoking was unobtainable for nearly 90% of the study sample from medical or personnel records, or from interview.

Of the cases 24% were in employment at the study end date (diagnosis or death) compared with only 11% of the controls.

For all leukaemias together cumulative exposure tended to be highly correlated with both mean intensity of exposure ($r = 0·84$) and maximum intensity of exposure ($r = 0·82$), but not with duration of employment ($r = 0·15$). Similar correlations were found for leukaemia subtypes.

Table 3 Odds ratios and (95% CIs) for selected variables for all leukaemia

Variable	*Cases n*	*Controls n*	*OR (95% CI)*	*Goodness of fit (P value)*
Cumulative exposure (continuous)	—	—	1·004 (0·99 to 1·02)	0·55
Cumulative exposure quintiles (ppm-y):				
< 0·26	12	76	(1) —	0·12
0·26–0·59	23	66	2·58 (1·12 to 5·92)	—
0·60–1·64	21	68	2·28 (0·95 to 5·43)	—
1·65–4·78	14	76	1·31 (0·54 to 3·19)	—
⩾ 4·79	20	68	2·13 (0·90 to 5·03)	—
Cumulative exposure working lifetime (ppm-y):				
< 0·45	22	109	(1)	0·66
0·45–4·49	47	172	1·42 (0·77 to 2·61)	—
4·5–44·9	20	69	2·48 (0·73 to 3·00)	—
⩾ 45	1	4	1·35 (0·14 to 12·8)	—
Duration of employment (continuous)	—	—	1·03 (1·00 to 1·05)	0·02
Years of employment:				
< 10	14	95	(1)	0·08
10–19	24	76	2·64 (1·20 to 5·82)	—
20–29	22	84	2·40 (1·03 to 5·62)	—
30–39	21	65	3·34 (1·33 to 8·41)	—
⩾ 40	9	34	2·75 (0·87 to 8·65)	—
Maximum intensity (continuous)	—	—	0·99 (0·82 to 1·20)	0·91
Maximum intensity (ppm):				
< 0·02	31	104	(1)	0·72
0·02–0·19	30	131	0·77 (0·44 to 1·35)	—
0·2–0·39	9	43	0·66 (0·28 to 1·53)	—
⩾ 0·4	20	76	0·88 (0·46 to 1·71)	—
Mean intensity (continuous)	—	—	0·97 (0·67 to 1·40)	0·86
Mean intensity (ppm):				
< 0·02	32	114	(1)	0·15
0·02–0·19	33	163	0·71 (0·41 to 1·24)	—
0·2–0·39	19	45	1·44 (0·74 to 2·79)	—
⩾ 0·4	6	32	0·65 (0·25 to 1·72)	—
Highest potential skin exposure:				
None	28	97	(1)	0·74
Low	8	24	1·16 (0·47 to 2·91)	—
Medium	35	154	0·77 (0·44 to 1·34)	—
High	19	78	0·83 (0·43 to 1·62)	
Date of hire:				
Before 1950	57	237	(1)	0·43
After 1950	33	117	1·28 (0·69 to 2·36)	
Employment status at study end date:				
Not employed	68	315	(1)	< 0·001
Employed	22	39	6·29 (2·51 to 15·77)	
Socioeconomic status:				
Blue collar	74	308	(1)	0·25
White collar	16	46	1·46 (0·78 to 2·73)	
Smoking:				
Non-smoker	5	18	(1)	0·50
Smoker	6	24	1·78 (0·34 to 9·21)	

ALL LEUKAEMIAS

The results for leukaemia subtypes show rather different patterns which are hidden in the results for all leukaemias. However, to put the subgroup analyses in context and to provide comparisons with previous studies the results for all leukaemias taken together are presented.

Table 3 gives ORs and 95% CIs for some of the main variables of interest for all leukaemia. The OR for cumulative exposure as a continuous variable was just > 1. This result, together with the result for cumulative exposure categorised into discrete ranges, suggests that there is little evidence of an increased risk of all leukaemias with increased cumulative exposure. Fitting duration of employment as a continuous variable gave the best fitting model. The result for duration of employment as a categorical variable shows the risk being consistently > 2 for all duration groups over 10 years. A test for trend was significant ($P < 0·05$) and approached the 5% significance for linearity.

Results of sensitivity analyses of uncertainties in product mix and quality and source of work histories showed similar patterns, although there were slight variations in the

magnitudes of the ORs. The patterns of risk did not change substantially when analyses were carried out excluding any exposures in the last five and 10 years before the date of diagnosis.

ACUTE LYMPHOBLASTIC LEUKAEMIA

There were seven cases of acute lymphoblastic leukaemia, including the only case who was previously employed by a company marketing benzene enriched products. This case had a much greater exposure to benzene than the other cases of acute lymphoblastic leukaemia. The mean cumulative exposure for all seven cases was 29·6 ppm-years compared with 2·0 ppm-years for controls (reducing to 0·2 and 1·3, respectively, if the case with high exposure to benzene and matched controls are excluded). Five of the seven cases started work after 1950. The OR for cumulative exposure examined as a continuous variable was 1·02 when all seven cases were included but fell to 0·32 when the case with very high exposure was excluded. The ORs for the exposure variables in discrete ranges decreased with increasing cumulative exposure (OR = 0·27, 95% CI 0·02 to 2·9 for ⩾ 0·45 compared with < 0·45 ppm-years) and maximum intensity (OR = 0·49, 95% CI 0·05 to 4·9 for ⩾ 0·02 compared with < 0·02 ppm). Four cases had worked for < 10 years, with a mean duration of 15·3 years for cases compared with a mean of 19·4 years for controls. The cases tended to start work at an older age (mean 36·6 years) compared with controls (mean 28·3 years). Five of the seven cases had no or low skin contact. Only one of the cases was in employment at the date of diagnosis or death. All seven were blue collar workers. Job histories were complete or almost complete for all cases and controls. Duration of employment < 10 years (OR = 6·9, 95% CI 0·7 to 72·9) compared with > 10 years, and date of hire after 1950 (OR = 6·8, 95% CI 0·7 to 64·8) compared with date of hire before 1950 were associated with increased risk.

