Exhibit 319

British Journal of Industrial Medicine 1987;44:365–381

An industry wide mortality study of chemical workers occupationally exposed to benzene. I General results

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ABSTRACT The cohort (7676) of this historical prospective study consisted of a group of male chemical workers from seven plants who had been occupationally exposed (continuously or intermittently) to benzene for at least six months and a comparison group of male chemical workers from the same plants who had been employed for at least six months during the same period but were never occupationally exposed to benzene. The observed mortality of the cohort, by cause, was compared with the expected based on the US mortality rates, standardised for age, race, sex, and calandar time. Standardised mortality ratios (SMRs) from all lymphatic and haematopoietic (lymphopoietic) cancer combined, leukaemia, non-Hodgkin's lymphoma (lymphosarcoma, reticulosarcoma, and other lymphoma), and non-Hodgkin's lymphopoietic cancer (non-Hodgkin's lymphoma and leukaemia) for the exposed group were slightly, but not significantly, raised above the national norm. These SMRs were considerably higher than those in the comparison group. When the group with no occupational exposure was used for direct comparison, the continuously exposed group experienced a relative risk from lymphopoietic cancer of 3·20 ($p < 0·05$). Furthermore, the Mantel-Haenszel chi-square showed that the association between continuous exposure to benzene and leukaemia was statistically significant ($p < 0·05$).

The first case report suggesting an association between exposure to benzene and leukaemia was given by Dolore and Borgomano in 1928.[1] Since then, numerous reports describing leukaemia among workers exposed to benzene have appeared.[2–6]

Thorpe reported an epidemiological survey of the incidence of leukaemia among active employees and annuitants from eight European petroleum plants.[7] For those who had been exposed to benzene, eight deaths from leukaemia were observed compared with 6·6 expected (SMR = 121, not significant). Among the non-exposed, the number of deaths observed was 10 with 16·7 expected (SMR = 60, not significant).

In a study of rubber hydrochloride workers who had been exposed to benzene 10 deaths from lymphatic and haematopoietic cancer were observed compared with 3·03 expected (SMR = 330, $p < 0·05$).[8–12] Specifically for leukaemia, there were seven observed deaths with only 1·25 expected (SMR = 560, $p < 0·01$). In another study of 594 workers exposed to benzene in the production of chlorobenzol, alkyl benzene, and ethyl Ott reported three cases of myelocytic leukaemia with 0·8 expected ($p < 0·047$).[13]

Vianna and Polan compared the crude mortality rates for lymphomas between men in 14 occupations with exposure to benzene in New York State (excluding New York City) with the state average.[14] The relative risks were 2·1 for lymphosarcoma, 1·6 for reticulum cell sarcoma, and 1·6 for Hodgkin's disease. Similarly, a relative risk of 3·34 was found to be associated with exposure to benzene in a case-control study in Olmsted County, Minnesota.[15]

Several epidemiological studies have found a significant mortality excess from leukaemia among workers exposed to solvents in the rubber industry.[16–19] The relation between this excess and benzene was less clear, however. In one study benzene was not the predominant solvent used and the authors were hesitant in ascribing benzene as the sole agent responsible for leukaemia.[16] In another study the

Accepted 5 August 1986

authors offered, as an explanation for the observed difference between coal and petroleum derived solvents, that there might have been contaminants in the coal derived solvents.[19]

Several recent epidemiological studies of petroleum refinery and petrochemical workers who are potentially exposed to petroleum products, including benzene, have also found excess in lymphopoietic cancers.[20-29] None of these petroleum refinery studies, however, provided any direct link between the observed mortality excess in lymphopoietic cancer and benzene, since the refinery workers studies were exposed to a variety of chemicals which might include benzene.

In a recent cohort study, however, the mortality experience of 454 employees who worked in benzene areas in a refinery was analysed.[30] No death due to lymphopoietic cancer was observed, whereas the expected death was 1·12 for lymphopoietic cancer and 0·42 for leukaemia. The cohort was small and the power to detect a modest increase in either lymphopoietic cancer or leukaemia was limited.

At present, there are several outstanding issues regarding the relation between exposure to benzene and increased risk of lymphatic and haematopoietic cancers. Firstly, none of the existing studies provides adequate information on exposure to benzene for any dose response analysis. Although the paper by Rinsky *et al* provides a fair amount of documentation of industrial hygiene data,[11] the lengthy discussion sheds little light on the mortality analysis. Secondly, the choice of an appropriate comparison is an important issue. In several studies analyses based on comparisons with the general population failed to detect an increased risk in lymphopoietic cancer or leukaemia. In the Thorpe study there was a slight non-significant excess of leukaemia among the refinery workers exposed to benzene when compared with the general population.[7] When compared with the non-exposed refinery workers, however, the risk was twofold. Similarly, in a cohort study of eight oil refineries in Britain[20] the leukaemia SMR, based on a comparison with the general population, was 94. A subsequent case-control study, however, using controls from other cohort members for comparison, found that a twofold risk of leukaemia was associated with exposure to benzene.[21] Thirdly, although some studies indicate that acute myelogenous leukaemia is the type frequently associated with exposure to benzene,[5 11 13] other reports show different cell types,[15 29] thus there is need for further investigations into the relation between exposure to benzene and lymphatic and haematopoietic cancers. This report summarises the findings of an industry wide mortality study of chemical workers occupationally exposed to benzene.

Methods and materials

STUDY DESIGN

The historical prospective mortality study was designed to include about 14 000 chemical workers from nine plants belonging to seven member companies of the Chemical Manufacturers Association (CMA). The cohort was to consist of two groups of workers.

Occupationally exposed group—Any worker with a total of at least six months at a job or jobs in the "continuous" or "intermittent" exposure category (see below) between 1 January 1946 and 31 December 1975.

Comparison group—Any worker with a total of at least six months of employment at the same plant between 1 January 1946 and 31 December 1975 and with completely no experience in either the continuous or intermittent category. Office personnel not directly engaged in plant operations were not included.

It was recognised that other chemicals besides benzene were also present at these plants and therefore workers who were occupationally exposed to benzene would have been potentially exposed to these other chemicals as well. It was thought that the availability of a group of workers from the same facilities, but not occupationally exposed to benzene, was important for internal comparison. Such an internal comparison would minimise the effects of concomitant exposures. Furthermore, such an internal comparison should also avoid several problems resulting from comparison with national mortality statistics, including the healthy worker effect and regional differences in cause specific mortality. Finally, as discussed earlier, internal comparison would probably increase the sensitivity of the study in detecting an increased risk in lymphopoietic cancer associated with occupational exposure to benzene.

EXPOSURE CLASSIFICATION

The continuous exposure category consisted of jobs in which a worker was assigned to a discrete area in which benzene was produced, separated, recovered, processed, or loaded unloaded, and potential exposure to benzene occurred on at least three days a week. Maintenance people assigned specifically to a benzene unit and laboratory quality control personnel working exclusively on samples from benzene units were also included. The intermittent exposure category could be described as "casual" exposure to benzene. It encompassed those jobs in which a worker was not assigned to a discrete area where benzene was produced, separated, recovered, processed, or loaded unloaded but the job required that the worker periodically worked in these areas, the pattern of which could not be characterised as continuous. The

group included maintenance workers assigned on a plant wide basis, laboratory quality control workers serving both benzene and non-benzene units, and workers assigned to loading/unloading where benzene was handled regularly but infrequently.

Cohort members were classified into three categories according to the histories of their occupational exposure to benzene.

Continuous exposure—Those with jobs totalling at least six months in either continuous or intermittent group and at least one job, regardless of duration, in the continuous group.

Intermittent exposure—Those with jobs totalling at least six months in the intermittent group only.

Comparison (no occupational exposure)—Those who had never had any exposed (continuous or intermittent) jobs.

DATA COLLECTION

It was decided by the participating companies that each company would be responsible for collecting its own data according to a common protocol. One company (plant 1) decided to contract out the data collection portion of the study; subsequently, the relevant employment records of the entire participating plant were microfilmed and the relevant information was coded for this company by a contract research team under the supervision of the project's principal investigator. A common protocol (modified slightly to suit the needs of individual companies), consisting of cohort definition, exposure classification scheme, and coding specifications, was provided to four companies who decided to collect data themselves. The remaining companies, all with existing plant wide studies of a comparable study design, decided to extract the eligible cohort members from the existing studies. Thus even though data collection was performed by different groups, a uniform cohort definition and a common protocol were used.

