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An industry wide mortality study of chemical workers occupationally exposed to benzene. II Dose response analyses

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ABSTRACT The data presented in this paper show statistically significant dose response relations between cumulative exposure to benzene (ppm-months) and mortality from both all lymphopoietic cancer combined and leukaemia. Chemical workers with a cumulative exposure to benzene of at least 720 ppm-months experienced a relative risk of 3·93 for lymphatic and haematopoietic cancer when compared with workers with no occupational exposure. The dose response relation between cumulative exposure and non-Hodgkin's lymphopoietic cancer was of borderline statistical significance ($p = 0·06$). No dose response relation was detected for any other causes of death.

In part I of this report were listed several issues regarding the epidemiological relation between exposure to benzene and lymphatic and haematopoietic cancers. It was pointed out that, among other things, none of the studies reviewed provided adequate information on exposure to benzene for any dose response analysis.

The study design and the general results of a cohort study of chemical workers exposed to benzene were given. Exposure information in terms of eight hour time weighted averages (TWA) and peak exposure was available. In part II here are presented dose response analyses by latency, duration of exposure, cumulative exposure (ppm-months), and peak exposure for several types of lymphatic and haematopoietic cancers. Epidemiologically, a positive dose response relation adds strength to the association between exposure to benzene and lymphatic and haematopoietic cancer.

Methods and materials

A detailed description of the cohort is given in part I of this report. Briefly, it consisted of a group of male chemical workers from seven plants who were occupationally exposed to benzene for at least six months between 1946 and 1975 and a comparison group of male chemical workers from the same plants who were employed for at least six months during the same period but were never occupationally exposed to benzene. Jobs with exposure to benzene were classified into two categories: continuous exposure and intermittent exposure.

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The exposed group consisted of 4602 chemical workers; 3536 were continuously exposed (some with intermittent exposure as well) and 1066 were intermittently exposed. The comparison group consisted of 3074 chemical workers from the same plants but with no occupational exposure to benzene. For the 7676 workers in the total cohort, vital status follow up until 31 December 1977 showed that 6463 (84·20%) were alive, 1036 (13·50%) had died, and 177 (2·31%) were of unknown status. Among those identified as dead, death certificates were obtained for 1013 (97·8%). Underlying causes of death were coded according to the 8th revision of the International Classification of Diseases. Cause specific mortality analyses were based on the standardised mortality ratio (SMR) using the United States population as comparison[2] or the Mantel-Haenszel chi-square and the corresponding relative risk (RR) using the group with no occupational exposure as comparison.[3] In part II, in addition to SMR analysis, dose response analysis based on the extension of the Mantel-Haenszel procedure with internal comparison was also conducted.[4] This procedure, which tests for a progressive trend by exposure groups without any assumption of the shape of the dose response relation (thus avoiding problems of non-linearity), is particularly appropriate, given the amount of imprecision in the historical exposure data in this study.

Exposure classification of jobs

CONTINUOUS CATEGORY

The continuous 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. These jobs were further categorised on the basis of eight hour TWA (time weighted average) and peak exposure to benzene (without regard to use of respirators) as follows:

Eight hour TWA	
Low	< 1 ppm
Medium	1–10 ppm
High	11–50 ppm
Very high	> 50 ppm
Peak	
Low	< 25ppm
Medium	25–100 ppm
High	> 100 ppm

Specifically, this category included, in addition to other groups

(1) Maintenance people assigned specifically to a benzene unit and

(2) Laboratory quality control workers if they were assigned to samples from benzene units only.

INTERMITTENT CATEGORY

The intermittent category could also 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; however, the job required that the worker periodically worked in these areas, the pattern of which could not be characterised as continuous. These jobs were further divided into three exposure groups (without regard to the use of respirators) as follows:

Peak	
Low	< 25 ppm
Medium	25–100 ppm
High	> 100 ppm

Specifically, this category included, in addition to other groups

(1) Maintenance people assigned on a plant wide basis.

(2) Laboratory quality control workers only if they served both benzene and non-benzene units.

(3) Workers assigned to loading/unloading where benzene was handled regularly but infrequently—for example, if barge loading was once a month.

The classification of each job by exposure was based on a uniform task approach, similar to the procedure proposed by Esmen.[5] A group of industrial hygienists from the participating companies who were familiar with the plant operations derived a list of 34 uniform tasks. Based on both job and location description, as well as a consideration of calendar time periods, each job encountered in the study was broken down into these 34 uniform tasks and the corresponding amount of time spent at each task. Based on available industrial hygiene measurements (current and past), changes in production and process modifications, a concentration level of benzene exposure was estimated for each task. Therefore, the exposure level for a particular task might change over time. An eight hour TWA for each job could be obtained by summing the products of the proportion of the time at each uniform task and the corresponding benzene concentration. It was thought that this uniform task approach was useful, since it provided a procedure for the industrial hygienists to consider carefully the exposure level associated with each particular task. It should be emphasised here that industrial hygiene data for some plants were limited before 1970.

Two plants did not use the uniform task approach to estimate exposure levels. At one (plant 6), jobs as indicated on previous employment records were not specific enough for exposure classification. The employment records were reviewed by long term supervisors and coworkers, however, and exposure levels were estimated by supervisors who had worked in the exposed department. At the other (plant 7), only a few individuals were exposed at the units included in the study. Work histories were not specific enough for exposure classification, and these individuals were identified through old medical records and lists of names included in a benzene monitoring programme. Their exposure levels were estimated by a long term industrial hygienist who based his determination primarily on area measurements.

Exposure classification of cohort members

Cohort members were classified into three categories according to their occupational benzene exposure histories—that is, their jobs before the end of the coded work histories:

Table 1 *Distribution by cumulative exposure (ppm-months) of cohort members in the continuous exposure group*

Cumulative exposure (ppm-months)	*Frequency*	%
< 180	1809	51·16
180–719	1047	29·61
⩾ 720	680	19·23
Total	3536	100·00

Table 2 *Distribution by maximum peak occupational exposure to benzene and exposure group*

Maximum peak	Intermittent exposure		Continuous exposure		Total	
	Frequency	%	Frequency	%	Frequency	%
<25 ppm	336	31·52	413	11·68	749	16·28
25–100 ppm	114	10·69	1272	35·97	1386	30·12
>100 ppm	616	57·79	1851	52·35	2467	53·61
Total	1066	100·00	3536	100·00	4602	100·00

Table 3 *Distribution by duration of occupational exposure to benzene and exposure group*

Years of exposure	Intermittent		Continuous		Total	
	Frequency	%	Frequency	%	Frequency	%
<1	182	17·07	334	9·45	516	11·21
1–4	377	35·37	1212	34·28	1589	34·53
5–9	145	13·60	590	16·69	735	15·97
10–14	79	7·41	414	11·71	493	10·71
15–19	76	7·13	271	7·66	347	7·54
20–24	77	7·22	263	7·44	340	7·39
25–29	66	6·19	320	9·05	385	8·39
30–34	50	4·69	107	3·03	157	3·41
≥35	14	1·31	25	0·71	39	0·85
Total	1066	100·00	3536	100·00	4602	100·00

Continuous exposure—Those with jobs totalling at least six months in either the 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 never had any exposed (continuous or intermittent) jobs.

