An epidemiological study of workers potentially exposed to ethylene oxide

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Abstract

This epidemiological study was of 18 728 employees at 14 United States facilities producing sterilised medical supplies and spices, who were potentially exposed to ethylene oxide (EO) for at least 90 days. The mortality of the cohort was studied to the end of 1988. A total of 1353 deaths was identified. The cohort had a significantly lower mortality than the general population from all causes, all cancers, and non-malignant diseases. In the entire cohort, mortality was not significantly increased from any of the cancer sites examined. In particular, no significant increase in mortality was found in the cancer sites of interest based on previous studies—namely, stomach, leukaemia (including major specific cell types), pancreas, and brain. The lack of an increased mortality for these cancer sites was further strengthened by the lack of a dose-response relation with duration of employment and latency. Among the men, a statistically significant increase in mortality from non-Hodgkin's lymphoma was found. There was no indication for a dose-response relation for non-Hodgkin's lymphoma and no specific job categories seemed to be responsible for the increase. Among the women, a deficit of non-Hodgkin's lymphoma was found, which was not consistent with the finding in the men. Therefore, the increase among the men did not seem to be related to exposure to EO.

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In 1979, two small Swedish investigations reported increased risks for leukaemia[1 2] and stomach cancer[2] among workers potentially exposed to ethylene oxide (EO). In 1981, the results of two slightly larger cohort studies of chemical workers exposed to EO in the United States[3] and Germany[4] were reported; neither study found any excess of cancer. More recently, a 1988 investigation[5] reported excess mortality from leukaemia and lymphoma among Italian workers licenced to handle a wide variety of chemical gases including EO. In 1989, the mortality pattern of 2876 United Kingdom workers exposed to EO (1471 involved in production of EO and 1405 in sterilisation with EO) was reported.[6] The mortality from cancer was similar to that expected and the authors concluded that no significant cancer risk would result from exposure levels similar to those found in the study. Similar findings of no association between cancer mortality and exposure to EO were reported in several other studies: in a cohort of 2658 chemical workers in Germany,[7] in a cohort of 2174 chemical workers in the United States,[8] and in a cohort of 2170 sterilisation workers in Sweden.[9]

The studies briefly reviewed had two major limitations in common. The two 1979 Swedish investigations were extremely small, with only slightly more than 200 subjects in each. Most of the other studies were also small, each with no more than two or three thousand workers. Although some of these studies had adequate statistical power to refute the 1979 Swedish findings, the power to detect a modest increase in risk of mortality from leukaemia (for example twofold) was low. In many of these studies, potential confounding exposures made a proper interpretation of the findings difficult.[1 5 8] The present report describes a large scale industry wide epidemiological study of workers employed at facilities that used EO for sterilising purposes.

Materials and methods

The study consisted of employees at 14 companies in the United States that used or had used EO for product sterilisation. Criteria for participation in the study included adequacy of personnel and exposure records, and absence of known leukemogens at the facilities. At 13 of the 14 companies, only hourly workers were included. Salaried employees either worked in non-exposed areas, or their employment

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records lacked sufficient detail to assess their exposure histories. At the remaining site, sufficient information was available to determine that salaried employees were exposed, and they were included in the cohort.

For exposure classification, we relied on reports of walk through surveys conducted at these sites by industrial hygienists from the National Institute for Occupational Safety and Health (NIOSH). Information was collected during these walk through surveys on industrial hygiene data, ventilation systems, engineering changes, and products used. Also, NIOSH conducted some EO measurements. Based on this information, areas with EO use were identified. These areas and areas sharing the same air system were assumed to have had potential exposure to EO. Roughly 20% of the employees in the cohort worked near sterilisers (operators), who were exposed to an eight hour time weighted average (eight hour TWA) of 4 to 5 ppm after 1978, and to an estimated eight hour TWA of 16 ppm before that time. For the rest of the cohort (production workers), the post 1978 eight hour TWA was roughly 2 ppm, and the pre 1978 eight hour TWA was estimated at 5 ppm. For short periods, the workers could have been exposed to higher concentrations of EO.