VITAL STATUS AND CAUSE OF DEATH DETERMINATION

Deaths among active employees and annuitants were identified through company records. Follow up of ex-employees through Social Security Administration and state motor vehicle departments was also conducted. For all cohort members reported to have died during the observation period, 1 January 1946 to 31 December 1977, death certificates were requested from appropriate state vital statistics departments. The underlying cause of death on all death certificates was coded by a qualified nosologist according to the 8th revision of the International Classification of Diseases.

DATA ON STUDY SUBJECTS IN THE FINAL COHORT

As stated earlier, nine plants from seven companies participated in the early stages of the study, and a cohort size of 14 000 was planned. One company, however, subsequently withdrew its two plants from the study. As a result, the study lost about 4000 potential cohort members. During data collection, one company found that records at its two plants were incomplete before 1957, and the cohort definition date for these two plants was moved from 1946 to 1957. This further reduced the original cohort size. The final cohort, consisting of seven plants from six companies, was smaller than initially planned.

Coded information on all individuals in the final cohort included all necessary demographic information and complete employment histories. For the purpose of this study, all non-benzene exposed segments of the work history were represented by a single code. As such, the entire work history of those in the comparison group was represented by a single segment.

DATA QUALITY ASSESSMENT

Once on computer tapes, the data were checked extensively for internal consistency, out of range or improper values, illogical sequence of dates, and cohort eligibility. Any questionable data were identified, investigated, and corrected.

The data in the study were supplied by the participating companies (except plant 1) and verified by the research team with respect to both the completeness and accuracy of the data. Completeness of the cohort for each plant was verified against Social Security quarterly reports.[31] Participating companies were asked to supply Social Security quarterly reports (form 941) for randomly selected years. From these reports, a random sample of names was selected and compared with the cohort. The number of reports per plant was proportional to the cohort size of that plant. The total number of names selected for cohort verification (cohort verification sample) was approximately 10% of the total cohort.

Any individual who appeared in the cohort verification sample but was not included in the cohort was identified. The participating plants were asked to supply a copy of the employment records of these individuals to the project team. These records were then reviewed in detail to determine whether the individuals were truly ineligible for inclusion in the cohort. This verification procedure turned out to be infeasible for one plant (plant 6) since the work histories from this plant were not specific enough for exposure classification, and the exposed employees were identified by long term supervisors. For the remaining six plants, an agreement rate of cohort completeness—that is, the number of individuals cor-

rectly included or excluded to the number of records examined—of 99·2% was obtained.

A second component of the data quality assessment was the determination of coding accuracy. A 10% random sample (stratified by plant) of cohort members was selected and their employment records were requested from the participating companies. The accuracy of the coded demographic and work history information was checked against the source documents. The overall error rate was 2·6%.

SUMMARY OF STUDY PARAMETERS BY PLANT

Since the study consisted of seven plants and each differed from others in some study parameters (such as first date benzene introduced at the plant and nature of the comparison group), it seems convenient to summarise various major study parameters by plant (table 1).

It should be noted from table 1 that cohort boundary, end of coded work history, and end of vital status observation differed slightly among some of the plants. The beginning date of cohort boundary was governed by the date when benzene was introduced at the plant, as well as by the earliest date with complete employment records. The closing date of cohort boundary was generally 1975, except that it was extended to 1976 and 1977 in two plants. For plant 7, two benzene consuming units were included in the study, and other benzene related units at this large chemical complex were not included. These two benzene consuming units included in the study ceased operation in 1963.

Because the data collection and data reduction of this multi-company study took longer than first expected, some companies finished coding sooner than the others. The end dates of coded work history and vital status determination differed slightly.

Table 1 also describes the nature of the comparison group by plant. For most plants, the comparison group consisted of all occupationally non-exposed workers at the same plant who satisfied the study criteria. For plant 2, which is a huge chemical complex with a large workforce, it was not feasible to include all occupationally non-exposed employees. Employees at the power house, who were not occupationally exposed to benzene, were chosen for comparison. For plant 3, which is a relatively small plant with the entire workforce exposed to benzene, the employees at a nearby facility belonging to the same company and with no occupational exposure to benzene were used for comparison.

STATISTICAL PROCEDURES

The most common summary index for assessing the risk of death in a population studied prospectively is the standardised mortality ratio (SMR). The United States national age cause race specific mortality rates for five year periods from 1946 to 1977 were applied to person-years of observation to obtain the number of deaths from a particular cause to be expected from an equal number of person-years of the same race and similar in age and calendar year. SMRs were computed by expressing the actually observed deaths as percentages of the expected. An SMR higher (lower) than 100 indicated an excess (deficit) in mortality. The actual computation was performed using a standard computer program.[32]

The SMR procedure is usually satisfactory if a comparable control group is available. When the general population is used for comparison, the problem of the so called healthy worker effect arises. In general, the use of an internal comparison can usually minimise the effect due to selection for health and any regional differences in mortality. Such internal comparison groups usually come from employees at the same facility unexposed to the agents under investigation. As discussed earlier, in several previous studies analyses based on comparisons between workers exposed to benzene and the general population failed to detect a risk of leukaemia, which was identified only when the exposed workers were compared with the non-exposed workers from the same facilities. Internal comparison groups, however, are usually much smaller than the general population, and the expected

Table 1 *Selected study parameters by plant*

Plant	*Date benzene introduced*	*Cohort boundary*	*End of work history*	*End of vital status observation*	*Nature of cohort*	*Method of exposure classification*	*Nature of comparison group*
1	1952	1952–76	1976	1977	Plant wide	Uniform task†	All non-exposed
2	1946	1946–75	1977	1977	Non-plant wide	Uniform task	Power house
3	1962	1962–75	1975	1976	Plant wide	Uniform task	A nearby plant
4	1922	1946–75	1977	1977	Plant wide	Uniform task	All non-exposed
5	1915	1957–77	1977	1977	Plant wide	Uniform task	All non-exposed
6	1946	1957–75	1976	1977	Plant wide	Review by supervisors	All non-exposed
7	1943	1949–63	1977	1977	Non-plant wide*	Area sample	All non-exposed

*Only two benzene consuming units were included. Other units with exposure to benzene were not included in this study.
†See part II of this paper for a description of the uniform task exposure classification.

deaths based on these groups will have considerable statistical variabilities. Since in testing the significance of SMR the number of expected deaths is treated as a constant, which is a reasonable assumption if the comparison group is large, SMR may not be appropriate for data based on small internal comparison groups. Under these circumstances, risk assessment comparing the exposed and the unexposed may be made through the use of relative risk. A commonly accepted methodology is the Mantel-Haenszel chi-square procedure.[33]

Results

DESCRIPTIVE STATISTICS

The number of female workers who satisfied the cohort criteria was so small that it was decided not to include them in the study. Altogether 7676 men satisfied the cohort criteria. The race distribution of these male cohort members was as follows: 6365 white, 707 non-white, and 604 unknown.

Table 2 shows the distribution of cohort members by exposure classification and by plant. Approximately 40% (3074) of the cohort were not occupationally exposed to benzene. Only 1066 individuals were in the intermittent group. The reason for the relatively small group size was that individuals with jobs in both continuous and intermittent exposure groups were classified in the continuous category. Two plants (plants 5 and 6) did not contribute to the intermittent group, primarily because the maintenance personnel were dedicated to the benzene units only and were included in the continuous group. The continuous exposure group consisted of 3536 cohort members, about 46% of the cohort.

Table 3 presents the distribution of year of birth for all cohort members. The distributions by exposure category appeared to be similar. Frequency by age at hire is given in table 4. Those hired in their 20s accounted for more than 60% of the total cohort. Relatively few cohort members were hired after age 35 (approximately 15%). Again the distributions were similar. The average duration of employment was 15·82 years for the total cohort, 13·00 years for the comparison group, 15·63 years for the intermittent exposure group, and 18·32 years for the continuous exposure group.