For each cohort member in the continuous exposure group, a cumulative exposure index in terms of ppm-months was calculated by summing the products of eight hour TWA and duration of all continuously exposed jobs since first exposure until the end of work history coding. Table 1 shows the number of cohort members by their cumulative exposure index. Three cumulative exposure groups were constructed: <180, 180–719, and ≥720 ppm-months. The first level, 180 ppm-months, is equivalent to a long term exposure of 0·5 ppm for 30 years or 1 ppm for 15 years, and so on. It should be emphasised that 180 ppm-months can also mean 15 ppm for one year. As such, the concept of a cumulative exposure index based on ppm-months does not distinguish between concentration and duration of exposure. The second level of 720 pp-months is equivalent to an exposure of 2 ppm for 30 years or 4 ppm for 15 years. Needless to say, these exposure groupings were arbitrary, except that they would shed some light on the low level range. Approximately 50% of the continuously exposed

Table 4 *Distribution by age at first occupational exposure to benzene*

Age at first exposure to benzene	Frequency	%
<20	122	2·65
20–24	1206	26·21
25–29	1256	27·29
30–34	805	17·49
35–39	539	11·71
40–44	306	6·65
45–49	176	3·82
50–54	116	2·52
55–59	53	1·15
60–64	22	0·48
65–69	0	0·00
70–74	0	0·00
75–79	1	0·02
Total	4602	100·00

Table 5 *Distribution by year of first occupational exposure to benzene*

Year of first exposure to benzene	Frequency	%
1908–34	170	3·69
1935–39	153	3·32
1940–44	448	9·73
1945–49	953	20·71
1950–54	884	19·21
1955–59	466	10·13
1960–64	599	13·02
1965–69	543	11·80
1970–74	359	7·80
1975–77	27	0·59
Total	4602	100·00

workers were exposed to less than 180 ppm-months, 30% to 180–719 ppm-months, and 20% to more than 720 ppm-months. It should be pointed out that, because of the nature of the estimated historical industrial hygiene data, these exposure groups should be viewed on a relative, rather than on an absolute, basis.

Another method used to relate benzene exposure level to mortality was through the use of peak exposure rather than cumulative exposure of eight hour TWA. Since each exposed job (intermittent or continuous) was characterised by a peak exposure, the cohort members could be classified according to their maximum peak exposure through their entire exposure history. Table 2 shows the distribution of the exposed cohort by maximum peak exposure. More than half those exposed were exposed to a ceiling level of more than 100 ppm at some time during their employment.

Table 3 shows the distribution of duration of exposure by exposure group. More than half the exposure cohort (54·26%) were exposed for five years or more. On the other hand, 516 individuals were exposed for between six months and a year. The average duration of exposure was 10 years. Table 4 gives the distribution by age at first exposure. The majority (56·15%) was first exposed before age 30 and only one individual was first exposed after age 65. The average age at first exposure was 30. Finally, the distribution by year of first exposure is presented in table 5. Slightly more than half (56·66%) were exposed for the first time before 1955. Thus, with regard to exposure to benzene, more than half the exposed cohort could have a latent period of at least 22 years.

Results

ANALYSIS BY DURATION OF EXPOSURE

Table 6 shows the observed numbers of deaths and

Table 6 *Observed deaths by cause and SMRs for all cohort members exposed to benzene by duration of occupational exposure to benzene*

	Duration of exposure					
	< 5 years		*5–14 years*		*⩾ 15 years*	
Cause of death (8th ICDA)	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*
All causes	263	88·6*	215	83·2†	232	87·8*
All cancers (140–209):	49	91·4	53	108·8	59	107·2
Cancer of buccal cavity and pharynx (140–149)	1	53·8	1	58·4	0	0
Cancer of digestive system (150–159):	10	67·1	7	49·8	16	102·0
Cancer of oesophagus (150)	2	119·8	0	0	2	118·4
Cancer of stomach (151)	1	31·4	2	64·6	3	94·3
Cancer of large intestine (153)	3	72·3	1	26·3	8	175·1
Cancer of liver (155–156)	1	90·1	0	0	0	0
Cancer of pancreas (157)	2	69·7	4	148·5	2	63·9
Cancer of respiratory system (160–163):	21	118·6	24	147·9	22	112·9
Cancer of lung (162–163)	20	120·2	24	157·5*	21	114·3
Cancer of bone (170)	0	0	1	373·4	1	398·4
Cancer of skin (172–173)	1	89·3	0	0	1	120·6
Cancer of prostate (185)	1	39·4	4	152·1	2	57·0
Cancer of bladder (188)	0	0	2	168·7	2	133·0
Cancer of kidney (189)	2	153·8	1	85·1	1	74·4
Cancer of brain and CNS (191–192)	1	40·5	3	181·8	2	133·4
Lymphatic & haematopoietic cancer (200–209):	7	118·0	8	163·1	4	82·6
Lymphosarcoma and reticulosarcoma (200)	1	76·3	1	89·2	2	179·5
Hodgkin's disease (201)	1	92·6	1	130·1	0	0
Leukaemia & aleukaemia (204–207)	2	88·5	4	215·8	1	54·0
Other lymphatic tissue cancer (202, 203, 208)	3	241·9	2	177·8	1	76·9
Benign neoplasms (210–239)	1	108·7	2	258·3	0	0
Diabetes mellitus (250)	4	96·4	2	54·1	3	76·8
Diseases of blood (280–289)	1	144·9	0	0	0	0
Diseases of circulatory system (390–458):	120	89·9	106	84·9	132	94·9
Arteriosclerotic heart disease (410–413)	83	92·9	68	81·8	95	97·9
Vascular lesions of CNS (430–438)	14	77·3	13	74·5	15	79·0
Non-malignant respiratory disease (460–519):	9	60·7	11	81·2	8	52·5
Pneumonia (480–486)	4	63·2	5	37·8	3	53·5
Emphysema (492)	3	98·0	5	170·1	4	98·6
Diseases of digestive system (520–577):	9	54·5	6	42·4*	2	14·9†
Cirrhosis of liver (551)	6	65·4	3	38·9	1	13·6*
Diseases of genitourinary system (580–629)	2	39·0	1	21·7	3	77·4
Accidents, poisonings, & violence (E800–E998)	54	112·0	27	85·6	21	105·7
Accidents (800–949)	40	123·9	18	85·9	12	92·3
Motor vehicle accidents (810–827)	20	125·5	12	126·1	9	165·7
Suicide (950–959)	5	55·0	1	15·4*	7	149·4

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

Table 7 *Observed deaths by cause and SMRs for continuously exposed cohort members by duration of continuous exposure to benzene*