The participating companies provided us with copies of employment records (microfilms, microfiche, hard copies, and computer tapes). From these records, basic demographic information and work history were coded and entered into our computerised data base. Although detailed employment histories available from employment records were not entered, we were able to create an exposure state for each employee in our data base. Based on the individual walk through surveys, it was possible to determine, on a job by job basis, which jobs in the employment histories involved potential exposure to EO. In several cases, the microfilmed work histories were incomplete or uninterpretable. Further information was sought from the participating companies for clarification. As a measure of quality control, 10% of the coded records were recoded. The disagreement rate was less than 2%. Errors detected were subsequently corrected.

The cohort consisted of 18 728 employees from 14 United States facilities, who were identified to have been potentially exposed to EO for 90 days or more. The vital status of the cohort was determined through the following sources. Roughly 90% of the cohort members were submitted to the Social Security Administration (SSA) for vital status follow up before SSA's policy change in 1988 of discontinuing such services. To supplement the SSA follow up, the remaining cohort as well as those unknown to SSA were checked against the Death Master File (DMF; a data base of 39 million deaths in the United States, 1937–88, purchased from SSA) and the National Death Index (NDI; a national mortality registry since 1979). Also, the participating companies provided vital status information on many of the cohort members.

Table 1 Distribution by vital status (on 31 December 1988) for all cohort members

Vital status	*Frequency (%)*
Alive	17375 (92·8)
Deceased	1353 (7·2)
With death certificate	1291 (95·4)
Without death certificate	62 (4·6)
Total	18728 (100·0)

For those cohort members known to have died, requests for copies of death certificates were made to appropriate state health departments. All those obtained were coded by a trained nosologist according to the 8th revision of the International Classification of Diseases (ICD-8) by the underlying cause of death. The United States national age-cause-sex-year specific death rates were used in calculating the number of expected deaths from a particular cause. Due to certain equal employment opportunity policy requirements, race information was not recorded in many employment records. Among those with such information, most workers were white. Furthermore, according to the participating companies, the workforce, especially in the past, was predominantly white. Based on these reasons, we calculated the expected deaths based on the rates for white persons in the United States. Cause specific standardised mortality ratios (SMRs) were computed by expressing the observed numbers of deaths as percentages of those expected.[10]

Results

The cohort comprised 8709 men and 10 019 women. Eighty per cent of the cohort were hired between 1960 and 1979, mostly in their twenties or early thirties. Around half worked for less than five years. Slightly more than 30% worked for 10 years or longer. The average duration of exposure for the entire cohort was five years, only about one year shorter than the average employment. The average year of first hire was 1969, and the average year of first exposure was 1970.

Table 1 presents the vital status of the cohort on 31 December 1988. A total of 1353 had definitely died. For the remaining 17 375, there were no death indications through any follow up sources. The exact number with unknown vital status could not be determined, as part of the cohort was not subject to a complete SSA follow up. Relying on the DMF or the NDI, or both, it was not possible to distinguish unknown from alive. The entire group of 17 375 was labelled collectively as alive. Death certificates were