Table 5 provides the vital status distribution for all cohort members at the end of the observation period. A total of 1036 individuals in the study was identified

Table 2 *Distribution of benzene exposure status by plant for all cohort members*

	Comparison (no exposure)		*Intermittent exposure*		*Continuous exposure*		*Total*	
Plant	*Frequency*	*%*	*Frequency*	*%*	*Frequency*	*%*	*Frequency*	*%*
1	210	18·52	489	43·12	435	38·36	1134	100·00
2	427	49·77	2	0·23	429	50·00	858	100·00
3	287	37·62	118	15·47	358	46·92	763	100·00
4	381	15·78	431	17·85	1602	66·36	2414	100·00
5	372	54·71	0	0·00	308	45·29	680	100·00
6	1162	78·89	0	0·00	311	21·11	1473	100·00
7	235	66·38	26	7·34	93	26·27	354	100·00
Total	3074	40·05	1066	13·89	3536	46·07	7676	100·00

Table 3 *Distribution of year of birth by exposure group*

Year of birth	*Total*		*Comparison*		*Intermittent*		*Continuous*	
	Frequency	*%*	*Frequency*	*%*	*Frequency*	*%*	*Frequency*	*%*
1870–99	271	3·53	104	3·38	65	6·10	102	2·89
1900–04	280	3·65	105	3·42	41	3·85	134	3·79
1905–09	482	6·28	164	5·33	80	7·50	238	6·73
1910–14	711	9·26	199	6·47	121	11·35	391	11·06
1915–19	817	10·64	228	7·42	126	11·82	463	13·09
1920–24	1000	13·03	323	10·51	131	12·29	546	15·44
1925–29	1096	14·28	391	12·72	120	11·26	585	16·54
1930–34	746	9·72	288	9·37	107	10·04	351	9·93
1935–39	795	10·35	351	11·42	114	10·69	330	9·33
1940–44	752	9·80	419	13·63	72	6·75	261	7·38
1945–49	366	4·77	225	7·32	52	4·88	89	2·52
1950–54	337	4·39	261	8·49	31	2·91	45	1·27
1955–59	23	0·30	16	0·52	6	0·56	1	0·03
Total	7676	100·00	3074	100·00	1066	100·00	3536	100·00

Table 4 *Distribution of age at hire by exposure group*

Age at hire	Total		Comparison		Intermittent		Continuous	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%
<20	512	6·67	252	8·20	68	6·38	192	5·43
20–4	2909	37·90	1286	41·83	343	32·18	1280	36·20
25–9	1920	25·01	677	22·02	296	27·77	947	26·78
30–4	1060	13·81	352	11·45	150	14·07	558	15·78
35–9	664	8·65	253	8·23	93	8·72	318	8·99
40–4	344	4·48	150	4·88	65	6·10	129	3·65
45–9	152	1·98	62	2·02	21	1·97	69	1·95
50–4	68	0·89	22	0·72	19	1·78	27	0·76
55–9	29	0·38	10	0·32	6	0·56	13	0·37
60–4	14	0·18	7	0·23	5	0·47	2	0·06
65–9	4	0·05	3	0·10	0	0·00	1	0·03
Total	7676	100·00	3074	100·00	1066	100·00	3536	100·00

as having died during the study period. Among these individuals, death certificates were obtained for 1013 (97·8%). The percentage of death certificates not retrieved in the comparison group (4·29%), however, was higher than those in the exposed groups (1·12% and 1·32%). At the end of the study period, the vital status of 177 terminated employees (2·31%) remained unknown. The percentage with unknown vital status by exposure category was comparable.

MORTALITY RESULTS BASED ON COMPARISON WITH THE UNITED STATES POPULATION

Race was not available from the employment records of 604 (7·87%) cohort members. Most of the cohort were white (90·0% among those with known race), however. For statistical analysis, these 604 individuals were assumed to be white. Since the leukaemia death rate among the United States white men was higher than in non-white men, this assumption might overestimate the expected deaths from leukaemia slightly and thus underestimate the corresponding SMR. Furthermore, the percentage of cohort members with unknown race varied between exposure categories (3% in the non-exposed, 24% in the intermittently exposed, and 7% in the continuously exposed), and the potential underestimate in leukaemia would also vary by exposure category.

TOTAL COHORT

Table 6 shows the observed and expected deaths by cause, SMRs, and their 95% confidence limits for the entire cohort. A total of 133 967·9 person-years from the 7676 cohort members was observed. The total number of deaths observed in the entire cohort was 1036, whereas 1253·06 were expected. The corresponding SMR of 82·7 was statistically significant at the 0·01 level.

Mortality from all cancers was also less than expected (214 observed, SMR = 89·2, not significant). When site specific cancers were examined, it was found that the observed mortality was either lower than or about equal to the expected. For example, mortality deficits were identified for cancers of the buccal cavity and pharynx, stomach, liver, and prostate. On the other hand, lung cancer and cancer of other lymphatic tissue showed a slight excess. There were 86 observed deaths from lung cancer, whereas only 76·5 were expected, yielding an SMR of 112·4. This SMR was not statistically significant at the 0·05 level, but the lower 95% confidence limit was 90·0. Seven deaths were due to cancer of the other lymphatic tissues, compared with 5·55 expected (SMR = 126·1, not significant). As a whole, lymphatic and haematopoietic (lymphopoietic) cancer mortality was slightly less than expected (22 observed, SMR =

Table 5 *Distribution by vital status* of cohort members by exposure group*

Vital status	Total		Comparison		Intermittent		Continuous	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Alive	6463	84·20	2672	86·92	860	80·68	2931	82·89
Dead:	1036	13·50	326	10·61	179	16·79	531	15·02
With death certificate	(1013)	(97·78)	(312)	(95·71)	(177)	(98·88)	(524)	(98·68)
Without death certificate	(23)	(2·22)	(14)	(4·29)	(2)	(1·12)	(7)	(1·32)
Unknown	177	2·31	76	2·47	27	2·53	74	2·09
Total	7676	100·00	3074	100·00	1066	100·00	3536	100·00

*Vital status was determined as of 31 December 1977 for this study, planned to be updated at close study date of 31 December 1976.

Table 6 *Observed and expected deaths by cause, SMRs, and their 95% confidence limits for all (7676) cohort members (person-years = 133 967·9)*

Cause of death (8th ICDA)	*Observed deaths*	*Expected deaths*	*SMR*	*Lower limit*	*Upper limit*
All causes	1036	1253·06	82·7†	77·7	87·9
All cancers (140–209)	214	239·85	89·2	77·7	102·0
Cancer of buccal cavity and pharynx (140–149)	3	8·27	36·3	7·3	106·0
Cancer of digestive system (150–159):	49	67·56	72·5*	53·7	95·9
Cancer of oesophagus (150)	7	7·11	98·5	39·4	202·9
Cancer of stomach (151)	6	13·96	43·0*	15·7	93·6
Cancer of large intestine (153)	17	19·49	87·2	50·8	139·7
Cancer of liver (155–156)	2	4·78	41·0	4·6	147·7
Cancer of pancreas (157)	14	13·21	100·0	54·9	177·8
Cancer of respiratory system (160–163):	88	81·28	108·3	86·9	133·4
Cancer of lung (162–163)	86	76·51	112·4	90·0	138·8
Cancer of bone (170)	2	1·31	152·7	17·1	551·2
Cancer of skin (172–173)	3	4·43	67·7	13·6	197·9
Cancer of prostate (185)	10	13·14	76·1	36·4	140·0
Cancer of bladder (188)	5	6·13	81·6	26·3	190·3
Cancer of kidney (189)	5	5·89	84·9	27·4	198·1
Cancer of brain and central nervous system (191–192)	8	7·98	100·3	43·2	197·5
Lymphatic and haematopoietic cancer (200–209):	22	24·36	90·3	56·6	136·7
Lymphosarcoma and reticulosarcoma (200)	5	5·52	90·6	29·2	211·4
Hodgkin's disease (201)	3	3·71	80·9	16·3	236·3
Leukaemia and aleukaemia (204–207)	7	9·36	74·8	30·0	154·1
Other lymphatic tissue cancer (22, 203, 208)	7	5·55	126·1	50·5	259·9
Benign neoplasms (210–239)	5	3·55	112·7	36·3	288·5
Diabetes mellitus (250)	11	17·89	61·5	30·7	110·0
Diseases of blood (280–289)	2	2·79	71·7	8·1	258·8
Diseases of circulatory system (390–458):	535	608·29	88·0*	80·7	95·7
Arteriosclerotic heart disease (410–413)	373	418·46	89·1*	80·3	98·7
Vascular lesions of central nervous system (430–438)	65	81·68	79·6	61·4	101·4
Non-malignant respiratory disease (460–519):	46	67·19	68·5*	50·1	91·3
Pneumonia (480–486)	22	26·48	83·1	52·0	125·8
Emphysema (492)	16	16·21	98·7	56·4	160·3
Diseases of digestive system (520–577):	24	66·98	35·8†	23·0	53·3
Cirrhosis of liver (551)	14	36·83	38·0†	20·8	63·8
Diseases of genitourinary system (580–629)	10	19·69	50·8*	24·3	93·4
Accidents, poisonings, and violence (E800–E998):	136	156·91	86·7	72·7	102·5
Accidents (800–949)	95	104·15	91·2	73·8	111·5
Motor vehicle accidents (810–827)	49	49·55	98·9	73·2	130·7
Suicide (950–959)	20	32·31	61·9*	37·8	95·6

*Significant at 0·05. †Significant at 0·01.