	Duration of exposure					
	< 5 years		*5–14 years*		*⩾ 15 years*	
Cause of death (8th ICDA)	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*
All causes	311	87·6	128	86·0	92	84·1
All cancers (140–209):	66	99·4	39	136·3	18	79·4
Cancer of buccal cavity and pharynx (140–149)	1	42·4	1	101·4	0	0
Cancer of digestive system (150–159):	14	75·1	7	85·1	5	78·0
Cancer of oesophagus (150)	3	140·9	0	0	1	140·6
Cancer of stomach (151)	2	50·8	2	110·9	1	76·1
Cancer of large intestine (153)	6	115·6	1	44·7	3	162·3
Cancer of liver (155–156)	1	73·5	0	0	0	0
Cancer of pancreas (157)	1	27·6	3	189·1	0	0
Cancer of respiratory system (160–163):	27	120·0	18	187·2*	4	50·1
Cancer of lung (162–163)	26	122·9	18	199·1*	3	39·8
Cancer of bone (170)	1	263·2	1	662·6	0	0
Cancer of skin (172–173)	1	78·7	0	0	0	0
Cancer of prostate (185)	4	122·3	2	119·7	0	0
Cancer of bladder (188)	1	64·5	0	0	2	334·1
Cancer of kidney (189)	3	184·1	0	0	1	182·7
Cancer of brain and CNS (191–192)	2	85·1	3	324·4	1	159·9
Lymphatic & haematopoietic cancer (200–209):	7	101·3	6	213·3	2	99·3
Lymphosarcoma and reticulosarcoma (200)	1	64·5	1	156·2	1	217·8
Hodgkin's disease (201)	1	87·7	1	237·4	0	0
Leukaemia & aleukaemia (204–207)	2	76·3	3	283·5	1	131·2
Other lymphatic tissue cancer (202, 203, 208)	3	193·6	1	149·1	0	0
Benign neoplasms (210–239)	2	185·2	1	234·7	0	0
Diabetes mellitus (250)	5	99·8	1	46·3	2	122·4
Diseases of blood (280–289)	1	123·5	0	0	0	0
Diseases of circulatory system (390–458):	146	87·9	62	85·5	61	107·4
Arteriosclerotic heart disease (410–413)	98	87·3	41	84·8	50	127·4
Vascular lesions of CNS (430–438)	17	75·8	7	67·7	7	87·7
Non-malignant respiratory disease (460–519):	15	82·2	5	63·2	1	16·0*
Pneumonia (480–486)	4	52·4	3	91·9	1	42·2
Emphysema (492)	8	202·5	2	113·1	0	0
Diseases of digestive system (520–577):	9	45·5	2	25·1*	1	17·8*
Cirrhosis of liver (551)	7	63·2	1	22·9	0	0
Diseases of genitourinary system (580–629)	1	16·8*	1	38·0	1	60·7
Accidents, poisonings, & violence (E800–E998)	55	111·4	12	69·2	6	67·7
Accidents (800–949)	37	112·8	6	52·3	4	69·2
Motor vehicle accidents (810–827)	21	134·8	3	57·3	3	122·4
Suicide (950–959)	7	72·6	1	27·8	1	49·0

*Significant at 0·05.

SMRs among the chemical workers exposed to benzene (continuous and intermittent) by duration of benzene exposure. No obvious increasing trend by duration of exposure was identified for any cause of death examined, except, perhaps, for stomach cancer and lymphosarcoma and reticulosarcoma. In each case, however, the number of deaths was small. No increasing trend was noted for either all lymphatic and haematopoietic cancer, leukaemia, or other lymphatic tissue cancer.

Those exposed to benzene for 5–14 years experienced an increased risk in lung cancer (table 6). The SMR was 157·5 (24 observed), statistically significant at the 0·05 level. Nevertheless, no trend by duration of employment for lung cancer was detected.

A similar analysis by duration of continuous exposure for the continuously exposed group was carried out, and the results are presented in table 7. A trend was found for lymphosarcoma and reticulosarcoma by duration of continuous exposure, although the number of deaths was small.

ANALYSIS BY LATENCY

Long latent periods are usually required for chronic diseases to develop and it is often more appropriate to examine mortality experience only after a certain lag period has elapsed. Table 8 presents the observed deaths by cause and SMRs for all cohort members exposed to benzene (intermittent and continuous) by latency since first exposure. A slightly increasing trend by latency was detected for all cancers, lung cancer, brain cancer, leukaemia, and arteriosclerotic heart disease. Table 8 also indicates that the SMR for other lymphatic tissue cancer among those with 10 to 19 years of latency was 455·6 (4 observed), statistically significant. In the same latency group mortality from motor vehicle accidents was also statistically significant (18 observed, SMR = 175·2).

Table 8 *Observed deaths by cause and SMRs for all cohort members exposed to benzene (intermittent and continuous exposure) by latency since first exposure*

	Latency since first exposure					
	< 10 years		*10–19 years*		*⩾20 years*	
Cause of death (8th ICDA)	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*
All causes	90	68·0†	201	87·2	419	91·8
All cancers (140–209):	16	82·8	41	101·1	104	106·7
Cancer of buccal cavity and pharynx (140–149)	0	0	1	67·6	1	29·9
Cancer of digestive system (150–159):	4	74·4	8	68·2	21	76·2
Cancer of oesophagus (150)	1	212·6	1	79·2	2	61·7
Cancer of stomach (151)	0	0	2	75·0	4	72·9
Cancer of large intestine (153)	1	69·5	2	64·9	9	112·4
Cancer of liver (155–156)	0	0	0	0	1	53·2
Cancer of pancreas (157)	2	215·4	2	90·0	4	72·2
Cancer of respiratory system (160–163):	4	76·0	17	129·7	46	131·3
Cancer of lung (162–163)	4	81·6	16	130·4	45	136·0
Cancer of bone (170)	0	0	2	397·2	1	243·9
Cancer of skin (172–173)	1	177·0	0	0	1	74·6
Cancer of prostate (185)	4	0	0	0	7	104·3
Cancer of bladder (188)	0	0	0	0	4	151·5
Cancer of kidney (189)	0	0	3	286·9	1	43·5
Cancer of brain and CNS (191–192)	1	94·4	2	118·4	3	124·0
Lymphatic & haematopoietic cancer (200–209):	3	102·3	8	175·9	8	97·6
Lymphosarcoma and reticulosarcoma (200)	1	161·3	1	89·4	2	110·5
Hodgkin's disease (201)	1	130·5	1	121·1	0	0
Leukaemia & aleukaemia (204–207)	1	87·5	2	116·9	4	128·6
Other lymphatic tissue cancer (202, 203, 208)	0	0	4	455·6*	2	83·7
Benign neoplasms (210–239)	0	0	2	268·7	1	91·7
Diabetes mellitus (250)	1	59·9	1	32·0	7	100·6
Diseases of blood (280–289)	0	0	0	0	1	108·7
Diseases of circulatory system (390–458):	31	63·0†	93	86·5	234	97·3
Arteriosclerotic heart disease (410–413)	19	62·0*	65	91·0	162	96·8
Vascular lesions of CNS (430–438)	2	31·4	11	78·8	29	84·8
Non-malignant respiratory disease (460–519):	5	89·2	6	54·4	17	63·0
Pneumonia (480–486)	4	147·8	3	61·1	5	50·0
Emphysema (492)	0	0	3	134·5	9	127·1
Diseases of digestive system (520–577):	1	13·5†	6	42·7*	10	44·2*
Cirrhosis of liver (551)	1	26·3	3	37·7	6	48·0
Diseases of genitourinary system (580–629)	1	35·0	1	24·7	4	59·6
Accidents, poisonings, & violence (E800–E998)	33	96·8	39	114·2	30	95·7
Accidents (800–949)	23	97·7	29	129·7	18	88·5
Motor vehicle accidents (810–827)	14	113·2	18	175·2*	9	109·2
Suicide (950–959)	3	50·4	3	40·8	7	100·3

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

Table 9 presents the results of a similar analysis by latency for the continously exposed group. An upward trend by latency was noted for brain cancer, leukaemia, diabetes mellitus, and arteriosclerotic heart disease.