Table 2 Observed and expected deaths by cause

Cause of death (ICDA-8)	All cohort members			
	Obs	Exp	SMR	(95% CI)
All causes of death (1–999)	1353	1846·52	73·3**	(69·5– 77·2)
All malignant neoplasms (140–209)	403	446·20	90·3*	(81·7– 99·6)
Cancer of buccal cavity and pharynx (140–149)	7	10·69	65·5	(26·3–134·9)
Cancer of digestive organs and peritoneum (150–159)	92	104·00	88·5	(71·3–108·5)
Cancer of oesophagus (150)	6	8·24	72·8	(26·7–158·4)
Cancer of stomach (151)	15	15·42	97·3	(54·5–160·5)
Cancer of large intestine (153)	39	39·81	98·0	(69·7–133·9)
Cancer of rectum (154)	6	10·18	58·9	(21·6–128·3)
All cancer of liver (155–156)	3	7·14	42·0	(8·7–122·7)
Cancer of pancreas (157)	20	20·69	96·7	(59·1–149·3)
Cancer of respiratory system (160–163)	119	108·68	109·5	(90·7–131·0)
Cancer of larynx (161)	5	4·02	124·5	(40·4–290·5)
All cancer of lung—primary and secondary (162–163)	112	103·70	108·0	(88·9–130·0)
Cancer of bone (170)	4	1·96	203·9	(55·6–522·0)
Cancer of skin (172–173)	9	8·23	109·4	(50·0–207·6)
Cancer of breast (females only) (174)	45	56·54	79·6	(58·1–106·5)
Cancer of cervix uteri (180)	8	11·56	69·2	(29·9–136·4)
Cancer of corpus uteri (181–182)	2	6·91	29·0	(3·5–104·6)
Cancer of all uterus (180–182)	10	18·52	54·0*	(25·9– 99·3)
Cancer of other genital organs (females only) (183–184)	11	18·54	59·3	(29·6–106·1)
Cancer of all genital organs (females only) (180–184)	21	37·14	56·6**	(35·0– 86·4)
Cancer of prostate (185)	9	11·27	79·8	(36·5–151·6)
Cancer of testis (186–187)	3	1·94	154·6	(31·9–451·8)
Cancer of bladder (188)	4	7·22	55·4	(15·1–141·9)
Cancer of kidney (189)	14	8·77	159·6	(87·3–267·8)
Cancer of brain and other central nervous system (191–192)	8	14·27	56·1	(24·2–110·5)
Cancer of thyroid (193)	1	1·10	90·8	(2·3–505·8)
Lymphosarcoma and reticulosarcoma (200)	9	8·32	108·2	(49·5–205·5)
Hodgkin's disease (201)	4	5·20	77·0	(21·0–197·1)
Leukaemia and aleukaemia (204–207)	14	16·17	86·6	(47·3–145·3)
Cancer of other lymphatic tissue (202–203) (208)	14	11·39	122·9	(67·2–206·3)
All lymphopoietic cancer (200–209)	43	42·05	102·2	(74·0–137·7)
Benign neoplasms (210–239)	8	6·60	121·2	(52·3–238·9)
Allergic, endocrine, metabolic, nutritional diseases (240–279)	29	42·13	68·8*	(46·1– 98·9)
Diabetes mellitus (250)	21	33·97	61·8*	(38·3– 94·5)
All diseases of blood and blood-forming organs (280–289)	3	5·29	56·7	(11·7–165·7)
All diseases of circulatory system (390–458)	501	774·69	64·7**	(59·1– 70·6)
Arteriosclerotic heart disease, including CHD (410–413)	337	517·74	65·1**	(58·3– 72·4)
All vascular lesions of CNS (430–438)	60	125·05	48·0**	(36·6– 61·8)
All respiratory diseases (460–519)	61	91·91	66·4**	(50·8– 85·3)
All pneumonia (480–486)	18	35·74	50·4**	(29·9– 79·6)
Emphysema (492)	10	18·05	55·4	(26·6–101·9)
Asthma (493)	2	3·41	58·6	(7·1–211·8)
All diseases of digestive system (520–577)	50	102·07	49·0**	(36·4– 64·6)
Cirrhosis of liver (571)	31	61·25	50·6**	(34·4– 71·8)
All external causes of death (800–998)	175	255·35	68·5**	(58·8– 79·5)
All accidents (800–949)	102	150·63	67·7**	(55·2– 82·2)
Motor vehicle accidents (810–827)	60	75·69	79·3	(60·5–102·0)
Suicide (950–959)	37	55·84	66·3**	(46·7– 91·3)
Unknown causes of death	62			

*$p < 0.05$; **$p < 0.01$.
For all cohort members, number at risk 18 728; person-years 329 774·4.
For male cohort members, number at risk 8709; person-years 147 554·1.
For female cohort members, number at risk 10 019; person-years 182 220·2.

obtained for 1291 deaths. There were 62 deaths (4·6%) for which death certificates were not obtained, although the rough dates of death were known in all but two cases.

Table 2 shows the cause specific mortality analysis. For the entire cohort there were 1353 deaths. The 62 deaths without a death certificate were included in the calculation of the overall SMR but not in the cause specific SMRs. Compared with the expected 1846·52 deaths, the overall SMR of 73·3 was significantly lower than 100. Thus the cohort as a whole experienced a significant mortality deficit of 27%. The deficit was primarily in diseases of the circulatory system and other non-malignant causes of death. For example, the SMR for diseases of the circulatory system was 64·7, significant at the 0·01 level.