As there were only one or two cases who had experienced each of the peak exposures the ORs for the different types of peaks and duration of time in these peaks were either not calculable or unstable due to small numbers.

Table 4 Odds ratios (95% CIs) for chronic lymphocytic leukaemia

Variable	*Cases n*	*Controls n*	*OR (95% CI)*	*Goodness of fit (P value)*
Cumulative exposure (continuous)	—	—	0·98 (0·91 to 1·05)	0·48
Cumulative exposure (quintiles) (ppm-y):				
< 0·26	1	23	(1)	0·01
0·26–0·59	12	27	10·57 (1·27 to 87·92)	—
0·60–1·64	9	22	11·21 (1·20 to 104·4)	—
1·65–4·78	2	28	1·33 (0·11 to 16·48)	—
⩾ 4·79	7	24	5·64 (0·64 to 49·61)	—
Cumulative exposure working lifetime (ppm-y):				
< 0·45	8	41	(1)	0·94
0·45–4·49	16	57	1·07 (0·40 to 2·86)	—
4·5–44·9	7	26	1·22 (0·38 to 3·89)	—
⩾ 45	0	2	0	—
Duration of employment (continuous)	—	—	1·06 (1·01 to 1·11)	0·01
Years of employment:				
< 20	10	53	(1)	0·42
20–29	10	35	1·81 (0·59 to 5·52)	—
⩾ 30	11	36	2·11 (0·63 to 7·03)	—
Maximum intensity (continuous)	—	—	0·61 (0·21 to 1·78)	0·17
Maximum intensity (ppm):				
< 0·02	15	33	(1)	0·06
0·02–0·19	8	49	0·31 (0·11 to 0·88)	—
0·2–0·39	2	19	0·16 (0·02 to 0·96)	—
⩾ 0·4	6	23	0·51 (0·17 to 1·56)	—
Mean intensity (continuous)	—	—	0·51 (0·09 to 3·00)	0·25
Mean intensity (ppm):				
< 0·02	16	40	(1)	0·08
0·02–0·19	8	60	0·25 (0·08 to 0·78)	—
0·2–0·39	5	16	0·65 (0·18 to 2·27)	—
⩾ 0·4	2	8	0·64 (0·13 to 3·23)	—
Highest potential skin exposure:				
None	12	31	(1)	0·06
Low	3	7	1·11 (0·24 to 5·17)	—
Medium	7	60	0·29 (0·10 to 0·85)	—
High	9	26	0·82 (0·28 to 2·41)	—
Date of hire:				
Before 1950	23	91	(1)	0·91
After 1950	8	33	0·94 (0·31 to 2·87)	
Employment status at study end date:				
Not employed	25	118	(1)	0·002
Employed	6	6	17·7 (2·04 to 153·3)	—
Socioeconomic status:				
Blue collar	21	107	(1)	0·01
White collar	10	17	3·66 (1·27 to 10·51)	—
Age started work:				
< 25	12	43	(1)	0·90
25–34	9	40	0·79 (0·29 to 2·18)	—
⩾ 35	10	41	0·87 (0·33 to 2·31)	—
Previous job driver	2	15	0·48 (0·10 to 2·30)	0·33
Years of work:				
< 20	—	—	1·68 (0·54 to 5·20)	0·08
⩾ 30	—	—	1·58 (0·42 to 5·87)	
White collar	—	—	3·46 (1·16 to 10·35)	
Years of work:				
< 20	—	—	2·16 (0·64 to 7·28)	0·02
⩾ 30	—	—	0·54 (0·09 to 3·37)	—
White collar	—	—	1·51 (0·14 to 16·74)	—
< 20 y work white collar	—	—	0·29 (0·01 to 6·62)	—
⩾ 30 y work white collar	—	—	11·36 (0·48 to 266·4)	—

CHRONIC LYMPHOCYTIC LEUKAEMIA

There were 31 cases of chronic lymphocytic leukaemia. The cases had a lower mean cumulative exposure (2·6 ppm-years) than the controls (3·6 ppm-years). However, in contrast to acute lymphoblastic leukaemia, the cases tended to have a longer duration of employment (mean 26·7 years) compared with controls (mean 21·7 years). There was no difference in the age of starting work. None of the cases had worked for < 10 years, compared with 21% of the controls. Nearly a third of the cases were white collar workers, compared with only 14% of the controls. This is reflected in the type of exposures experienced, with fewer cases (58%) than controls (75%) ever experiencing peaks, and more cases (48%) than controls (31%) with either no or low skin contact. Two of the controls had poor work histories, and 10 of the cases (32%) and 21 of the controls (17%) had partially complete work histories.

Table 4 gives the ORs and 95% CIs for selected variables in conditional logistic models. The OR for cumulative exposure as a continuous variable was < 1. Analysis of cumulative exposure categorised into discrete ranges again showed no clear trend of increased risk with increasing exposure. The high ORs in the lowest categories of quintiles were due mainly to the lowest quintile, the base category, against which the other categories were compared, containing only one

case. Combination of the first two quintiles would reduce the ORs for the remaining three to 1·57, 0·27, and 1·12, respectively. Associations with mean and maximum intensity, both as continuous and categorical variables, were negative. There is thus no evidence for an increasing risk with increased exposure. The ORs for experiencing any of the peaks (not shown) were < 1. Starting work at the age of 25 or above compared with starting work before 25, date of hire 1950 or later compared with date of hire before 1950, and having a previous job as a driver compared with not having a previous job as a driver had low ORs showing no increased risk of chronic lymphocytic leukaemia for these variables. The OR for potential skin exposure was highest in the low exposure category.