ANALYSIS BY CUMULATIVE EXPOSURE

As stated earlier, for each job that was classified as continuously exposed, an eight hour time weighted average benzene exposure level (ppm) was estimated. For all cohort members in the continuous exposure group, a cumulative exposure index in terms of ppm-months was computed, and each of their person-years under observation was associated with a particular cumulative index (ppm-months) as well. These person-years were grouped in the appropriate cumulative exposure category in calculating SMRs.

Table 10 shows the analysis by cumulative exposure. The three cumulative exposure categories (< 180, 180–719, ⩾720 ppm-months) discussed earlier were used in the analysis. Since comparing indirectly adjusted SMRs (even though all based on the same standard population) among different cumulative exposure groups might not be appropriate if the underlying age distributions differed, the latter were examined. There were slightly larger proportions of person-years in the younger age groups in the non-exposed than in the heavily exposed group. The overall distributions, however, were not dissimilar, and a comparison based on SMRs would not be inappropriate.

It is noted from table 10 that those with a cumulative exposure of 180–719 ppm-months experienced a statistically significant increased risk of lung cancer (19 observed, SMR = 173·7), and those with < 180 ppm-months were at a significantly raised risk

Table 9 *Observed deaths by cause and SMRs for continuously exposed cohort members by latency since first occupational exposure*

	Latency since first exposure					
	< 10 years		*10–19 years*		*⩾ 20 years*	
Cause of death (8th ICDA)	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*
All causes	76	68·6	170	93·1	285	89·1
All cancers (140–209):	14	86·2	41	126·5	68	98·5
Cancer of buccal cavity and pharynx (140–149)	0	0	1	84·3	1	42·0
Cancer of digestive system (150–159):	5	107·9	5	53·0	16	83·3
Cancer of oesophagus (150)	1	223·7	1	91·8	2	88·5
Cancer of stomach (151)	1	85·9	1	46·2	3	80·4
Cancer of large intestine (153)	2	168·8	1	41·2	7	123·9
Cancer of liver (155–156)	0	0	0	0	1	78·1
Cancer of pancreas (157)	1	126·0	1	56·0	2	51·2
Cancer of respiratory system (160–163):	4	89·9	18	171·2*	27	107·4
Cancer of lung (162–163)	4	96·6	16	162·6	27	113·6
Cancer of bone (170)	0	0	1	513·3	1	357·1
Cancer of skin (172–173)	1	219·9	0	0	0	0
Cancer of prostate (185)	0	0	2	150·4	4	86·2
Cancer of bladder (188)	0	0	0	0	3	163·9
Cancer of kidney (189)	0	0	3	368·4	1	60·6
Cancer of brain and CNS (191–192)	1	117·9	2	155·5	3	170·5
Lymphatic & haematopoietic cancer (200–209):	2	84·8	7	198·2	6	102·7
Lymphosarcoma and reticulosarcoma (200)	1	199·7	1	115·8	1	77·5
Hodgkin's disease (201)	1	166·6	1	159·8	0	0
Leukaemia & aleukaemia (204–207)	0	0	2	151·3	4	181·8
Other lymphatic tissue cancer (202, 203, 208)	0	0	3	423·3	1	58·5
Benign neoplasms (210–239)	0	0	2	347·1	1	129·9
Diabetes mellitus (250)	1	71·2	2	79·2	5	102·7
Diseases of blood (280–289)	0	0	0	0	1	156·3
Diseases of circulatory system (390–458):	27	64·0*	75	87·5	167	99·7
Arteriosclerotic heart disease (410–413)	16	62·9	55	97·7	118	99·9
Vascular lesions of CNS (430–438)	3	51·4	7	60·1	21	90·4
Non-malignant respiratory disease (460–519):	4	83·6	7	79·4	10	53·1
Pneumonia (480–486)	3	126·4	2	50·1	3	43·4
Emphysema (492)	0	0	4	227·2	6	120·0
Diseases of digestive system (520–577):	2	32·1	6	54·5	4	24·9†
Cirrhosis of liver (551)	1	31·0	4	64·1	3	33·0*
Diseases of genitourinary system (580–629)	1	40·3	0	0	2	44·5
Accidents, poisonings, & violence (E800–E998)	26	95·8	27	103·6	20	89·3
Accidents (800–949)	18	97·0	17	99·6	12	83·1
Motor vehicle accidents (810–827)	12	125·0	9	115·5	6	102·0
Suicide (950–959)	2	42·8	2	36·2	5	98·2

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

of motor vehicle accidents (20 observed, SMR = 177·7). No increasing trend by cumulative exposure to benzene, however, was detected for either cause of death.

In fact, based on SMRs, no increasing trend by cumulative exposure was found for any cause of death examined except for lymphatic and haematopoietic cancer, lymphosarcoma and reticulosarcoma, and, perhaps, leukaemia. For convenience, the observed deaths, expected deaths, SMRs, and their 95% confidence limits for all lymphopoietic cancer, leukaemia, non-Hodgkin's lymphoma, and non-Hodgkin's lymphopoietic cancer by cumulative exposure to benzene are presented in table 11. The rationale for these groupings of causes of death is given in part I.[1] As a baseline for comparison, the occupationally non-exposed group is also included in the table. Based on table 11, there was clearly a monotonic increasing trend of lymphopoietic cancer SMR by cumulative exposure. The SMRs, in increasing cumulative exposure order, were 34·6, 91·3, 146·8, and 175·2. The increase did not appear to be linear but rose more steeply in the low exposure range and became flatter at the high exposure levels.

The dose-response relation for leukaemia was not strictly monotonic; the SMR rose from 0 to 96·8, dropped slightly to 78·2 and rose back to 275·8. The number of deaths from leukaemia in each of the cumulative exposure groups was small, and the associated statistical variability was large.

For non-Hodgkin's lymphoma (lymphosarcoma, reticulosarcoma, and other lymphatic tissue cancer), the SMRs rose from 50·8 in the comparison group, through 116·7 in the < 180 ppm-months group to 186·3 in the 180–719 ppm-months group, and dropped to 74·6 in the > 720 ppm-months group.