90·3). This slight deficit came from lymphosarcoma and reticulosarcoma (5 observed, SMR = 90·6). Hodgkin's disease (3 observed, SMR = 80·9), and leukaemia (7 observed, SMR = 74·8). In the entire cohort only seven deaths were from leukaemia.

Two deaths were due to diseases of blood and blood forming organs, compared with 2·79 expected (SMR = 71·7, not significant).

Mortality from disease of the circulatory system was significantly less than expected (535 observed, SMR = 88·0, $p < 0·05$). The deficit came primarily from arteriosclerotic heart disease (373 observed, SMR = 89·1, $p < 0·05$).

It should be noted that, contrary to the non-significant excess found in lung cancer, mortality from non-malignant respiratory disease was significantly less than expected (46 observed, SMR = 68·5, $p < 0·05$).

CONTINUOUS EXPOSURE GROUP

Before we discuss the results in the continuously exposed group, a brief explanation of how person-years were counted is necessary. Since this group consisted of individuals with at least six months of occupational exposure (continuous or intermittent) and at least one of the exposed jobs fell into the continuous category, person-years started after six months of exposure (continuous or intermittent) or on the first day of continuous exposure, whichever was later. It should be noted that the start of person-years in this group was governed by date of exposure and not by date of employment. The average difference between first date of exposure and first date of employment, however, was only 2·14 years.

Among the 3536 individuals who were classified as continuously exposed to benzene, 531 deaths were observed, compared with 613·12 expected (table 7). The overall SMR was 86·6, statistically significant at the 0·01 level. The number of observed deaths from cancer (123) was slightly, but not significantly, more than the expected (117·71).

Mortality from cancer of the digestive system was

Table 7 *Observed and expected deaths by cause, SMRs, and their 95% confidence limits for all (3536) cohort members continuously exposed to benzene (person-years = 64 482·5)*

Cause of death (8th ICDA)	*Observed deaths*	*Expected deaths*	*SMR*	*Lower limit*	*Upper limit*
All causes	531	613·12	86·6†	79·4	94·3
All cancers (140–209)	123	117·71	104·5	86·8	124·8
Cancer of buccal cavity and pharynx (140–149)	2	4·11	48·7	5·9	175·8
Cancer of digestive system (150–159):	26	33·27	78·2	51·1	114·6
Cancer of oesophagus (150)	4	3·79	105·5	28·7	269·7
Cancer of stomach (151)	5	7·06	70·8	22·9	165·5
Cancer of large intestine (153)	10	9·27	107·9	51·9	198·3
Cancer of liver (155–156)	1	2·43	41·2	1·0	228·9
Cancer of pancreas (157)	4	6·49	61·6	16·8	157·6
Cancer of respiratory system (160–163):	49	40·10	122·2	90·2	161·7
Cancer of lung (162–163)	47	37·74	124·5	91·4	165·7
Cancer of bone (170)	2	0·63	317·4	38·4	1145·8
Cancer of skin (172–173)	1	2·13	47·0	1·2	261·0
Cancer of prostate (185)	6	6·45	93·1	34·1	202·7
Cancer of bladder (188)	3	2·86	105·0	21·6	306·9
Cancer of kidney (189)	4	2·86	140·0	38·1	358·0
Cancer of brain and central nervous system (191–192)	6	3·90	153·9	56·4	335·2
Lymphatic and haematopoietic cancer (200–209):	15	11·74	127·8	71·4	210·9
Lymphosarcoma and reticulosarcoma (200)	3	2·65	113·0	23·3	330·6
Hodgkin's disease (201)	2	1·78	112·2	13·6	405·1
Leukaemia and aleukaemia (204–207)	6	4·43	135·4	49·6	294·9
Other lymphatic tissue cancer (22, 203, 208)	4	2·77	144·7	39·4	370·0
Benign neoplasms (210–239)	3	1·78	169·0	34·8	494·1
Diabetes mellitus (250)	8	8·81	90·9	39·2	178·8
Diseases of blood (280–289)	1	1·34	74·4	1·9	413·1
Diseases of circulatory system (390–458):	269	295·46	91·0	80·4	102·7
Arteriosclerotic heart disease (410–413)	189	199·90	94·5	81·5	109·0
Vascular lesions of central nervous system (430–438)	31	40·74	76·1	51·7	108·1
Non-malignant respiratory disease (460–519):	21	32·44	64·7*	40·0	99·0
Pneumonia (480–486)	8	13·27	60·3	26·0	118·7
Emphysema (492)	10	7·34	136·2	65·5	250·4
Diseases of digestive system (520–577):	12	33·34	36·0†	18·6	62·8
Cirrhosis of liver (551)	8	18·55	43·1*	18·6	84·9
Diseases of genitourinary system (580–629)	3	10·25	29·3*	6·0	85·6
Accidents, poisonings, and violence (E800–E998):	73	75·59	96·6	75·8	121·5
Accidents (800–949)	47	50·07	93·9	68·9	124·9
Motor vehicle accidents (810–827)	27	23·27	116·0	76·3	168·9
Suicide (950–959)	9	15·28	58·9	27·0	111·8

*Significant at 0·05. †Significant at 0·01.

less than the expected, but the corresponding SMR of 78·2 was not significant. On the other hand, lung cancer mortality rose by some 25%, with an SMR of 124·5, but the rise was not statistically significant.

Mortality excesses were found for cancers of the bone (2 observed, SMR = 317·4), kidney (4 observed, SMR = 140·0), and brain (6 observed, SMR = 153·9). The number of observed deaths in each case was small, however, and none of the SMRs was statistically significant.

In this group of chemical workers with continuous exposure to benzene 15 deaths from lymphatic and haematopoietic cancer occurred, whereas 11·74 were expected (SMR = 127·8, not significant). Among the 15 deaths, three were due to lymphosarcoma and reticulosarcoma (SMR = 113·0, not significant) and two to Hodgkin's disease (SMR = 112·2, not significant). Six deaths were from leukaemia, compared with 4·43 expected based on the United States population experience. The leukaemia SMR (135·4) was not significant at the 0·05 level. For cancer of the other lymphatic tissues, four deaths were observed with 2·77 expected (SMR = 144·7, not significant).

Only one death was ascribed to diseases of the blood and blood forming organs. Based on an expected 1·34, the SMR was 74·4.

Mortality from disease of the circulatory system was not significantly less than the expected (269 observed, SMR = 91·0). Similarly, only a small non-significant deficit was found for arteriosclerotic heart disease (189 observed, SMR = 94·5).

INTERMITTENT EXPOSURE GROUP

The group of 1066 individuals with only intermittent exposure to benzene contributed a total of 19 512·6 person-years (table 8). Overall mortality was slightly but not significantly less than the expected (179 observed, SMR = 89·1). The number of deaths from cancer (38) was almost identical to the expected (38·1).