The ORs were greater than unity for three variables, duration of employment as a continuous and categorical variable, socioeconomic status (white collar compared with blue collar), and employment status at the end date (employed compared with not employed). The influence of other variables on duration of employment was explored in models, as well as socioeconomic status and employment status at the end date on variables characterising exposure. Inclusion of employment status did not substantially alter the ORs of any of the other variables but always remained significant itself. There seemed to be an interaction between duration of employment and socioeconomic status, with the highest risk being for white collar workers with over 30 years duration of employment.

The results were not substantially altered by sensitivity analyses according to product mix or quality and source of the work history.

Similar patterns were found for latency analyses excluding the last five and 10 years of exposure, although there was a tendency for

Table 5 Odds ratios (95% CIs) for acute myeloid and monocytic leukaemia

Variable	*Cases n*	*Controls n*	*OR (95% CI)*	*Goodness of fit (P value)*	*OR*	
					*White oil**	*Black oil†*
Cumulative exposure (continuous)	—	—	1·00 (0·96 to 1·04)	0·95	1·00	1·00
Cumulative exposure (quintiles) (ppm-y):						
< 0·26	6	35	(1)	0·75	(1)	(1)
0·26–0·59	5	17	1·88 (0·49 to 7·16)	—	2·57	1·67
0·60–1·64	6	23	1·68 (0·46 to 6·11)	—	1·60	1·47
1·65–4·78	6	24	1·60 (0·44 to 5·79)	—	2·16	1·78
⩾ 4·79	8	22	2·38 (0·65 to 8·73)	—	3·21	2·16
Cumulative exposure working lifetime (ppm-y):						
< 0·45	7	46	(1)	0·18	(1)	(1)
0·45–4·49	15	51	2·17 (0·77 to 6·09)	—	1·95	1·61
4·5–44·9	9	23	2·82 (0·82 to 9·38)	—	2·78	2·28
⩾ 45	0	1	0	—	0	0
Duration of employment (continuous)	—	—	1·03 (0·99 to 1·07)	0·19	—	—
Years of employment:						
< 10	7	48	(1)	0·38	—	—
10–19	10	29	2·65 (0·88 to 7·93)	—	—	—
20–29	8	23	2·76 (0·79 to 9·58)	—	—	—
30–39	5	16	2·86 (0·66 to 12·29)	—	—	—
⩾ 40	1	5	1·86 (0·12 to 29·52)	—	—	—
Maximum intensity (continuous)	—	—	0·66 (0·28 to 1·52)	0·22	0·68	0·69
Maximum intensity (ppm):						
< 0·02	6	32	(1)	0·86	(1)	(1)
0·02–0·19	13	47	1·45 (0·51 to 4·10)	—	1·35	1·62
0·2–0·39	5	14	1·69 (0·46 to 6·17)	—	1·70	2·27
⩾ 0·4	7	28	1·34 (0·37 to 4·86)	—	1·53	1·56
Mean intensity (continuous)	—	—	0·68 (0·17 to 2·82)	0·57	0·77	0·72
Mean intensity ((ppm):						
< 0·02	6	34	(1)	0·13	(1)	(1)
0·02–0·19	14	56	1·34 (0·48 to 3·74)	—	1·20	1·31
0·2–0·39	10	18	2·76 (0·90 to 8·48)	—	2·89	2·84
⩾ 0·4	1	13	0·43 (0·05 to 4·05)	—	0·43	0·46
Highest potential skin contact:						
None	6	30	(1)	0·84	Does not	(1)
Low	3	12	1·19 (0·26 to 5·42)	—	converge	1·70
Medium	16	51	1·54 (0·54 to 4·39)	—		1·56
High	6	28	1·11 (0·32 to 3·87)	—		1·35
Date of hire:						
Before 1950	15	63	(1) (0·46 to 3·17)	0·69	—	—
After 1950	16	58	1·21 —	—	—	—
Ever employed as previous driver	4	4	1·71 (0·49 to 6·03)	0·41	—	—
Employment status at study end date	11	26	2·97 (0·95 to 9·27)	0·06	—	—
Socioeconomic status:						
Blue collar	29	108	(1) (0·12 to 2·53)	0·42	—	—
White collar	2	13	0·56	—	—	—
Age started work (continuous)	—	—	1·01 (0·96 to 1·05)	0·75	—	—
Age started work:						
< 25	14	49	(1)	0·90	—	—
25–34	12	50	0·84 (0·36 to 1·93)	—	—	—
⩾ 35	5	22	0·81 (0·25 to 2·62)	—	—	—

*Assumes exposure to white oil products which contain benzene.
†Assumes exposure to black oil products which do not contain benzene.

the ORs for all exposure categories to reduce as the lagged exposure increased from zero to 10 years. For example, the ORs for cumulative exposure 0·45–4·5 compared with < 0·45 ppm-years reduced from 1·07 for no lagged exposure to 0·87 for a lag of five years and to 0·79 for a lag of 10 years. The corresponding ORs for ⩾ 4·5 ppm-years compared with < 0·45 were 1·22, 1·06, and 0·88.