The SMRs for non-Hodgkin's lymphopoietic cancer increased with cumulative exposure to benzene;

Table 10 *Observed deaths by cause and SMRs for all cohort members continuously exposed to benzene by cumulative exposure*

	Cumulative exposure (ppm-months)					
	< 180		*180–719*		*⩾720*	
Cause of death (8th ICDA)	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*
All causes	259	90·5	181	98·6	91	63·5†
All cancers (140–209):	56	102·5	45	129·4	22	77·8
Cancer of buccal cavity and pharynx (140–149)	1	51·7	1	83·0	0	0
Cancer of digestive system (150–159):	12	77·9	9	89·7	5	63·9
Cancer of oesophagus (150)	3	166·4	1	82·6	0	0
Cancer of stomach (151)	2	61·5	2	89·3	1	63·9
Cancer of large intestine (153)	5	117·0	2	74·8	3	129·4
Cancer of liver (155–156)	0	0	1	133·3	0	0
Cancer of pancreas (157)	2	66·6	1	52·1	1	63·8
Cancer of respiratory system (160–163):	23	123·3	19	163·3	7	71·3
Cancer of lung (162–163)	22	125·4	19	173·7*	6	64·8
Cancer of bone (170)	0	0	1	531·8	1	678·1
Cancer of skin (172–173)	1	100·8	0	0	0	0
Cancer of prostate (185)	2	69·1	4	193·2	0	0
Cancer of bladder (188)	2	153·2	0	0	1	139·3
Cancer of kidney (189)	2	151·0	2	245·0	0	0
Cancer of brain and CNS (191–192)	3	164·3	2	180·6	1	103·5
Lymphatic & haematopoietic cancer (200–209):	5	91·3	5	146·8	5	175·2
Lymphosarcoma and reticulosarcoma (200)	1	81·2	1	131·6	1	151·0
Hodgkin's disease (201)	0	0	1	191·6	1	240·5
Leukaemia & aleukaemia (204–207)	2	96·8	1	78·2	3	275·8
Other lymphatic tissue cancer (202, 203, 208)	2	155·4	2	244·9	0	0
Benign neoplasms (210–239)	2	239·1	1	188·9	0	0
Diabetes mellitus (250)	5	121·7	2	75·4	1	49·0
Diseases of blood (280–289)	1	156·4	0	0	0	0
Diseases of circulatory system (390–458):	115	84·3	94	106·8	60	84·6
Arteriosclerotic heart disease (410–413)	77	83·5	65	112·9	47	93·8
Vascular lesions of CNS (430–438)	12	63·9	14	108·0	5	55·6
Non-malignant respiratory disease (460–519):	14	93·2	6	62·1	1	12·9†
Pneumonia (480–486)	4	64·3	4	96·7	0	0
Emphysema (492)	7	210·8	2	98·1	1	50·4
Diseases of digestive system (520–577):	10	63·4	1	10·2†	1	12·8†
Cirrhosis of liver (551)	7	79·2	1	18·7	0	0
Diseases of genitourinary system (580–629)	1	21·0	2	58·8	0	0
Accidents, poisonings, & violence (E800–E998)	48	130·8	22	96·4	3	18·7†
Accidents (800–949)	31	128·2	14	92·5	2	18·6†
Motor vehicle accidents (810–827)	20	177·7*	6	85·0	1	20·2
Suicide (950–959)	4	55·4	4	90·9	1	27·4

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

Table 11 *Observed deaths, expected deaths, SMRs, and 95% confidence intervals for lymphatic and haematopoietic cancer, leukaemia, non-Hodgkin's lymphoma, and non-Hodgkin's lymphopoietic cancer by cumulative occupational exposure to benzene*

Cause of death (8th ICD)	*Variable*	*Non-exposed*	*< 180 ppm-months*	*180–719 ppm-months*	*⩾720 ppm-months*
Lymphatic and haematopoietic cancer (200–209)	Obs	3	5	5	5
	Exp	8·68	5·48	3·41	2·85
	SMR	34·6	91·3	146·8	175·2
	95% CI	7·1–101·1	29·5–213·3	47·5–343·0	56·7–409·3
Leukaemia and aleukaemia (204–207)	Obs	0	2	1	3
	Exp	3·40	2·07	1·28	1·09
	SMR	0	96·8	78·2	275·8
	95% CI	—	11·7–349·4	2·0–434·4	56·9–806·4
Non-Hodgkin's lymphoma (200, 202, 203)	Obs	2	3	3	1
	Exp	3·94	2·57	1·61	1·34
	SMR	50·8	116·7	186·3	74·6
	95% CI	6·2–183·4	24·1–341·2	38·4–544·7	1·9–414·4
Non-Hodgkin's lymphopoietic cancer (200, 202–207)	Obs	2	5	4	4
	Exp	7·34	4·64	2·89	2·23
	SMR	27·2*	107·8	138·4	164·6
	95% CI	3·3–79·5	34·9–251·9	37·7–354·0	44·8–421·0

*Statistically significant at the 0·05 level.
(Lymphatic and haematopoietic cancer includes non-Hodgkin's lymphoma, Hodgkin's disease, and leukaemia.)

Table 12 *Mantel-Haenszel relative risks and extension chi-squares for lymphatic and haematopoietic cancer, leukaemia, non-Hodgkin's lymphoma, and non-Hodgkin's lymphopoietic cancer by cumulative occupational exposure to benzene, adjusted for age and race*

Cause of death (8th ICD)	*Cumulative exposure (ppm-months)*	*Observed deaths*	*Relative risk*	*Chi-square for trend*	*p Value*
Lymphatic and haematopoietic cancer (200–209)	Non-exposed	3	1·00		
	<180	5	2·10		
	180–719	5	2·95	5·42*	0·02
	⩾720	5	3·93		
Leukaemia and aleukaemia (204–207)	Non-exposed	0			
	<180	2			
	180–719	1	Undefined	6·46*	0·01
	⩾720	3			
Non-Hodgkin's lymphoma (200, 202, 203)	Non-exposed	2	1·00		
	<180	3	1·40		
	180–719	3	2·23	0·14	0·71
	⩾720	1	1·07		
Non-Hodgkin's lymphopoietic cancer (200, 202–207)	Non-exposed	2	1·00		
	<180	5	2·71		
	180–719	4	2·96	3·64	0·06
	⩾720	4	4·12		

*Statistically significant at the 0·05 level.
(Lymphatic and haematopoietic cancer includes non-Hodgkin's lymphoma, Hodgkin's disease, and leukaemia.)

Table 13 *Observed deaths by cause and SMRs for all cohort members exposed to benzene by maximum peak occupational exposure*