Table 8 *Observed and expected deaths by cause, SMRs, and their 95% confidence limits for all (1066) cohort members intermittently exposed to benzene (person-years = 19 512·6)*

Cause of death (8th ICDA)	Observed deaths	Expected deaths	SMR	Lower limit	Upper limit
All causes	179	200·88	89·1	76·5	103·2
All cancers (140–209)	38	38·93	97·6	68·9	134·1
Cancer of buccal cavity and pharynx (140–149)	0	1·34	0	—	—
Cancer of digestive system (150–159):	7	11·18	62·6	25·1	129·0
Cancer of oesophagus (150)	0	1·15	0	—	—
Cancer of stomach (151)	1	2·35	42·6	1·1	236·8
Cancer of large intestine (153)	2	3·21	62·3	7·5	224·8
Cancer of liver (155–156)	0	0·82	0	—	—
Cancer of pancreas (157)	4	2·16	184·9	50·4	472·8
Cancer of respiratory system (160–163):	18	13·12	137·2	81·2	216·8
Cancer of lung (162–163)	18	12·34	145·9	86·3	230·4
Cancer of bone (170)	0	0·21	0	—	—
Cancer of skin (172–173)	1	0·68	146·4	3·7	813·5
Cancer of prostate (185)	1	2·21	45·2	1·1	251·4
Cancer of bladder (188)	1	1·04	96·0	2·4	533·6
Cancer of kidney (189)	0	0·95	0	—	—
Cancer of brain and central nervous system (191–192)	0	1·24	0	—	—
Lymphatic and haematopoietic cancer (200–209):	4	3·85	104·0	28·3	265·9
Lymphosarcoma and reticulosarcoma (200)	1	0·87	114·6	2·9	636·5
Hodgkin's disease (201)	0	0·56	0	—	—
Leukaemia and aleukaemia (204–207)	1	1·49	67·0	1·7	372·2
Other lymphatic tissue cancer (22, 203, 208)	2	0·88	226·0	27·4	816·1
Benign neoplasms (210–239)	0	0·57	0	—	—
Diabetes mellitus (250)	1	2·89	34·6	0·9	192·5
Diseases of blood (280–289)	0	0·45	0	—	—
Diseases of circulatory system (390–458):	89	99·89	89·1	71·7	109·6
Arteriosclerotic heart disease (410–413)	57	68·61	83·1	62·8	107·7
Vascular lesions of central nervous system (430–438)	11	13·47	81·7	40·8	146·1
Non-malignant respiratory disease (460–519):	7	10·92	64·1	25·7	132·2
Pneumonia (480–486)	4	4·22	94·7	25·8	242·2
Emphysema (492)	2	2·70	74·2	9·0	267·9
Diseases of digestive system (520–577):	5	10·48	47·7	15·4	111·5
Cirrhosis of liver (551)	2	5·60	35·7	4·3	129·0
Diseases of genitourinary system (580–629)	3	3·21	93·3	19·2	272·9
Accidents, poisonings, and violence (E800–E998):	29	22·64	128·1	86·0	184·0
Accidents (800–949)	23	15·25	150·8	95·5	226·5
Motor vehicle accidents (810–827)	14	7·13	196·2*	107·2	329·2
Suicide (950–959)	4	4·82	83·0	22·6	212·2

*Significant at 0·05.

Mortality from cancer of the digestive system was lower than expected (7 observed, SMR = 62·6, not significant). Mortality due to pancreatic cancer was raised (4 observed, SMR = 184·9, not significant). Lung cancer was also in excess when compared with the United States population (18 observed, SMR = 145·9, not significant). Four deaths were ascribed to lymphatic and haematopoietic cancer, close to the expected (3·85). Only one death from leukaemia occurred, compared with 1·49 expected. Mortality from cancer of other lymphatic tissue was twice the expected (2 observed, SMR = 226·0, not significant).

None of the cause specific mortality was found to be significant, except for motor vehicle accidents. Fourteen fatal motor vehicle accidents occurred in this group, whereas only 7·13 were expected. The corresponding SMR of 196·2 was significant at the 0·05 level.

TOTAL EXPOSED GROUP

For the group consisting of both the continuously and intermittently exposed individuals, person-years started after six months of exposure (intermittent or continuous) in this group. Those with mixed exposure contributed more person-years in this analysis than in the analysis for the continuously exposed group if the early part of their exposure was intermittent. For this reason, the number of person-years in this analysis was larger than the sum of the person-years for the separate analyses for the continuous and intermittent exposure groups. A total of 4602 chemical workers was classified in this group and a total of 85069·9 person-years was observed.

For this group (table 9), overall mortality was significantly lower than the expected (710 observed, SMR = 86·6, $p < 0·05$) but cancer mortality was as expected (161 observed, SMR = 102·3). Mortality from cancer of the digestive system was lower than expected (33 observed, SMR = 73·9, not significant). Sixty five deaths from lung cancer occurred, whereas the expected was 50·25. The lung cancer SMR of 129·3 was of borderline significance ($p = 0·05$).

Table 9 *Observed and expected deaths by cause, SMRs, and their 95% confidence limits for all (4602) cohort members intermittently or continuously exposed to benzene (person-years = 85 069·9)*

Cause of death (8th ICDA)	*Observed deaths*	*Expected deaths*	*SMR*	*Lower limit*	*Upper limit*
All causes	710	819·49	86·6†	80·4	93·2
All cancers (140–209)	161	157·36	102·3	87·1	119·3
Cancer of buccal cavity and pharynx (140–149)	2	5·47	36·6	4·4	132·0
Cancer of digestive system (150–159):	33	44·67	73·9	50·7	103·9
Cancer of oesophagus (150)	4	4·97	80·5	21·9	205·9
Cancer of stomach (151)	6	9·47	63·4	23·2	138·1
Cancer of large intestine (153)	12	12·53	95·8	49·4	167·2
Cancer of liver (155–156)	1	3·27	30·6	0·8	169·9
Cancer of pancreas (157)	8	5·69	92·1	39·7	181·5
Cancer of respiratory system (160–163):	67	53·41	125·4	97·3	159·4
Cancer of lung (162–163)	65	50·25	129·3	99·9	165·0
Cancer of bone (170)	2	0·85	235·5	28·5	850·2
Cancer of skin (172–173)	2	2·83	70·7	8·6	255·3
Cancer of prostate (185)	5	8·68	80·6	32·4	166·2
Cancer of bladder (188)	4	3·91	102·2	27·8	261·4
Cancer of kidney (189)	4	3·83	104·5	28·5	267·3
Cancer of brain and central nervous system (191–192)	6	5·17	116·0	42·5	252·7
Lymphatic and haematopoietic cancer (200–209):	19	15·68	121·1	73·0	189·3
Lymphosarcoma and reticulosarcoma (200)	4	3·55	112·8	30·7	288·4
Hodgkin's disease (201)	2	2·37	84·4	10·2	304·6
Leukaemia and aleukaemia (204–207)	7	5·96	117·4	47·1	242·0
Other lymphatic tissue cancer (22, 203, 208)	6	3·66	163·8	60·0	356·8
Benign neoplasms (210–239)	3	2·36	127·0	26·2	371·4
Diabetes mellitus (250)	9	11·75	76·6	35·1	145·3
Diseases of blood (280–289)	1	1·81	55·3	1·4	307·0
Diseases of circulatory system (390–458):	358	397·54	90·1*	81·0	99·9
Arteriosclerotic heart disease (410–413)	246	269·53	91·3	80·2	103·5
Vascular lesions of central nervous system (430–438)	42	54·53	77·0	55·5	104·2
Non-malignant respiratory disease (460–519):	28	43·61	64·2*	42·8	92·8
Pneumonia (480–486)	12	17·63	68·1	35·1	118·8
Emphysema (492)	12	10·06	119·3	61·5	208·2
Diseases of digestive system (520–577):	17	44·10	38·6†	22·4	61·7
Cirrhosis of liver (551)	10	24·27	41·2†	19·8	75·7
Diseases of genitourinary system (580–629)	6	13·62	44·1*	16·1	96·0
Accidents, poisonings, and violence (E800–E998):	102	99·59	102·4	83·4	124·4
Accidents (800–949)	70	66·24	105·7	82·6	133·6
Motor vehicle accidents (810–827)	41	30·88	132·8	95·2	180·2
Suicide (950–959)	13	20·29	64·1	34·1	109·5

*Significant at 0·05, †Significant at 0·01.

Among the chemical workers exposed to benzene, 19 deaths were due to lymphatic and haematopoietic cancer compared with 15·68 expected (SMR = 121·1). Among them, seven deaths were attributed to leukaemia with 5·96 expected (SMR = 117·4) and six to cancer of other lymphatic tissues with 3·66 expected (SMR = 163·8). None of these excesses was statistically significant.