ACUTE MYELOID AND MONOCYTIC LEUKAEMIA

Acute myeloid and monocytic leukaemia were considered together because of their similar aetiology.[38] There were 31 cases of acute myeloid and monocytic leukaemia included in the analysis, all but one being myeloid. (One further case was excluded as all four controls were erroneously matched for age). In all but one case of acute myeloid and monocytic leukaemia this was given as the underlying cause of death on the death certificate, the remaining one being identified from cancer registration only. Most of the cases (94%) were blue collar workers, compared with 89% of the controls. The cases and controls had similar mean cumulative exposures (cases 3·7 ppm-years, controls 3·8 ppm-years), with the range of exposure for the controls being much greater (up to 103·8 ppm-years) than for the cases (up to 22·3 ppm-years). The cases had a slightly longer mean duration of exposure (19·1 years) than controls (16·6 years), with no difference in the age of starting work. More controls (40%) had worked for < 10 years than cases (23%). Cases had slightly more exposure to peaks than controls (75% cases, 66% controls), and slightly more medium or high skin contact (cases 71%, controls 65%). There were no cases or controls in this data set with poor work histories, but five cases (16%) and 16 controls (13%) had partially complete work histories.

Table 5 shows the ORs of acute myeloid and monocytic leukaemia for exposure variables, potential confounding variables, and other variables. Unlike the lymphatic subgroups duration of employment was not the variable most closely related to risk. The ORs for cumulative exposure categorised into discrete ranges showed a tendency to increase as exposure increased, and a similar pattern was found as mean intensity of exposure as a categorical variable increased. A test for trend for cumulative exposure gave a probability value of 0·09, and a test for a linear trend was not significant. There were no cases with a cumulative exposure above 45 ppm-years, the fourth category of the working lifetime categorisation. To explore the risk between 4·5 and 45 ppm-years, ORs were calculated for different cut off

Table 6 Odds ratios (95% CIs) for conditional logistic regression models for acute myeloid and monocytic leukaemia

Variable	*OR (95% CI)*	*Goodness of fit (P value)*	*OR*	
			White oil	*Black oil*
Model 1:				
Cumulative exposure:				
0·45–4·49	1·82 (0·63 to 5·29)	0·12	1·70	1·26
⩾ 4·5	2·48 (0·73 to 8·47)	—	2·37	1·98
Employed at study end date	2·61 (0·81 to 8·41)	—	2·63	2·86
Model 2:				
Mean intensity:				
0·02–0·19	1·23 (0·43 to 3·48)	0·06	1·14	1·17
0·2–0·39	2·66 (0·84 to 8·47)	—	2·64	2·76
⩾ 0·4	0·42 (0·04 to 3·94)	—	0·41	0·42
Employed at study end date	2·92 (0·92 to 9·29)	—	2·64	3·05
Model 3:				
Cumulative exposure:				
0·45–4·49	2·82 (0·89 to 8·89)	0·19	2·54	2·02
⩾ 4·5	3·71 (0·99 to 13·94)	—	3·71	2·81
Date of hire				
After 1950	2·08 (0·66 to 6·58)	—	2·07	1·83
Model 4:				
Mean intensity:				
0·02–0·19	1·45 (0·51 to 4·11)	0·16	1·31	1·42
0·2–0·39	3·26 (1·00 to 10·57)	—	3·32	3·35
⩾ 0·4	0·47 (0·05 to 4·38)	—	0·47	0·51
Date of hire				
After 1950	1·67 (0·58 to 4·83)	—	1·65	1·64
Model 5:				
Years at peak exposure (weekly, > 3 ppm, 15–60 minutes)	1·05 (1·00 to 1·10)	0·04	1·06	1·04
Model 6:				
Cumulative exposure:				
0·45–4·49	1·57 (0·49 to 5·09)	0·19	0·94	1·19
⩾ 4·5	1·31 (0·25 to 6·98)	—	0·63	1·04
Years at peak exposure (weekly, > 3 ppm, 15–60 minutes)	1·04 (0·98 to 1·11)	—	1·08	1·04
Model 7:				
Ever experienced peak (weekly, > 3 ppm, 15–60 minutes)	1·86 (0·63 to 5·48)	0·24	2·19	2·13
Model 8:				
Cumulative exposure:				
0·45–4·49	0·34 (0·04 to 2·59)	0·49	0·35	0·18
⩾ 4·5	0·38 (0·04 to 3·28)	—	0·41	0·26
Ever experienced peak exposure (weekly, > 3 ppm, 15–60 minutes)	4·72 (0·57 to 39·03)	—	5·42	9·41

Table 7 Acute myeloid and monocytic leukaemia

Variable	Excluding job confidence score 3			Excluding job confidence scores 2 and 3			Excluding work histories from majority interview			Including work histories from personnel records only		
	Cases n	Controls n	OR	Cases n	Controls n	OR	Cases n	Controls n	OR	Cases n	Controls n	OR
Cumulative exposure (ppm-y):												
< 0·45	7	46	(1)	7	44	(1)	7	42	(1)	6	31	(1)
0·45–4·49	15	51	2·17	13	40	2·13	14	45	1·94	12	26	1·42
⩾ 4·5	9	24	2·82	6	21	1·62	7	21	2·18	2	15	0·33
Mean intensity (ppm-y):												
< 0·02	6	34	(1)	5	29	(1)	6	30	(1)	5	19	(1)
0·02–0·19	14	56	1·34	13	49	1·30	13	50	1·23	11	33	0·85
0·2–0·39	10	18	2·76	7	15	2·14	8	16	2·16	4	13	0·73
⩾ 0·4	1	12	0·46	1	12	0·39	1	12	0·42	0	7	0