	Maximum peak exposure					
	<25 ppm		*25–100 ppm*		*>100 ppm*	
Cause of death (8th ICDA)	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*
All causes	135	91·7	280	94·5	295	78·4†
All cancers (140–209):	35	125·5	63	113·3	63	85·3
Cancer of buccal cavity and pharynx (140–149)	1	106·1	1	51·3	0	0
Cancer of digestive system (150–159):	7	87·2	14	83·6	12	60·3
Cancer of oesophagus (150)	1	132·8	2	85·0	1	53·7
Cancer of stomach (151)	2	118·8	3	75·3	1	26·3
Cancer of large intestine (153)	2	84·6	5	122·3	5	82·3
Cancer of liver (155–156)	0	0	1	75·8	0	0
Cancer of pancreas (157)	2	129·5	2	64·4	4	99·1
Cancer of respiratory system (160–163):	12	130·4	26	141·5	29	112·2
Cancer of lung (162–163)	11	127·1	25	145·2	29	118·9
Cancer of bone (170)	0	0	0	0	2	490·5
Cancer of skin (172–173)	1	194·1	0	0	1	65·0
Cancer of prostate (185)	2	121·5	4	103·3	1	31·6
Cancer of bladder (188)	3	389·2	0	0	1	55·6
Cancer of kidney (189)	0	0	1	83·8	3	154·5
Cancer of brain and CNS (191–192)	1	110·0	5	340·2*	0	0
Lymphatic & haematopoietic cancer (200–209):	4	141·5	7	140·8	8	101·5
Lymphosarcoma and reticulosarcoma (200)	1	154·2	2	188·2	1	54·5
Hodgkin's disease (201)	0	0	1	143·3	1	80·0
Leukaemia & aleukaemia (204–207)	1	89·9	2	108·5	4	132·9
Other lymphatic tissue cancer (202, 203, 208)	2	322·8	2	150·7	2	116·5
Benign neoplasms (210–239)	0	0	1	120·6	2	178·4
Diabetes mellitus (250)	4	191·9	4	90·6	1	19·0
Diseases of blood (280–289)	1	299·5	0	0	0	0
Diseases of circulatory system (390–458):	59	79·8	143	100·6	156	86·1
Arteriosclerotic heart disease (410–413)	40	78·8	87	99·9	119	90·3
Vascular lesions of CNS (430–438)	8	80·1	21	88·6	13	62·4
Non-malignant respiratory disease (460–519):	9	112·4	7	43·2*	12	61·9
Pneumonia (480–486)	4	128·4	2	26·9*	6	84·6
Emphysema (492)	4	200·4	2	66·1	6	119·1
Diseases of digestive system (520–577):	4	52·4	7	46·6*	6	28·0†
Cirrhosis of liver (551)	3	74·4	4	50·8	3	24·3†
Diseases of genitourinary system (580–629)	1	42·6	4	62·8	1	20·4
Accidents, poisonings, & violence (E800–E998)	18	107·0	45	132·8	39	79·8
Accidents (800–949)	15	132·4	29	131·3	26	79·3
Motor vehicle accidents (810–827)	10	187·5	16	162·8	15	95·5
Suicide (950–959)	2	55·0	4	74·4	7	62·1

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

Table 14 *Mantel-Haenszel relative risks and extension chi-squares for lymphatic and haematopoietic cancer, leukaemia, non-Hodgkin's lymphoma and non-Hodgkin's lymphopoietic cancer by cumulative occupational exposure to benzene, adjusted for age and race*

Cause of death (8th ICD)	*Cumulative exposure (ppm-months)*	*Observed deaths*	*Relative risk*	*Chi-square for trend*	*p Value*
Lymphatic and haematopoietic cancer (200–209)	Non-exposed	3	1·00		
	<180	5	2·10		
	180–719	5	2·95	5·42*	0·02
	⩾720	5	3·93		
Leukaemia and aleukaemia (204–207)	Non-exposed	0			
	<180	2			
	180–719	1	Undefined	6·46*	0·01
	⩾720	3			
Non-Hodgkin's lymphoma (200, 202, 203)	Non-exposed	2	1·00		
	<180	3	1·40		
	180–719	3	2·23	0·14	0·71
	⩾720	1	1·07		
Non-Hodgkin's lymphopoietic cancer (200, 202–207)	Non-exposed	2	1·00		
	<180	5	2·71		
	180–719	4	2·96	3·64	0·06
	⩾720	4	4·12		

*Statistically significant at the 0·05 level.
(Lymphatic and haematopoietic cancer includes non-Hodgkin's lymphoma, Hodgkin's disease, and leukaemia.)

Table 15 *Mantel-Haenszel relative risk and chi-squares for lymphatic and haematopoietic cancer, leukaemia, non-Hodgkin's lymphoma, and non-Hodgkin's lymphopoietic cancer between chemical workers first occupationally exposed before and after age 30, adjusted for age and race*

Cause of death (8th ICD)	*Observed deaths*		*Relative risk*	*Mantel-Haenszel chi-square*	*p Value*
	First exposed >30	*First exposed <30*			
Lymphatic and haematopoietic cancer (200–209)	14	5	1·51	0·58	0·43
Leukaemia and aleukaemia (204–207)	5	2	1·09	0·01	0·92
Non-Hodgkin's lymphoma (200, 202, 203)	8	2	2·52	1·33	0·25
Non-Hodgkin's lymphopoietic cancer (200, 202–207)	13	4	1·72	0·92	0·34

(Lymphatic and haematopoietic cancer includes non-Hodgkin's lymphoma, Hodgkin's disease, and leukaemia.)

starting at 27·2 for the comparison group and rising to, in increasing cumulative exposure order, 107·8, 138·4, and 164·6.

Table 12 presents the Mantel-Haenszel RRs and the corresponding extension chi-squares for all lymphatic and haematopoietic cancer, leukaemia, non-Hodgkin's lymphoma, and non-Hodgkin's lymphopoietic cancer, by cumulative exposure to benzene adjusted for age and race. For all lymphatic and haematopoietic cancer, the RR rose steadily from 1·00 in the comparison group to 3·93 in the ⩾720 ppm-month group. The corresponding Mantel-Haenszel extension chi-square, which measured the significance of the upward trend, was 5·42, statistically significant ($p = 0·02$). For leukaemia, the RRs were infinitely large and undefined, since no death from leukaemia was observed for the occupationally non-exposed. The Mantel-Haenszel extension chi-square for leukaemia was 6·46, and the corresponding p value was 0·011. Therefore, dose response relations for leukaemia, and the broader category of lymphatic and haematopoietic cancer, were statistically significant. For non-Hodgkin's lymphoma, the RR rose from 1·00 in the comparison group to 2·23 in the 180–720 ppm-months group and dropped to 1·07 for the ⩾720 ppm-months group; and there was no statistical evidence for a dose response relation. For non-Hodgkin's lymphopoietic cancer, the RR rose steadily from 1·00 in the comparison group to 4·12 in the ⩾720 ppm-months group, but this dose response relation was of borderline statistical significance ($p = 0·06$).

ANALYSIS BY PEAK EXPOSURE

Each exposed job (intermittent or continuous) was characterised by a peak exposure. Cause specific SMRs were calculated for maximum peak exposure; <25, 25–100, and >100 ppm. In this calculation person-years were classified by the preceding maximum peak exposure. The cause specific SMRs by maximum peak exposure are presented in table 13. Again, to ensure similarity of age distributions when

comparing indirectly adjusted SMRs, the percentage compositions of the maximum peak exposure groups were examined and were found to be generally similar.

The only obvious increasing dose-response relation from table 13 was that for leukaemia. Including the comparison group as the baseline, the leukaemia SMRs were 0, 89·9, 108·5, and 132·9 in order of rising maximum peak exposure. These SMRs, however, were based on few observed deaths.

Table 14 shows the analysis by maximum peak exposure using the Mantel-Haenszel extension procedure. For lymphatic and haematopoietic cancer, the RRs for all three peak exposure categories were around threefold when compared with the comparison group. The corresponding chi-square was 2·10 ($p = 0·15$). For leukaemia, the RRs were undefined, but the extension chi-square was 2·91 ($p = 0·09$). For non-Hodgkin's lymphoma, the RRs did not show any pattern ($p = 0·81$). For non-Hodgkin's lymphopoietic cancer, the RRs for all three peak exposure categories were around three to fourfold, with no significant dose response relation. Thus no statistically significant trend was detected for either all lymphatic and haematopoietic cancer, leukaemia, non-Hodgkin's lymphoma, or non-Hodgkin's lymphopoietic cancer by maximum peak exposure to benzene.