A smaller but significant deficit was also found for the category all malignant neoplasms. The 403 observed deaths were significantly less than the 446·20 expected. There was no significant increase in mortality from any site specific cancers. In particular, there was no increased mortality from cancer of the digestive system, stomach, pancreas, or brain, or from leukaemia. For leukaemia, there were 14 observed deaths, lower than the 16·17 expected. For the broad category of lymphopoietic cancer, the

Male cohort members				*Female cohort members*			
Obs	*Exp*	*SMR*	*(95% CI)*	*Obs*	*Exp*	*SMR*	*(95% CI)*
837	1086·79	77·8**	(72·5– 83·4)	516	759·73	67·9**	(62·1– 74·1)
216	213·25	101·3	(88·2–115·7)	187	232·95	80·3**	(69·2– 92·6)
5	7·10	70·4	(22·9–164·4)	2	3·59	55·7	(6·7–201·1)
49	53·93	90·9	(67·2–120·1)	43	50·07	85·9	(62·1–115·7)
5	5·99	83·5	(27·1–194·8)	1	2·26	44·3	(1·1–247·1)
7	9·19	76·2	(30·6–157·0)	8	6·23	128·4	(55·4–253·0)
22	17·60	125·0	(78·3–189·2)	17	22·20	76·6	(44·6–122·6)
3	5·39	55·6	(11·5–162·5)	3	4·79	62·7	(12·9–183·2)
0	3·31			3	3·83	78·3	(16·1–228·7)
10	11·17	89·5	(42·9–164·6)	10	9·51	105·1	(50·4–193·3)
78	77·44	100·7	(79·6–125·7)	41	31·23	131·3	(94·2–178·1)
5	3·20	156·4	(50·8–365·1)	0	0·82		
72	73·64	97·8	(76·5–123·1)	40	30·06	133·1	(95·1–181·2)
2	1·09	183·4	(22·2–662·5)	2	0·87	229·5	(27·8–829·2)
4	4·57	87·5	(23·8–224·0)	5	3·66	136·8	(44·4–319·2)
0	0·00			45	56·54	79·6	(58·1–106·5)
0	0·00			8	11·56	69·2	(29·9–136·4)
0	0·00			2	6·91	29·0	(3·5–104·6)
0	0·00			10	18·52	54·0*	(25·9– 99·3)
0	0·00			11	18·54	59·3	(29·6–106·1)
0	0·00			21	37·14	56·6**	(35·0– 86·4)
9	11·27	79·8	(36·5–151·6)	0	0·00		
3	1·94	154·6	(31·9–451·8)	0	0·00		
4	5·12	78·2	(21·3–200·1)	0	2·10		
9	5·30	169·8	(77·6–322·3)	5	3·47	144·1	(46·8–336·2)
6	7·26	82·7	(30·3–180·0)	2	7·01	28·5	(3·5–103·1)
0	0·37			1	0·73	136·5	(3·4–760·5)
7	4·31	162·3	(65·2–334·4)	2	4·00	50·0	(6·0–180·5)
4	3·00	133·1	(36·3–340·9)	0	2·19		
9	8·66	103·9	(47·5–197·2)	5	7·50	66·6	(21·6–155·5)
11	5·78	190·3	(95·0–340·5)	3	5·61	53·5	(11·0–156·3)
32	22·22	144·0	(98·5–203·3)	11	19·83	55·5*	(27·7– 99·2)
1	2·92	34·3	(0·9–191·0)	7	3·68	190·1	(76·4–391·8)
15	18·55	80·9	(45·3–133·4)	14	23·57	59·4*	(32·5– 99·6)
13	15·06	86·3	(46·0–147·6)	8	18·91	42·3**	(18·3– 83·4)
1	2·43	41·1	(1·0–229·3)	2	2·86	69·9	(8·5–252·6)
329	480·52	68·5**	(61·3– 76·3)	172	294·17	58·5**	(50·1– 67·9)
231	346·90	66·6**	(58·3– 75·8)	106	170·84	62·0**	(50·8– 75·0)
35	61·21	57·2**	(39·8– 79·5)	25	63·84	39·2**	(25·3– 57·8)
39	58·29	66·9**	(47·6– 91·5)	22	33·61	65·4*	(41·0– 99·1)
12	21·56	55·7*	(28·8– 97·2)	6	14·18	42·3*	(15·5– 92·1)
6	13·22	45·4*	(16·7– 98·8)	4	4·83	82·8	(22·6–212·0)
0	1·36			2	2·06	97·3	(11·8–351·5)
37	59·31	62·4**	(43·9– 86·0)	13	42·76	30·4**	(16·2– 52·0)
24	36·87	65·1*	(41·7– 96·9)	7	24·38	28·7**	(11·5– 59·2)
124	184·56	67·2**	(55·9– 80·1)	51	70·79	72·0*	(53·6– 94·7)
75	110·83	67·7**	(53·2– 84·8)	27	39·80	67·8*	(44·7– 98·7)
47	55·36	84·9	(62·4–112·9)	13	20·33	63·9	(34·0–109·3)
25	36·84	67·9	(43·9–100·2)	12	19·01	63·1**	(32·6–110·3)
42				20			