Table 8 Odds ratios (95% CI) for lagged analyses for acute myeloid and monocytic leukaemia

Cumulative exposure (ppm-y)	Excluding exposures before date of diagnosis of: 0 years		5 years		10 years	
	OR (95% CI)	Goodness of fit	OR (95% CI)	Goodness of fit	OR (95% CI)	Goodness of fit
< 0·45	(1)	0·18	(1)	0·16	(1)	0·10
0·45–4·49	2·17 (0·77 to 6·09)	—	2·10 (0·70 to 6·25)	—	2·32 (0·83 to 6·45)	—
4·5–44·9	2·82 (0·82 to 9·38)	—	3·06 (0·92 to 10·18)	—	3·67 (1·03 to 13·07)	—
⩾ 45	0	—	—	—	—	—

points equivalent to intensities of 0·2, 0·3, and 0·4 ppm for 45 years—that is, cumulative exposure (*a*) between 4·5 and 9 ppm-years (OR = 2·54, 95% CI 0·64 to 10·10) and > 9 ppm-years (OR = 2·93, 95% CI 0·63 to 13·59), (*b*) between 4·5 and 13·5 ppm-years (OR = 2·65, 95% CI 0·75 to 9·40) and > 13·5 ppm-years (OR = 2·88, 95% CI 0·37 to 22·32), and (*c*) between 4·5 and 18 ppm-years (OR = 2·90, 95% CI 0·85 to 9·90) and > 18 years (OR = 1·64, 95% CI 0·15 to 18·19).

The mean cumulative exposure for the controls was influenced by several high estimates. These also affected the OR for cumulative exposure as a continuous variable which was 1·0, but was 1·09 when the four controls with cumulative exposures > 23 ppm-years were excluded. The ORs for mean intensity and maximum intensity of exposure as continuous variables were < 1.

There was little evidence for an increased risk of acute myeloid and monocytic leukaemia associated with date of hire, socioeconomic status, and age at starting work. The OR for being employed at the end date compared with not being employed was increased, although it was not nearly as high as that for chronic lymphocytic leukaemia (table 4).

Table 6 gives the results of fitting different variables with cumulative exposure and mean intensity of exposure categorised into discrete ranges, and an example of the effect of including a variable defining a peaked exposure (weekly, > 3 ppm, 15–60 minutes). Inclusion of employment status at the end date with cumulative exposure or mean intensity slightly reduced the ORs for the exposure categories. Inclusion of date of hire after 1950 compared with date of hire before 1950 increased the ORs for cumulative exposure and mean intensity. No interaction effect was found for this variable. Inclusion of variables relating to peaks tended to decrease the ORs for the categories of cumulative exposure and give high OR values for the peak variable.

Although the general patterns remain the same, the values of the ORs for exposure variables did vary if different exposure estimates were used for those work history lines where uncertainty existed whether exposure occurred through handling white oils or whether black oils were handled. The last two columns of tables 5 and 6 show these ORs, black oil indicates an assumption that these products (which do not contain benzene) were handled, and white oil indicates an assumption that these products (which do contain benzene) were handled.

Table 7 gives the results for cumulative exposure and mean intensity of exposure for four sets of data evaluating the sensitivity of the results to the quality of the work histories. The patterns are similar for the two data sets defined by excluding work histories with job confidence score 3 (poor) and work histories mainly taken from interviews. No increase in ORs was found for the data set which excludes work histories with job confidence scores 2 and 3 (poor and partially complete) and for the data set which only includes work histories from personnel records. However, the numbers of cases and controls on which these results were based were much reduced, especially at higher levels of exposure and in the data set which only includes work histories from personnel records.

When analyses were carried out for acute myeloid and monocytic leukaemia excluding the past five and 10 years of exposure, the general patterns remained (table 8). Although the ORs were not substantially altered, there was a tendency for the ORs for the categories of cumulative exposure and mean intensity to increase, and for the fit of the models to improve, as the lag increased from zero to 10 years.