UNEXPOSED GROUP

As stated earlier, 3704 individuals in the cohort were not directly associated with any benzene related units for any time during their entire work history. Table 10 presents the cause specific mortality analysis of this comparison group. Similar to the exposed group, these occupationally non-exposed chemical workers also experienced a significant mortality deficit (326 observed, SMR = 75·2, $p < 0·01$). In addition, however, this comparison group also experienced a significant deficit in total cancer mortality (53 observed, SMR = 74·4, $p < 0·01$).

In this group lung cancer mortality was slightly, but not significantly, less than expected (21 observed, SMR = 80·0). Only three deaths were due to lymphatic and haematopoietic cancer when 8·68 were expected. The SMR of 34·6 was of borderline statistical significance ($p = 0·05$). This deficit probably reflects the fact that no death from leukaemia occurred when 3·40 were expected. Assuming a Poisson distribution, the probability of observing no deaths from leukaemia when expecting 3·40 was 0·033.

Since the United States male mortality rates were used in calculating the expected deaths in all the SMR analyses, comparisons between different exposure groups may be based on the SMRs presented in tables 7–10. Comparing indirectly adjusted SMRs, however, may not be appropriate if the groups being compared differ with respect to the factors adjusted.[34] In the calculations here the major adjustment is age. We have examined the age distributions of the person-years among the three exposure groups and found

Table 10 *Observed and expected deaths by cause, SMRs, and their 95% confidence limits for all (3074) cohort members occupationally unexposed to benzene (person-years = 48 898·0)*

Cause of death (8th ICDA)	Observed deaths	Expected deaths	SMR	Lower limit	Upper limit
All causes	326	433·57	75·2†	67·2	83·8
All cancers (140–209)	53	82·49	64·2†	48·0	84·1
Cancer of buccal cavity and pharynx (140–149)	1	2·80	35·8	0·9	198·6
Cancer of digestive system (150–159):	16	22·89	69·9	39·9	113·5
Cancer of oesophagus (150)	3	2·14	140·0	28·9	409·4
Cancer of stomach (151)	0	4·49	0	—	—
Cancer of large intestine (153)	5	6·96	71·8	23·2	167·7
Cancer of liver (155–156)	1	1·62	61·7	1·6	342·5
Cancer of pancreas (157)	6	4·52	132·9	48·7	289·5
Cancer of respiratory system (160–163):	21	27·87	75·4	46·5	115·2
Cancer of lung (162–163)	21	26·26	80·0	49·4	122·3
Cancer of bone (170)	0	0·46	0	—	—
Cancer of skin (172–173)	1	1·60	62·4	1·6	346·4
Cancer of prostate (185)	3	4·46	67·3	13·9	196·9
Cancer of bladder (188)	1	2·22	45·0	1·1	250·1
Cancer of kidney (189)	1	2·06	48·4	1·2	269·1
Cancer of brain and central nervous system (191–192)	2	2·81	71·2	8·6	257·0
Lymphatic and haematopoietic cancer (200–209):	3	8·68	34·6	7·1	101·1
Lymphosarcoma and reticulosarcoma (200)	1	1·97	50·8	1·3	282·4
Hodgkin's disease (201)	1	1·34	74·7	1·9	415·2
Leukaemia and aleukaemia (204–207)	0	3·40	0	—	—
Other lymphatic tissue cancer (22, 203, 208)	1	1·89	53·0	1·3	294·2
Benign neoplasms (210–239)	1	1·19	83·7	2·1	465·3
Diabetes mellitus (250)	2	6·14	32·6	3·9	117·7
Diseases of blood (280–289)	1	0·98	102·0	2·6	566·5
Diseases of circulatory system (390–458):	177	210·95	83·9*	72·0	97·2
Arteriosclerotic heart disease (410–413)	127	148·93	85·3	71·1	101·5
Vascular lesions of central nervous system (430–438)	23	27·15	84·7	53·6	127·2
Non-malignant respiratory disease (460–519):	18	23·58	76·3	45·2	120·6
Pneumonia (480–486)	10	8·85	113·0	54·3	207·8
Emphysema (492)	4	6·15	65·0	17·7	166·4
Diseases of digestive system (520–577):	7	22·88	30·6†	12·3	63·1
Cirrhosis of liver (551)	4	12·56	31·9*	8·7	81·5
Diseases of genitourinary system (580–629)	4	6·07	65·9	18·0	168·6
Accidents, poisonings, and violence (E800–E998):	34	57·32	59·3†	41·0	82·9
Accidents (800–949)	25	37·91	66·0*	42·5	97·3
Motor vehicle accidents (810–827)	8	18·67	42·9†	18·5	84·4
Suicide (950–959)	7	12·02	58·2	23·4	120·1

*Significant at 0·05. †Significant at 0·01.

that the age compositions were comparable. Therefore, a comparison of SMRs would not be inappropriate.

As shown in tables 9 and 10, the overall SMR for the exposed group (continuous and intermittent) was slightly higher than that for the comparison group (86·6 v 75·2), even though both were significantly less than the United States norm. A substantial difference was noted for the all cancer SMRs for the different exposure groups (102·3 for the exposed v 64·2 for the comparison group).

Although SMRs for cancer of the digestive system were similar for the occupationally exposed and unexposed (73·9 v 69·9), the SMRs differed considerably for specific organs. For cancers of the oesophagus, liver, and pancreas the SMRs among the occupationally unexposed were much higher than those in the exposed group, although the numbers of deaths in all three cases were small. Mortality from lung cancer in the occupationally exposed group was substantially higher than that in the comparison group. Differences in the same direction were also observed for bone cancer, bladder cancer, kidney cancer, and cancer of the brain and other parts of the central nervous system.

There was a substantial difference in mortality from lymphatic and haematopoietic cancer between the occupationally exposed and the comparison groups. The corresponding SMRs were 121·1 (19 observed) and 34·6 (3 observed), respectively, a ratio of 3·5-fold. The increase came almost entirely from non-Hodgkin's lymphopoietic cancers (non-Hodgkin's lymphomas and leukaemias). For lymphosarcoma and reticulosarcoma, the difference was more than twofold; and for other lymphatic tissue cancer the difference was more than threefold. For leukaemia, the SMR for the exposed was 117·4 (7 observed) whereas there was no observed death due to leukaemia among the unexposed. For Hodgkin's disease the SMRs were somewhat similar (84·4 for the exposed v 74·7 for the comparison group). Thus, based on these SMRs, the occupationally exposed

group experienced considerably higher mortality risk from non-Hodgkin's lymphopoietic cancer (particularly leukaemia) than the occupationally unexposed workers at the same facilities.

Mortality from benign neoplasms was higher in the exposed group than in the comparison group. But the SMR for diseases of the blood and blood forming organs among the exposed was less than the comparison group. Only one death attributed to this cause was observed in either group, however.

Mortality from disease of the circulatory system was comparable between the two groups and so were diseases of the digestive and genitourinary systems. For pneumonia, the occupationally exposed workers experienced a lower mortality than the occupationally unexposed, whereas for emphysema, the opposite was observed. Finally, the SMR for motor vehicle accidents for the occupationally exposed (132·8) was much higher than that for the occupationally unexposed (42·9).

MORTALITY RESULTS BASED ON INTERNAL COMPARISON

As mentioned earlier, the Mantel-Haenszel chi-square procedure was used, in addition to comparing SMRs, in assessing the difference in cause specific mortality risk between the occupationally exposed and occupationally unexposed workers. Table 11 shows the Mantel-Haenszel relative risks and chi-squares for all lymphatic and haematopoietic cancers combined between chemical workers occupationally exposed (intermittently or continuously) and those occupationally non-exposed to benzene, adjusted for both age and race. Some preliminary analyses adjusting for age, race, and plant showed the contribution from the last variable, plant, was negligible and therefore plant was not included in the final analyses in order to simplify the computation. Among the white men, the relative risk (RR) was 4·66 ($p = 0·030$) and among non-white men 0·79 (not significant). For both races combined, the RR was 2·99, of borderline statistical significance ($p = 0·054$).