observed mortality (43 deaths) was similar to that expected (42·05 deaths). There was a slightly increased mortality from cancer of the other lymphatic tissue (14 observed deaths *v* 11·39 expected), but the increase was not statistically significant. For cancer of the bone, there were four observed deaths, about twice the expected number of 1·96 deaths. The corresponding SMR of 203·9 was not statistically significant. There was also a non-significant increase in mortality from kidney cancer (SMR 159·6).

Overall, both sexes showed a mortality pattern similar to the entire cohort, with the women experiencing a slightly more favourable mortality than the men. For example, there was a non-significant increase of cancer of the other lymphatic tissue (SMR = 190·3) in the men, but a non-significant deficit (SMR = 53·5) in the women.

Table 3 presents the cause specific SMRs by duration of employment and latency for the entire cohort. There was no significant increase in any of the cancer sites for any duration of employment. For all malignant neoplasms, the SMR was 72·0 ($p < 0·01$, based on 84 observed deaths) for those with 10–19 years of employment. There was no obvious upward trend for any of the cancer sites. For leukaemia, the highest SMR was found among those with the

shortest employment (three months to one year). For cancer of the other lymphatic tissue, there was no indication of any upward trend by duration of employment.

Analysis by duration of employment was also performed separately for men and women. No significant trend was found in either analysis and the detailed results are not reported here. The data were also analysed by truncated duration of employment (ignoring any employment within the past five years of observation). The results were similar to those based on full duration of employment.

No mortality pattern by latency for any cancer site was detected. For both stomach cancer and pancreatic cancer, the highest SMR was found among those with a latency shorter than 10 years. Similar analyses by latency for the men and the women were also performed. No obvious pattern occurred in either sex.

Analyses thus far indicated that the SMR for cancer of the other lymphatic tissue (ICD 202, 203, and 208) was increased among the men. This group of lymphopoietic cancer was simply the residual, however, in the broad group of lymphopoietic cancer (ICD 200–209), and was difficult to interpret beyond its statistical context.

A more meaningful way to examine the data would be to evaluate the group of lymphomas commonly known as non-Hodgkin's lymphoma but even for this the definition has not always been consistent. For example, Green defined non-Hodgkin's lymphoma as "reticulosarcoma, lymphosarcoma, and giant follicular lymphoma."[11] According to the county cancer statistics of the National Cancer Institute (NCI) published in 1987, non-Hodgkin's lymphoma includes ICD-8 codes 200 (lymphosarcoma and reticulum cell sarcoma) and 202 (other neoplasms of lymphoid tissue).[12] Because the NCI definition has been used widely, it was used in our analysis. The SMR computer program used for previous calculations did not provide rates for non-Hodgkin's lymphoma. We relied on mortality from non-Hodgkin's lymphoma published by NCI[12] in calculating the expected number of deaths from non-Hodgkin's lymphoma.

Table 4 shows the observed and expected deaths and SMRs for non-Hodgkin's lymphoma for the entire cohort and for each sex. There was a statistically significant increase among the men but not among the women. Table 5 presents the analysis of non-Hodgkin's lymphoma by duration of employment and latency. Some statistically significant increases were seen in some subgroups among the men, but an upward trend was not evident. No increase or upward trend was detected among the women.

Most occupational cohort studies do not analyse leukaemia by cell type, primarily because of the scarcity of specific data. Furthermore, most computer programs for calculating SMRs do not provide separate estimates by cell type. Recent investigations, however, show that leukaemia is a group of several distinct malignancies with different clinical and epidemiological features,[13] and should be analysed by cell type whenever possible.