Table 9 Odds ratios (95% CIs) for chronic myeloid leukaemia

Variable	Cases n	Controls n	OR (95% CI)	Goodness of fit (P value)	OR White oil	OR Black oil
Cumulative exposure (continuous)	—	—	1·004 (0·94 to 1·07)	0·89	1·003	1·005
Cumulative exposure (quintiles) (ppm-y):						
< 0·60	3	16	(1)	0·78	(1)	(1)
0·60–1·64	3	12	1·39 (0·24 to 7·91)	—	0·98	1·63
1·65–4·78	3	6	2·45 (0·41 to 14·65)	—	2·94	2·64
⩾ 4·79	2	10	1·05 (0·15 to 7·36)	—	1·12	1·14
Cumulative exposure (working lifetime) (ppm-y):						
< 0·45*	0	10	(1)	0·74	(1)	(1)
0·45–4·49	9	24	—	—	—	—
4·5–44·9	2	10	0·76 (0·14 to 4·06)	—	0·76	0·76
⩾ 45	0	0	—	—	—	—
Duration of employment (continuous)	—	—	1·04 (0·96 to 1·12)	0·28	—	—
Years of employment:						
< 20	4	14	(1)	0·92	—	—
20–39	5	21	0·71 (0·11 to 4·51)	—	—	—
⩾ 40	2	9	0·63 (0·06 to 6·85)	—	—	—
Maximum intensity (continuous)	—	—	0·81 (0·30 to 2·18)	0·60	0·82	0·82
Maximum intensity (ppm):						
< 0·02	3	14	(1)	0·88	(1)	(1)
0·02–0·19	4	18	1·02 (0·20 to 5·21)	—	0·99	1·02
0·2–0·39	2	4	2·26 (0·29 to 17·57)	—	2·68	2·26
⩾ 0·4	2	8	1·16 (0·15 to 8·87)	—	1·03	1·16
Mean intensity (continuous)	—	—	1·004 (0·16 to 6·28)	0·997	0·98	1·02
Mean intensity (ppm):						
< 0·02	3	15	(1)	0·88	(1)	(1)
0·02–0·19	5	20	1·26 (0·27 to 5·82)	—	1·30	1·26
0·2–0·39	2	4	2·30 (0·30 to 17·39)	—	2·26	2·30
⩾ 0·4	1	5	1·06 (0·09 to 12·47)	—	0·90	1·06
Date of hire:						
Before 1950	9	34	(1)	0·61	—	—
After 1950	2	10	0·50 (0·03 to 7·61)	—	—	—
Socioeconomic status:						
Blue collar	10	39	(1)	0·84		
White collar	1	5	0·80 (0·09 to 6·85)	—	—	—
Age started work (continuous)	—	—	1·01 (0·95 to 1·08)	0·75	—	—
Age started work:						
< 25	3	20	(1)	0·33	—	—
25–34	6	13	2·88 (0·63 to 13·28)	—	—	—
⩾ 35	2	11	1·23 (0·18 to 8·42)	—	—	—
Cumulative exposure:						
0·60–1·64	—	—	3·29 (0·40 to 27·08)	0·38	2·33	6·87
1·65–4·78	—	—	4·83 (0·54 to 43·21)	—	6·32	7·32
⩾ 4·79	—	—	0·74 (0·10 to 5·62)	—	0·82	0·82
Age started work:						
25–34	—	—	6·45 (0·85 to 49·00)	—	6·41	10·48
⩾ 35	—	—	2·22 (0·22 to 22·48)	—	2·19	2·29
Maximum intensity:						
0·02–0·2	—	—	1·50 (0·24 to 9·21)	0·66	1·50	1·50
⩾ 0·2	—	—	1·30 (0·22 to 7·72)	—	1·30	1·30
Age started work:						
25–34	—	—	3·15 (0·53 to 18·83)	—	3·15	3·15
⩾ 35	—	—	1·29 (0·16 to 10·46)	—	1·29	1·29
Mean intensity:						
0·02–0·19	—	—	1·75 (0·33 to 9·28)	0·61	1·84	1·75
⩾ 0·2	—	—	1·56 (0·21 to 11·33)	—	1·41	1·56
Age started work:						
25–34	—	—	3·25 (0·58 to 18·35)	—	3·42	3·25
⩾ 35	—	—	1·30 (0·14 to 11·85)		1·38	1·30
Cumulative exposure:						
0·60–1·65	—	—	1·69 (0·25 to 11·37)	0·57	1·22	1·84
1·65–4·78	—	—	2·98 (0·42 to 21·03)	—	3·83	3·11
⩾ 4·79	—	—	1·49 (0·17 to 12·83)	—	1·55	1·55
Years at peak exposure (monthly, >3ppm, 1–15 minutes)	—	—	1·42 (0·85 to 2·37)	—	1·39	1·41

*Categories analysed are < 45 ⩾ 4·5.

CHRONIC MYELOID LEUKAEMIA

There were 11 cases of chronic myeloid leukaemia. (One case of acute myeloid leukaemia also had chronic myeloid leukaemia on the death certificate but was classified as acute myeloid leukaemia for this study). Nine of the 11 cases were in the skilled manual socioeconomic group. Four of the controls had poor work histories with seven of the cases (64%) and 12 of the controls (27%) having almost complete work histories. Nine cases had a cumulative exposure between 0·45 and 4·5 ppm-years, (mean 5·4 ppm-years for cases, 4·9 ppm-years for controls), with no cases having a cumulative exposure of < 0·45 ppm-years. Five cases had an mean intensity between 0·02 and 0·2 ppm. Seven cases had more than 30 years duration of employment (mean for cases 29·8, controls 26·5).

Table 9 shows these patterns. The first two quintiles of cumulative exposure and the categories < 0·45 and 0·45–4·49 of working lifetime cumulative exposure have been combined as there were no cases in the first

quintile (< 0·45). Increasing duration of employment analysed as a continuous variable was associated with increased risk. The ORs for cumulative exposure and mean intensity as continuous variables were just > 1. There was no evidence of an increasing risk with increasing categories of cumulative exposure, duration of exposure, maximum intensity, or mean intensity of exposure, with the only increased ORs being in categories 0·2–0·4 ppm for maximum and mean intensity of exposure, based on only two cases.

The ORs for experiencing peaks were not calculable as all the cases experienced some kind of peak—that is, there were no cases in the "never experienced a peak and cumulative exposure in the lowest working lifetime category" group. Unlike the results for acute myeloid and monocytic leukaemia, duration of employment ⩾ 20 years compared with < 20 years, date of hire 1950 or later compared with date of hire before 1950, and white collar workers compared with blue collar workers showed reduced ORs and inclusion of these variables with other variables in conditional logistic regression models did not improve the fit of any of the variables. There is thus no evidence of an increased risk of chronic myeloid leukaemia with these variables.

Starting work at the age of > 25, compared with < 25, acted as a negative confounding variable by increasing the ORs for the lower cumulative exposure categories and to a lesser extent for the lower mean and maximum intensity categories. No significant interactions were found with any of the potential confounding variables, including age started work, or other variables.

Similar to the results for acute myeloid leukaemia, some of the results were sensitive to choice of exposure estimate where there was uncertainty as to product mix. The last two columns of table 9 show the ORs for exposure to white and black oil. However, the general patterns already described were not altered for these estimates. The patterns were also similar for sensitivity analyses by quality and source of work history.