ANALYSIS BY AGE AT FIRST EXPOSURE

Cause specific SMRs were calculated by age at first occupational exposure (before 30 and after 30). For lymphatic and haematopoietic cancer, the SMRs were 83·5 (5 observed) and 144·4 (14 observed) for the <30 and $\geqslant 30$ groups, respectively. The Mantel-Haenszel relative risk and chi-square were also calculated (table 15). Although the lymphopoietic cancer RR was 1·51 for those who were first occupationally exposed after age 30 when compared with those first occupationally exposed before 30, the result was not statistically significant. For leukaemia, the SMRs were 89·9 (2 observed) and 133·7 (5 observed) for the <30 and $\geqslant 30$ groups respectively. The Mantel-Haenszel relative risk for leukaemia by age at first exposure was 1·09 ($p = 0·92$). For non-Hodgkin's lymphoma, the SMRs were 79·7 (2 observed) and 170·2 (8 observed) for the <30 and $\geqslant 30$ groups, respectively. The corresponding RR between the two groups was 2·52 ($p = 0·25$). Similarly, there was no significant association between age at first occupational exposure and mortality risk due to non-Hodgkin's lymphopoietic cancer.

Discussion and conclusion

One interesting finding in this study was that analysis indicated that duration of exposure was not a particularly sensitive parameter for quantification of either leukaemia or other lymphopoietic cancer mortality risk. When analysed by cumulative exposure (ppm-months), however, statistically significant dose response relations were detected for leukaemia and the broader category of all lymphopoietic cancer. For all lymphatic and haematopoietic cancer, those with more than 720 ppm-months of exposure to benzene experienced nearly a fourfold risk (RR = 3·93) when compared with the occupationally unexposed group. The Mantel-Haenszel extension chi-square for the upward trend in lymphopoietic cancer was 5·42 ($p = 0·02$). For leukaemia, the Mantel-Haenszel chi-square was 6·46 ($p = 0·01$). For non-Hodgkin's lymphoma, no dose response relation was detected. When non-Hodgkin's lymphoma was combined with leukaemia, however, a monotonic increasing trend was seen (those with $\geqslant 720$ ppm-months experienced an RR of 4·12), and this dose response relation approached statistical significance ($p = 0·06$). It should be pointed out that the concept of cumulative exposure (ppm-months) does not distinguish between concentration and duration of exposure to benzene.

When the data were analysed by maximum peak exposure to benzene, no significant dose response relation was identified. The findings in this study suggested that cumulative exposure (ppm-months), and not peak exposure, was the major parameter in quantifying mortality risk from lymphopoietic cancer. This conclusion must be viewed with caution, however, since the analysis did not take frequency of peak exposure into consideration, owing to the limitations in peak exposure data and the methodological difficulties in incorporating frequency or duration of peak exposure in analysis.

A review of the deaths from leukaemia in this study (table 16) indicated that none was from acute myeloid leukaemia, the cell type frequently associated with exposure to benzene in some of the previous studies.[6-8] Four of the seven deaths from leukaemia in this study were lymphatic leukaemia (1 acute, 2 chronic, and 1 unspecified), two were chronic myeloid leukaemias, and one was acute leukaemia (unspecified). The proportion of lymphatic leukaemias (57%) was only slightly higher than the corresponding figure (44%) among men in the Third National Cancer Survey.[9] On the other hand, other studies have shown excess of lymphatic leukaemia among workers exposed to benzene[10] and among petroleum refinery workers.[11] This study did not provide enough cases of leukaemia for a definitive analysis on leukaemia cell types.

Table 16 indicates that three deaths were due to multiple myeloma. Among the four deaths from lymphopoietic cancer in the intermittent exposure group, two were from multiple myeloma. Decoufle *et al*,

Table 16 *Characteristics of 22 deaths from lymphatic and haematopoietic cancer*

Case	*Exp*	*Plant*	*Race*	*COD*	*DOB*	*DOH*	*First exp*	*DOT*	*DOD*	*Age*	*Yrs exp*	*Yrs Cont exp*	*ppm-mos*	*Max TWA*	*Max peak*	*Yrs latency*
1	C	3	W	202·2	1919	09/60	09/60	02/74	02/74	55·0	7·2	7·2	43	L	L	13·4
2	C	4	N	201·X	1935	04/60	05/60	04/70	05/71	36·2	1·8	1·6	192	H	M	11·0
3	C	4	W	200·0	1902	06/42	08/54	02/57	02/57	54·2	0·9	0·2	14	M	M	2·5
4	C	4	W	204·1	1920	04/55	04/55	08/69	08/69	48·7	9·9	9·9	524	H	H	14·3
5	C	4	N	204·9	1897	08/28	03/29	10/55	10/57	59·9	14·9	14·6	1361	H	H	28·6
6	C	4	W	205·1	1907	06/42	11/42	01/71	09/71	64·2	5·8	1·9	120	H	M	28·9
7	C	4	W	202·2	1918	05/63	05/63	06/71	12/73	55·8	1·3	1·3	334	H	M	10·6
8	C	4	N	203·X	1907	03/40	11/52	05/63	02/64	57·0	2·3	2·3	14	L	L	11·3
9	C	5	W	204·0	1905	11/25	03/26	12/67	07/75	70·2	12·2	12·2	731	M	M	49·4
10	C	5	W	200·0	1900	07/33	07/33	12/62	11/74	74·5	26·8	26·8	1512	M	M	41·4
11	C	5	W	205·1	1913	09/39	04/56	04/73	03/75	61·8	1·2	1·2	7	L	L	18·9
12	C	6	W	207·0	1927	10/47	10/47	12/76	06/77	49·6	29·2	29·2	851	M	H	29·7
13	C	2	W	202·2	1928	08/50	10/50	05/54	08/72	44·4	1·7	1·7	601	H	H	21·9
14	C	2	W	201·X	1910	10/40	07/67	07/74	04/76	65·4	7·0	7·0	2522	H	H	8·7
15	C	7	W	200·1	1921	01/51	06/54	09/71	11/71	50·1	8·9	8·9	533	M	H	17·4
16	I	1	W	204·1	1927	01/69	01/69	01/75	01/75	47·6	1·4				H	6·0
17	I	4	W	200·0	1894	10/23	10/23	10/59	01/62	67·3	35·4				L	38·2
18	I	4	N	203·X	1913	06/37	09/59	10/76	06/77	64·0	6·6				M	17·8
19	I	4	W	203·X	1913	03/49	03/49	08/69	04/70	56·4	20·4				H	21·1
20	U	4	W	201·X	1892	09/33	09/33	10/56	10/56	64·1						
21	U	4	N	200·1	1884	12/42	12/42	07/50	02/53	68·7						
22	U	6	W	202·2	1905	09/47	09/47	06/70	02/77	71·4						

Key:
Exposure
C = Continuous
I = Intermittent
U = Unexposed

Race
W = White
N = Non-white

Peak exposure
L = Low (< 25 ppm)
M = Medium (25–100 ppm)
H = High (> 100 ppm)

Eight hour TWA
L = Low (< 1 ppm)
M = Medium (1–10 ppm)
H = High (11–50 ppm)
VH = Very high (> 50 ppm)

COD = Cause of death
DOH = Date of hire
First Exp = Date of first exposure
DOT = Date of termination/separation
DOD = Date of death
Age = Age at death
Yrs exp = Years of continuous and intermittent exposure
Yrs cont exp = Years of continuous exposure
Max TWA = Maximum eight hour TWA
Max peak = maximum peak exposure

based on a small cohort study, suggested a possible link between benzene and multiple myeloma.[12] The standard computer program used in the present project did not provide an SMR for multiple myeloma, but a separate calculation indicated that the expected number (adjusted for age and race) of deaths from multiple myeloma based on United States male mortality was 0·56. The multiple myeloma SMR for the intermittent exposure group was thus 357·1, with a 95% confidence interval of 43·2–1289·3 (not significant). This group was relatively small and could detect only risk ratios of at least 14-fold with reasonable statistical power (80%) at the 0·05 confidence level. Furthermore, the small number of deaths from multiple myeloma in the exposed groups and none in the comparison group did not lend the data to a direct comparison (Mantel-Haenszel procedure). Thus the study did not offer any firm data on the relation between exposure to benzene and multiple myeloma.