To supplement our overall leukaemia analysis based on all cell types combined, we have further analysed the data by the four common cell types (table 6). The expected numbers were based on United States rates published by Selvin *et al.*[14] No unusual mortality pattern by leukaemia cell type was

Table 3 Observed deaths by cause and SMR for all cohort m by duration of employment and latency

Cause of death (ICDA-8)
All causes of death
All malignant neoplasms
Cancer of buccal cavity and pharynx
Cancer of digestive organs and peritoneum
Cancer of oesophagus
Cancer of stomach
Cancer of large intestine
Cancer of rectum
All cancer of liver
Cancer of pancreas
Cancer of respiratory system
Cancer of larynx
All cancer of lung—primary and secondary
Cancer of bone
Cancer of skin
Cancer of breast
Cancer of cervix uteri
Cancer of corpus uteri
Cancer of all uterus
Cancer of other genital organs
Cancer of all genital organs
Cancer of prostate
Cancer of testis
Cancer of bladder
Cancer of kidney
Cancer of brain and other central nervous system
Cancer of thyroid
Lymphosarcoma and reticulosarcoma
Hodgkin's disease
Leukaemia and aleukaemia
Cancer of other lymphatic tissue
All lymphopoietic cancer
Benign neoplasms
Allergic, endocrine, metabolic, nutritional
Diabetes mellitus
All diseases of blood and blood-forming organs
All diseases of circulatory system
Arteriosclerotic heart disease, including CHD
All vascular lesions of CNS
All respiratory diseases
All pneumonia
Emphysema
Asthma
All diseases of digestive system
Cirrhosis of liver
All external causes of death
All accidents
Motor vehicle accidents
Suicide
Unknown causes of death

*$p < 0.05$; **$p < 0.01$.