There was no change in the results when exposures were excluded for the five years before the date of diagnosis. There was a slight reduction of the OR for the cumulative exposures categories assuming a lagged exposure of 10 years (OR = 0·40, 95% CI 0·05 to 3·5 for ⩾ 4·5 compared with < 4·5 ppm-years).

Discussion

Although this is the largest case-control study to be carried out to investige the risk of leukaemia associated with exposure to benzene, there are still only 91 cases, and fewer when the leukaemia subtypes are considered. The study may be subject to errors inherent to case-control studies, such as bias in selection of controls and recall bias.[32] About 20% of the work histories were incomplete (sometimes due to reliance on interviews for obtaining the information). Although many of these were minor omissions, it was necessary to make some assumptions to complete the work histories. Analysis by smoking and previous jobs was restricted due to incomplete information.

The limitations of the methods for estimating exposure are discussed in detail in a separate paper.[33] Incomplete or missing information which had to be assumed—for example, hygiene data for base estimates, data on closed terminals and on product source—contributed to uncertainties in the exposure estimates. However, a validation procedure with independent hygiene data showed that the methods of estimation produced reasonable estimates when compared with known sampling results.

A restriction of this study, which was perhaps not anticipated before exposure estimation, is that the ranges of both intensity and cumulative exposure are narrow. Half the study sample had < 1 ppm-years of cumulative exposure, with over 80% < 5 ppm-years. The precision of this study to estimate risks > 10 ppm-years is therefore reduced.

In general cumulative exposure was highly correlated with both mean and maximum intensity of exposure but not with duration of exposure. The lack of correlation with duration of exposure was partly due to about a third of the study sample having background or population levels of exposure to benzene for their entire working life.

An attempt was made to characterise the peaked nature of the exposure experienced in oil distribution centres with a qualitative classification combining frequency, intensity, and duration of exposure. The classifications have been assigned primarily from the job titles in the work histories, but take into account the type of terminal. They are limited in their use for describing in any detail the quantitative nature of peak exposure and should therefore be interpreted with caution.

The results for all leukaemias taken together are obscured by the differing patterns of risk found in the leukaemia subtypes. However, the OR for cumulative exposure when treated as a continuous variable was almost exactly the same as that found by Schnatter *et al* in the analysis of the Canadian data.[30] The influence of chronic lymphocytic leukaemia on the results for total leukaemia is reflected in the dominance of duration of employment as the variable that best related to risk of leukaemia, and the lack of such a relation with either cumulative exposure or intensity. There was also a suggestive relation with duration of employment in the Canadian study.

There were only seven cases of acute lymphoblastic leukaemia. This tended to occur in workers employed after 1950 for a short duration who experienced low cumulative exposure with few peaks. The ORs did not increase with increasing exposure. There was no evidence that the cases of acute lymphocytic leukaemia left employment after a short time due to any adverse working conditions. There have been very few published reports of an association of acute lymphoblastic leukaemia with exposure to benzene and the results from this study support this.

The risk of chronic lymphocytic leukaemia seemed to be related most closely to duration of employment with the highest risk occurring in white collar workers with long employment. These workers had background or population levels of exposure to benzene. Many cases occurred when in employment. There was no evidence for an association of risk with any exposure variables, and no evidence of an increasing risk with increasing cumulative exposure, mean intensity, or maximum intensity. The higher ORs in the lowest categories of quintiles were an artifact of the definition of the categories, chosen to be consistent with the analyses for the other subtypes. The ORs for any type of peak exposure were low or not calculable showing that any exposure that was experienced did not occur in the form of peaks. As previously stated, there has been little evidence in previous studies of a relation between exposure to benzene and chronic lymphocytic leukaemia and our results seem to substantiate this.

Acute myeloid leukaemia has been most frequently reported as being associated with exposure to benzene.[3 5 8] In contrast with chronic lymphocytic leukaemia 94% of cases of acute myeloid and monocytic leukaemia in the current study occurred in blue collar workers. Risk of acute myeloid and monocytic leukaemia was highest in men with cumulative exposure of 4·5–45 ppm-years compared with cumulative exposure < 0·45 ppm-years. Only one man (a control) had cumulative exposures > 45 ppm-years. There was no association with cumulative exposure when analysed as a continuous variable. The excess of cases with cumulative exposures of 4·5–45 ppm-years occurred particularly in men with daily or weekly peaks of exposure. Risk also increased to > 2 for an mean intensity of 0·2–0·4 ppm compared with < 0·02 ppm. No clear trend was found in analyses of risk according to maximum intensity of exposure. The recent reanalysis of the Pliofilm cohort showed double the risk of all leukaemias (nine out of 14 were acute myeloid leukaemias) at 55 ppm-years cumulative exposure.[21]

It was not possible to assess the effect of smoking on the risk of acute myeloid and monocytic leukaemia in this study due to lack of data. Siegel[12] reviewed 12 studies which investigated the risk of myeloid leukaemia in smokers, and found 10 of them to be consistent with an increased risk of about 1·5. Smoking is thus not a potent confounder and would be unlikely to affect the shape of a dose-response relation. However, it could be an additional source of benzene which, in this study, could not be taken into account, and could also be an effect modifier.