When the continuously exposed workers were compared directly with the occupationally non-exposed, the RR for lymphatic and haematopoietic cancer was 5·30 ($p = 0·020$) for white men, 0·81 (not significant) for non-white men, and 3·20 ($p = 0·041$) for all men. These RRs, Mantel-Haenszel chi-squares, and corresponding p values are also shown in table 11. Thus there was significant mortality excess from lymphopoietic cancer between the continuously exposed and the occupationally non-exposed among white men and among all men. The number of deaths among the non-white men was too small for any firm conclusion.

The Mantel-Haenszel procedure was also used to compare leukaemia mortality between the

Table 11 *Mantel-Haenszel relative risk and chi-squares for lymphatic and haematopoietic cancer between chemical workers occupationally exposed and not exposed to benzene, adjusted for age and race*

Exposure groups compared	*Race*	*Observed deaths:*		*Relative risk*	*Mantel-Haenszel chi-square*	*p Value*
		Exposed	*Non-exposed*			
Total exposed (continuous and intermittent) v comparison	White	15	2	4·66	4·71*	0·03
	Non-white	4	1	0·79	0·16	0·70
	Both	19	3	2·99	3·72	0·05
Continuously exposed v comparison	White	12	2	5·30	5·39*	0·02
	Non-white	3	1	0·81	0·05	0·82
	Both	15	3	3·20	4·19*	0·04

*Statistically significant at the 0·05 level.

Table 12 *Mantel-Haenszel relative risk and chi-squares for leukaemia between chemical workers occupationally exposed and not exposed to benzene, adjusted for age and race*

Exposure groups compared	*Race*	*Observed deaths:*		*Relative risk*	*Mantel-Haenszel chi-square*	*p Value*
		Exposed	*Non-exposed*			
Total exposed (continuous and intermittent) v comparison	White	6	0	Undefined	3·58	0·06
	Non-white	1	0	Undefined	0·18	0·67
	Both	7	0	Undefined	3·73	0·05
Continuously exposed v comparison	White	5	0	Undefined	4·26*	0·04
	Non-white	1	0	Undefined	0·23	0·63
	Both	6	0	Undefined	4·42*	0·04

*Statistically significant at the 0·05 level.

occupationally exposed and the occupationally non-exposed groups. Relative risk, however, could not be computed for leukaemia, since there was no death from leukaemia in the comparison group. In this case the denominator of the relative risk was zero, and the relative risk ratio would be infinitely large and mathematically undefined. Mantel-Haenszel chi-square, however, could be computed. Table 12 shows that the association between occupational exposure to benzene (intermittent or continuous) and leukaemia approached statistical significance in white men ($p = 0.058$) as well as in all men ($p = 0.053$). The same table also shows that the association between continuous exposure to benzene and leukaemia was statistically significant among the white men ($p = 0.039$) and among all men ($p = 0.036$).

In addition to leukaemia, SMRs for the subcategories "lymphosarcoma and reticulosarcoma" and "other lymphatic tissue cancer" among the occupationally exposed chemical workers were higher than those among the occupationally non-exposed. An additional direct comparison between the exposed (continuous and intermittent) and the comparison group was made for non-Hodgkin's lymphopoietic cancer (non-Hodgkin's lymphoma and leukaemia combined). Because some non-Hodgkin's lymphomas have been reported to have ended in leukaemia either as a natural progression of the disease or owing to medical treatments, and because there has been a diagnostic overlap between these lymphomas and leukaemia, it was thought that these two categories should be combined for analysis.

Table 13 shows that the Mantel-Haenszel RR for non-Hodgkin's lymphopoietic cancer between the total exposed group (continuous and intermittent) and the comparison group was 8·60 ($p = 0.016$) for the white men and 3·71 ($p = 0.042$) for both races combined. For non-whites, the numbers of deaths were too few for discussion. Between the continuously exposed and the occupationally non-exposed the RR was 9·60 ($p = 0.011$) for the white men and 3·77 ($p = 0.037$) for both races combined.

It was noted earlier that the SMR for kidney cancer for the continuously exposed (140·0) was three times that for the occupationally unexposed (48·4). Even though based on small numbers this finding is interesting, since a recent animal study indicated that male rats exposed to unleaded gasoline (containing benzene) developed renal carcinoma (International Research and Development Corporation, technical report, 1982). In addition, a recent major industry wide study on employees at oil distribution centres in the United Kingdom found that drivers with potential exposure to downstream gasoline experienced a significant excess of kidney and suprarenal cancer.[35] It was thought, therefore, that a direct comparison of kidney cancer mortality between the continuously exposed and the occupationally unexposed based on the Mantel-Haenszel procedure was warranted. The relative risk for kidney cancer between the continuously exposed and occupationally non-exposed groups was 2·62, not statistically significant (table 14). Therefore, the data did not show any statistically significant relation between kidney cancer and

Table 13 *Mantel-Haenszel relative risk and chi-squares for non-Hodgkin's lymphopoietic cancer (non-Hodgkin's lymphoma and leukaemia) between chemical workers occupationally exposed and not exposed to benzene, adjusted for age and race*

Exposure groups compared	*Race*	*Observed deaths:* *Exposed*	*Non-exposed*	*Relative risk*	*Mantel-Haenszel chi-square*	*p Value*
Total exposed (continuous and intermittent) v comparison	White	14	1	8·60	5·84*	0·02
	Non-white	3	1	0·48	0·48	0·49
	Both	17	2	3·71	4·14*	0·04
Continuously exposed v comparison	White	11	1	9·60	6·33*	0·01
	Non-white	2	1	0·43	0·60	0·44
	Both	13	2	3·77	4·34*	0·04

*Statistically significant at the 0·05 level.

Table 14 *Mantel-Haenszel relative risk and chi-squares for kidney cancer between chemical workers continuously exposed and occupationally non-exposed to benzene, adjusted for age and race*

Race	*Observed deaths:* *Continuously exposed*	*Non-exposed*	*Relative risk*	*Mantel-Haenszel chi-square*	*p Value*
White	2	1	2·00	0·33	0·55
Non-white	2	0	Undefined	0·36	0·55
Both	4	1	2·62	0·51	0·48

occupational exposure to benzene. It should be pointed out, however, that the number of deaths (5) was small.

Discussion and conclusion

This study, designed specifically to detect any adverse cause specific mortality resulting from occupational exposure to benzene, was based on a group of chemical workers occupationally exposed to benzene and a group from the same plants not occupationally exposed to benzene. As discussed earlier, the provision of an internal comparison group was designed to minimise several problems resulting from comparing an occupational cohort with the general population. Such an internal comparison group is regarded as the most appropriate basis for comparison in occupational mortality studies.[36 37] In particular, comparisons based on internal groups were found to be more sensitive in detecting the association between leukaemia and occupational exposure to benzene,[7 21] and in demonstrating a suggested increase in lymphoma mortality with increased exposure among refinery workers.[23 24] On the other hand, an internal comparison group is much smaller than the general population and introduces a certain amount of statistical variabilities. By using an internal comparison group, one compares the exposed group against a sample estimate rather than with a population constant. If the comparison group chosen experiences a mortality deficit (as compared with the general population), significant or otherwise, the effect will be to magnify the relative risk of those exposed.

In addition to the advantage of having an internal comparison group, the study is also the first large scale epidemiological mortality study in which the jobs of all exposed cohort members were characterised quantitatively by an eight hour time weighted average as well as by a peak benzene exposure level. The dose response analyses will be presented in part II of this paper. Ott *et al* provided cumulative exposure levels for the workers studied, but that study was relatively small in size and no leukaemia analysis by cumulative exposure level was reported.[13] Instead, only mortality from cardiovascular disease and all cancers was analysed by cumulative benzene level. The existing reports lack epidemiological data on the dose response relation between exposure to benzene and leukaemia, as well as lymphopoietic cancers.

Most previous studies have focused on the possible relation between occupational exposure to benzene and leukaemia. Whereas a few have also shown that individuals potentially exposed to benzene might be at a higher risk of developing various types of lymphoma,[11 22–24 26] the available epidemiological evidence is equivocal.