Table 16 gives a summary of the exposure histories of the deaths from lymphopoietic cancer. The cumulative exposure ranged from 7 ppm-months to 2522 ppm-months. Also listed in the table are the maximum eight hour TWAs. According to the work histories, three cases (case numbers 1, 8, and 11) were never exposed to an eight hour TWA of more than 1 ppm, and none of the cases was exposed to the "very high" eight hour TWA (> 50 ppm). The maximum peak exposures are also listed for all the deaths from lymphopoietic cancer in the table. Four cases were never exposed to a peak level of more than 25 ppm.

Table 16 also shows the latent period for each death from lymphopoietic cancer. Among the continuously exposed, the average latent period for lymphopoietic cancer was 20·5 years, and among the intermittently exposed 20·8 years. The average latent period for leukaemia among all seven cases was 25·1 years. These latent periods were longer than those observed in previous studies.

In closing, it should be pointed out that there are several limitations in this study. Most are typical of a historical mortality study of industrial populations. Firstly, although both the percentage lost to follow up and the proportion of outstanding death certificates were low, 2·3% and 2·2% respectively, it was possible, but unlikely, that some deaths from lymphopoietic

cancer might have been missed. This omission, however, could occur in both the exposed and unexposed groups.

Secondly, the results of cohort verification indicated an error rate of 0·8%. Although this error rate was extremely small, the small number of individuals inadvertently excluded could subsequently have died from lymphopoietic cancer. Again, this could happen in both the exposed and the unexposed groups.

Thirdly, based on a 10% random sample of the cohort, coding accuracy was estimated at 97·4%. A small amount of coding error seems to be unavoidable in a large scale study such as this.

Fourthly, historical exposure levels for the early part of the study were limited for some of the plants. The problem was partially dealt with by the uniform task approach. This required the breakdown of exposed jobs into specific uniform tasks, for which benzene exposure levels could be estimated more readily. It should be pointed out that any misclassification in occupational exposure to benzene would tend to reduce and not increase the likelihood of detecting dose response relations. Furthermore, analyses by cumulative benzene exposure identified significant dose response relations only for leukaemia, as well as the broader category of all lymphopoietic cancer.

Fifthly, presumably those occupationally exposed to benzene were also exposed to other chemicals. This problem of concomitant exposures was partially dealt with by comparing them with occupationally non-exposed workers. Furthermore, the significant dose response relations between benzene and all lymphopoietic cancer or leukaemia would discredit any theory of concurrent exposures, unless the latter were some sort of benzene related "impurities," whose exposure levels were highly correlated with those of benzene. Employment history other than that with the participating plants was not available and not considered.

Sixthly, the cohort size was small for several specific analyses. For example, the dose response relation between leukaemia and cumulative exposure was based on a small number of deaths, and the statistical variabilities were considerable. Furthermore, the absence of any deaths from leukaemia in the comparison group presented a technical difficulty: relative risk for leukaemia between the occupationally exposed and unexposed groups was undefined. Similarly, the number of deaths due to non-Hodgkin's lymphoma was also small. Although the relative risk for non-Hodgkin's lymphoma for white male workers in the continuous exposure group was fivefold, it did not reach statistical significance ($p = 0{\cdot}12$). Also, as discussed earlier, the study was too small to offer any firm data on the relation between exposure to benzene and multiple myeloma. The final study cohort suffered from the withdrawal of two major plants from the study, and a reduction of cohort members, as well as a loss of person-years due to the unforeseen incompleteness of employment records before 1957 at two other plants. The presence of dose response relations partially ameliorates the problem of small numbers.

Seventhly, there was no practical means of checking the comparability of the exposed and the comparison groups with regard to some non-occupational risk factors. In this study the internal comparison group was simply those workers from the same facilities who were not occupationally exposed to benzene. Data collection and death ascertainment for both groups were conducted in an identical manner. We have examined the comparability of several demographic and occupational parameters (such as year of birth and age at hire), and found no major differences, although the duration of employment of the comparison group was somewhat shorter than that of the exposed. There were more unobtained death certificates in the comparison group, but it seemed unlikely that these minor differences could account for the observed mortality difference in lymphopoietic cancer. Although one may raise the question regarding the comparability in starting person-years of the exposed and comparison groups, since the early years of employment are generally associated with a greater healthy worker effect. Calculations showed that the delay in starting person-years in the exposed group was only 2·14 years. Although any difference in age and race was adjusted in the analysis, the possibility of some unknown confounding factors existing between the two groups remained. In controlled clinical trials such confounding factors can be eliminated by randomisation. In observational studies such as this one, however, randomisation is not feasible. Based on data available from this study, we can only say that there was no evidence to suspect that such confounding factors existed. The dose response relations further discredit any theory of unknown confounding factors between the exposed and the comparison groups, since various levels of cumulative exposure within the exposed group were compared. In this regard it should be noted that the overall SMRs for the occupationally exposed groups and the comparison group were not dissimilar (86·6 *v* 75·2). In fact the $\geqslant 720$ ppm-months group experienced the lowest overall mortality (SMR = 63·5, $p < 0{\cdot}01$), indicating that this group, although with the highest SMRs for all lymphopoietic cancer and leukaemia, was not otherwise generally unhealthy.

Finally, being a mortality study, the investigation not only inherited all the problems associated with death certificates (diagnostic accuracy, for example) but also suffered from the lack of in depth clinical

information.

Despite these limitations, the study has shown that chemical workers occupationally exposed to benzene experienced significant mortality excess from leukaemia, as well as the broader category of all lymphatic and haematopoietic cancer, when compared with chemical workers who were not occupationally exposed to benzene. This result of leukaemia excess was consistent with some of the findings of previous epidemiological reports, but the cell types were not typical of those reported in many earlier studies. The data further show significant dose response relations between cumulative benzene exposure and excess mortality from leukaemia and the broader category of all lymphatic and haematopoietic cancer. Although significant dose response relations were established, the precise shape of the dose-response curves was less definite due to the variability of the available data (particularly the estimated historical data). As such, although the dose response relation has added strength to the association between exposure to benzene and leukaemia and lymphatic and haematopoietic cancer, the estimated historical industrial hygiene data were not precise enough for absolute quantitative risk assessment.

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