There were 11 cases of chronic myeloid leukaemia. There was no evidence of an increased risk as cumulative exposure, maximum intensity, mean intensity, and duration of employment increased, either as continuous or categorical variables. There were no cases with an exposure < 0·45 ppm-years, with nine of the 11 being exposed between 0·45 and 4·5 ppm-years. Most were blue collar workers with long service. Similar patterns of peak exposure were found in chronic myeloid leukaemia as in acute myeloid and monocytic leukaemia. It is known that a proportion of chronic myeloid leukaemia cases do progress to acute myeloid leukaemia,[38] but this occurred in only one case in this study (included in acute myeloid and monocytic leukaemia with haematological evidence provided by the hospital). Chronic myeloid leukaemia is also related to the Philadelphia chromosome anomaly.[38]

We analysed the sensitivity of the results to the source of the work histories. In general the patterns were similar although the magnitude of the ORs and width of CIs varied. A potential source of bias might have been introduced through information being more readily available for surviving controls, particularly from interviews. However, results were similar when these data were excluded. In data sets which included only work histories taken mainly from personnel records which still exist the patterns were similar for three of the leukaemia subtypes but different for acute myeloid and monocytic leukaemia. However, the numbers of cases and controls were greatly reduced, adding to the uncertainty of the estimates and the predominance of random variation. The strict criteria of inclusion of the data sets from existing personnel records meant that some fairly reliable work histories were excluded. Examples of exclusions are; short service workers (< 5 years) where the personnel record does not exist any more, although the original cohort data were abstracted from personnel records; histories from regular medical records which were consistent for job title and location; and complete work histories which had most of the history from medical records but some from personnel records. It was not possible to carry out analyses examining the sensitivity of the estimates to the quality of the terminal information.

There were occasional inconsistencies in results for some exposures when analysed as continuous variables or categorised into discrete ranges. This suggests that the assumptions inherent in the analysis as a continuous variable may not be justified. As Rothman[35] has pointed out, categorisation facilitates the estimation of the ORs for different levels of exposure without the relational constraints imposed for continuous variables.

In several of the subtype analyses, date of hire had a significant effect on the risk, with the risks generally being higher for those who started work after 1950. It should be noted, however, that this nested case-control study is derived from a cohort with criteria for entry including at least one continuous year's work between 1950 and 1975. Thus, men who both joined and left before 1950 were not included in the cohort. The lack of inclusion of any leukaemia cases occurring before 1950 means that the risk before 1950 cannot be adequately evaluated.

The other confounding variable which showed consistently raised ORs was employment status at each subject's study end date,

with ORs being high for those in employment. Employment status at the study end date is highly correlated with duration of employment. A larger proportion of the controls had shorter service, and so were less likely to be employed at the case's date of diagnosis or death. This variable was included primarily to assess the existence of a healthy worker effect, the process by which those remaining employed tend to be healthier than those leaving employment. Under the assumption that there was no effect of exposure on risk of disease, study members who were employed for longer will on average have a higher cumulative exposure than those with shorter employment histories, but due to the healthy worker effect, risk may seem lower in the higher cumulative exposure group.[39] Exposure may thus seem to be protective. If the ORs for exposure variables go up when this variable is included this would be evidence of such an effect. In the present study there was little evidence of a healthy worker effect occurring for any of the leukaemia subtypes. In fact, there was a tendency for the exposure ORs to go down slightly or remain the same when employment status was included in the models.

Conclusions

This study on assessment of the risk of leukaemia with exposure to low concentrations of benzene emphasises the importance of recognising that the separate leukaemia subtypes may have different aetiologies. This has been substantiated by the varying patterns of risk shown in these results, particularly between the lymphocytic and myelogenous groups.

The limitations of the study discussed earlier should be taken into account when interpreting these results, including the wide CIs of some of the estimates, the poor fit of some of the models, and inconsistencies between the results obtained when the variables characterising exposure are continuous or categorical. There is no evidence in this study of an association between exposure to benzene and lymphocytic leukaemia, either acute or chronic. There is some suggestion of a relation between exposure to benzene and myeloid leukaemia, in particular acute myeloid and monocytic leukaemia. The nature of the exposure experienced for this disease also seemed to be peaked. However, in view of the limitations, doubt remains as to whether the risk of acute myeloid and monocytic leukaemia is increased by cumulative exposures of < 45 ppm-years.

This study estimated ORs for exposed versus less exposed oil distribution workers in the United Kingdom. It was limited in the range of exposures experienced by the study sample. A tendency for risk of acute myeloid and monocytic leukaemia to be associated with peaked exposure has been found in the present study but further work is needed to confirm this relation epidemiologically, including quantification of peaks, and to explore possible toxicological mechanisms that could explain it.

The completeness of the work histories varied and information from personnel records had sometimes to be supplemented with information from other sources, such as medical and pension records and interviews. Some attempt has been made to carry out analyses exploring the robustness of the results to uncertainties in the quality and source of this information. Some inconsistencies have arisen from these analyses. Further work is recommended to review the work histories and redefine their quality. Further exploration of the choice of cut offs for categories of variables, perhaps with smoothing techniques, would also be useful to investigate the apparent discrepancies between results for some variables analysed both continuously and categorically into discrete ranges. The development of ranges around the exposure estimates would enable other sensitivity analyses to be carried out.

Although this study grouped acute myeloid and acute monocytic leukaemias for analysis, others, including the recent benzene risk characterisation carried out for the European Commission,[40] considered all acute non-lymphocytic leukaemias as an entity, although acute myeloid leukaemia is the predominant cell type. There were three cases of other acute leukaemia in this study (one aleukaemic leukaemia, one erythroleukaemia, one acute leukaemia not specified but with pathological evidence of thrombocytopenia and possible aplastic anaemia) which could thus be included in a new grouping. However, these additions are unlikely to alter the results substantially.

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1 International Steering Committee of Medical Editors, Uniform requirements for manuscripts submitted to biomedical journals. *BMJ* 1979;**1**:532–5.
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