One of the difficulties in separating certain haematopoietic cancers from one another is that certain amounts of overlap appear to occur. Medical publications are replete with reports documenting the transitions from certain lymphomas and multiple myelomas to leukaemia.[38–43] A leukaemic phase has long been recognised in some non-Hodgkin's lymphoma cases,[44] and leukaemic transformation of lymphoid cells is considered a part of the natural course of some non-Hodgkin's lymphomas[45] and lymphoma in general.[46] In addition, some patients with lymphoma or multiple myeloma may subsequently develop leukaemia as a result of their medical treatments.[42 47 48]

These transitions or progressions from lymphoma to leukaemia are further complicated by the historical changes in nomenclature and the diagnostic overlap between the two disorders.[48–50] In fact, some haematologists consider that certain lymphomas—for example, lymphocytic lymphoma—and leukaemias such as chronic lymphocytic leukaemia "simply represent different clinical expressions of the same neoplastic process"[50] and that lymphoma and lymphoblastic leukaemia "simply seem to be different initial manifestations of a single neoplastic disorder."[43]

Recent immunological studies have shown that there are stem cells that appear to have the capacity to develop into the following different cell lines: T cell lymphocytes, plasma cells, granulocytic series cells, erythrocytes, and monocytes.[51] Further work by Bakhshi *et al* showed that the major clone in chronic myelocytic leukaemia affected cells capable of lymphocyte, granulocyte, and erythrocyte differentiations,[52] leading to the conclusion that transformation events occur at an early multipotent stem cell level.[53]

Based on the above considerations, we thought that it would be appropriate to combine lymphoma and leukaemia in some of the analyses. This approach has also been recommended recently by other investigators.[22 48]

The group exposed to benzene in this study did not show any significant mortality excess from all lymphatic and haematopoietic cancers combined when compared with the United States male population, although some of the lymphopoietic cancer SMRs were slightly raised. When the SMRs for the occupationally exposed group (continuous and intermittent) were compared with those for the occupationally unexposed, however, a considerable difference was observed for all lymphopoietic cancer (121·1 *v* 34·6), lymphosarcoma and reticulosarcoma (112·8 *v* 50·8), leukaemia (117·4 *v* 0), and other lymphatic tissue cancer (163·8 *v* 53·0). The difference in SMRs for Hodgkin's disease between the two groups was much smaller (84·4 *v* 74·7). Hence, mortality from all non-Hodgkin's lymphopoietic cancers (non-

Hodgkin's lymphoma and leukaemia) was higher in the benzene exposed group than in the comparison group.

In particular, a direct comparison of mortality from all lymphopoietic cancer based on the Mantel-Haenszel procedure between workers (white and non-white) continuously exposed and those not occupationally exposed showed a relative risk of 3·20, statistically significant at the 0·05 level. The excess mortality from lymphopoietic cancer came from the white men (RR = 5·30, p = 0·02). Among the non-whites, the number of deaths was too small to draw any firm conclusion. In the same group of continuously exposed workers six deaths from leukaemia were observed. In the comparison group, although slightly smaller in size, no death from leukaemia occurred. Although the relative risk could not be computed for leukaemia (since the denominator was zero), the Mantel-Haenszel chi-square was statistically significant (for white men, chi-square = 4·26, p = 0·04), indicating that the relation between continuous exposure to benzene and leukaemia mortality was significant. For non-Hodgkin's lymphoma, the Mantel-Haenszel RR among the white men in the continuous exposure group was 5·02 but did not reach statistical significance (p = 0·12). When non-Hodgkin's lymphoma was combined with leukaemia, the corresponding RR was 9·60 and statistically significant (p = 0·01). Thus these direct comparisons confirmed the significant association between occupational exposure to benzene and leukaemia, all lymphopoietic cancer, as well as non-Hodgkin's lymphopoietic cancer, with leukaemia contributing significantly to the latter two broader categories.

Although a direct comparison based on the Mantel-Haenszel procedure between the exposed and the non-exposed groups was not performed for most other causes of death, a comparison of cause specific SMRs between these groups indicated that the comparison group experienced a more favourable mortality than the exposed group for several causes of death, even though the SMRs for some causes were below the population norm in both groups. It should be emphasised that some of the SMRs were based on small numbers of deaths and the corresponding statistical variabilities were considerable. For this reason, we will limit our discussion to causes of death with at least five observed deaths in the total cohort.

The following causes of death, in addition to all lymphopoietic cancer, leukaemia, and non-Hodgkin's lymphoma, showed that the SMRs in the exposed group were higher than those in the comparison group: all cancers, stomach cancer, lung cancer, kidney cancer, brain cancer, benign neoplasms, diabetes mellitus, and emphysema. One logical question to ask is: were the occupationally exposed and non-exposed groups different in some other risk factors besides exposure to benzene? It is impossible to answer this question completely, based only on the data available from this study. Several cancer sites noted above are related to tobacco, however, and the possible impact of cigarette smoking on the observed differences may be assessed, at least on a qualitative basis. Listed below are the cancer mortality ratios, from an American Cancer Society survey, among men with a history of cigarette smoking compared with men who never smoked regularly[54]:

Cancer site	*Age 45–64*	*Age 65–79*
All cancers	2·14	1·76
Lung	7·84	11·59
Bladder	2·00	2·96
Kidney	1·42	1·57
Stomach	1·42	1·26
Leukaemia	1·40	1·68
Lymphoma	1·38	0·80

Smoking histories were not available in the present study and statistical analyses between the occupationally exposed and non-exposed groups could not be adjusted for cigarette smoking. The observed differences between the two groups, however, may be discussed in view of the magnitude of the above cancer mortality ratios between smokers and non-smokers. Smoking has such an enormous impact on lung cancer that the observed difference in lung cancer mortality between the occupationally exposed and non-exposed groups could have been due to smoking. For other cancer sites, the impact due to smoking is much smaller and it would be unlikely that the observed mortality differences between the occupationally exposed and non-exposed groups resulted from smoking alone, unless all the occupationally exposed workers were smokers and all the occupationally non-exposed were non-smokers.

On the other hand, the observed difference in mortality from emphysema between the exposed and the comparison groups might have been attributed to smoking. Lacking smoking histories, however, a definitive conclusion regarding emphysema cannot be drawn based on the present study. Finally, the similarity in mortality from diseases of the circulatory system did not support the assumption of different smoking patterns between the exposed and the comparison group.

In concluding part I of this report, the major general results were as follows. When compared with the United States population, SMRs from all lymphatic and haematopoietic (lymphopoietic) cancer combined, leukaemia, non-Hodgkin's lymphoma (lymphosarcoma, reticulosarcoma, and other lymphoma), and non-Hodgkin's lymphopoietic cancer (non-Hodgkin's lymphoma and leukaemia) for the exposed

group were slightly, but not significantly, raised above the national norm. These SMRs were considerably higher than those in the comparison group. When the group with no occupational exposure was used for comparison, the exposed group (continuous and intermittent) experienced a lymphopoietic cancer RR of 2·99 (borderline significance). This excess was primarily due to seven deaths from leukaemia in the exposed group and none in the comparison group. The leukaemia deficit in the comparison group had the effect of magnifying the relative risk of the exposed. For the continuously exposed group, the lymphopoietic cancer RR was 3·20 ($p < 0·05$). The RR for leukaemia using the comparison group as the baseline could not be computed. The Mantel-Haenszel chi-square, however, showed that the association between exposure to benzene (continuous or intermittent) and leukaemia was of borderline significance, and that between continuous exposure to benzene and leukaemia was statistically significant ($p < 0·05$). The RR for non-Hodgkin's lymphoma among white men in the continuously exposed group was 5·02 but not significant ($p = 0·12$). The RR for non-Hodgkin's lymphopoietic cancer (all lymphopoietic cancer minus Hodgkin's disease) for the continuously exposed group was 3·77 ($p < 0·05$). This RR was similar to that for all lymphopoietic cancer (3·20) because the risk for Hodgkin's disease in this group was similar to the comparison group.

Dose response analyses based on latency, duration of exposure, cumulative exposure (ppm-months), and peak exposure for several categories of lymphatic and haematopoietic cancers will be presented in part II in which a discussion of cell types will also be presented.

I express my appreciation to the Chemical Manufacturers Association (CMA) and to the 18 companies that comprise the CMA Benzene Panel sponsoring the study. I especially thank the six companies whose plants provided the cohorts for this study and whose personnel provided the basic data and continuing help. Finally, I recognise the valuable efforts of Carol Stack, the CMA benzene programme manager. Dr Abraham M Lilienfeld served as a consultant to this project.

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