Duration of employment (y)											*Latency of employment (y)*							
<1		*1–4*		*5–9*		*10–19*		*≥20*			*<10*		*10–19*		*20–29*		*≥30*	
Obs	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*		*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*	*Obs*	*SMR*
237	89·1**	365	76·7**	238	73·9**	310	66·7**	203	63·8**		286	58·3**	543	78·4**	354	82·9**	170	72·1**
55	90·1	115	102·6	86	111·1	84	72·0**	63	79·8		81	76·9*	166	92·8	111	101·0	45	86·6
1	69·8	2	77·9	1	55·6	2	69·7	1	49·4		0		4	92·0	3	111·3	0	
12	94·2	28	117·2	14	78·0	22	76·8	16	77·0		19	90·1	34	84·1	27	97·0	12	81·9
0		3	164·2	1	72·2	2	86·4	0			0		3	89·6	3	141·5	0	
1	52·9	6	169·7	5	185·9	1	23·8	2	64·5		5	150·1	4	67·8	3	75·9	3	134·7
5	102·5	7	75·8	5	72·5	12	109·4	10	127·7		4	51·2	15	97·2	14	128·9	6	105·4
1	81·1	3	128·3	0		1	35·9	1	48·6		2	94·8	2	51·4	2	73·9	0	
0		0		1	79·1	1	50·9	1	71·8		0		1	36·6	2	105·7	0	
5	199·2	8	171·1	1	28·5	4	69·7	2	47·0		6	152·4	8	98·6	3	52·6	3	102·1
19	129·7	33	127·9	26	147·1	20	69·6	21	96·3		19	84·9	53	120·2	34	119·9	13	93·9
0		1	109·5	1	152·9	1	92·2	2	235·7		0		1	62·4	3	286·8	1	186·6
19	135·8	31	125·9	24	142·4	19	69·3	19	91·3		18	84·7	51	121·1	31	114·4	12	90·8
0		1	174·4	1	301·3	0		2	725·5		2	289·8	0		1	258·2	1	563·4
2	133·8	3	119·0	1	69·8	2	112·2	1	100·1		1	37·5	5	147·2	3	192·5	0	
3	36·5	11	68·3	18	166·3	11	75·4	2	29·4		15	95·2	18	72·4	10	79·7	2	58·9
3	168·8	2	55·3	1	42·6	0		2	192·2		4	94·9	1	20·3	3	154·6	0	
1	122·4	0		0		1	50·5	0			0		2	70·1	0		0	
4	153·8	2	37·4	1	27·2	1	21·0	2	93·5		4	69·0	3	38·5	3	78·9	0	
1	39·2	3	59·4	0		4	80·9	3	120·4		0		8	100·1	1	22·3	2	154·2
5	96·9	5	48·0	1	13·9*	5	51·4	5	107·8		4	37·7*	11	69·5	4	48·3	2	82·5
0		0		5	299·6	1	31·6	3	80·9		0		3	90·6	2	60·7	4	111·9
0		2	273·9	1	309·6	0		0			2	189·9	1	156·5	0		0	
0		0		2	171·4	1	48·8	1	55·0		0		2	79·7	2	95·4	0	
3	249·6	4	185·1	1	67·6	5	217·6	1	61·3		0		6	170·5	5	221·9	3	283·8
0		5	118·4	2	80·6	0		1	53·8		3	66·8	1	16·9*	3	103·6	1	103·5
0		0		0		1	332·0	0			0		1	228·1	0		0	
1	79·2	3	132·9	2	136·9	2	98·6	1	76·7		3	124·9	5	154·2	0		1	122·6
0		1	55·4	1	109·1	1	108·5	1	219·9		1	41·8	2	107·7	0		1	397·7
4	152·5	4	88·1	0		4	106·5	2	81·4		3	60·8	5	82·5	5	147·0	1	56·5
0		3	109·4	5	259·1	3	97·9	3	140·4		2	85·0	3	65·5	7	234·1	2	136·9
5	75·2	11	94·8	9	124·3	10	99·9	8	122·3		10	81·1	15	93·4	12	130·4	6	134·7
0		4	212·1	1	84·4	3	191·6	0			1	49·3	5	190·0	1	73·3	1	173·5
3	53·8	7	67·0	5	66·5	5	44·4	9	122·7		3	29·9*	10	61·2	9	87·0	7	129·6
1	23·2	4	48·9	5	82·5	4	43·2	7	113·9		2	26·0*	6	45·7*	9	105·0	4	87·4
1	124·8	0		1	103·0	1	78·3	0			1	59·1	1	51·0	1	93·5	0	
72	79·3*	114	66·5**	72	53·7**	153	71·3**	90	54·9**		54	36·4**	208	73·8**	156	74·1**	83	62·1**
51	84·4	74	65·8**	50	57·0**	106	73·6**	56	49·5**		35	37·5**	149	78·5**	101	70·0**	52	57·6**
7	51·4	11	40·7**	6	26·6**	22	61·9*	14	53·2*		5	21·5**	21	48·3**	22	64·4*	12	49·8*
11	95·8	13	61·4	12	77·1	13	53·2*	12	62·2		9	45·5*	22	66·8	22	93·8	8	50·8
3	64·7	5	58·2	2	31·4	5	53·5	3	44·1		5	57·0	5	40·1*	4	47·4	4	66·0
3	151·7	0		3	105·5	3	60·0	1	22·0		1	33·9	6	92·7	1	19·4	2	57·5
0		1	100·1	0		1	124·1	0			0		0		2	336·2	0	
10	63·2	17	60·2*	5	27·2**	9	35·5**	9	63·0		12	40·2	19	44·6**	12	56·6*	7	83·3
6	59·9	10	56·6	2	18·0**	6	40·3*	7	92·6		5	26·4**	13	48·4**	9	75·4	4	112·4
57	95·7	58	61·9**	36	80·5	19	46·2**	5	30·9**		90	68·3**	70	79·0*	11	41·3**	4	47·8
30	84·3	34	61·5**	19	74·1	15	62·9	4	38·9*		50	63·5**	40	80·2	9	55·6	3	51·6
17	87·1	22	74·3	13	104·3	8	78·3	0			35	78·8	21	91·0	4	63·2	0	
11	86·1	12	59·1	11	113·3	3	32·5*	0			16	61·2*	19	89·4	2	30·0	0	
21		17		12		8		4			23		20		14		5	

seen, although the numbers in each specific cell type were small. In particular, for acute myeloid leukaemia (AML), which has been linked to prolonged exposures to chemicals such as benzene, the SMR was 51·5. As well as the three deaths certified as AML, one death was coded as acute leukaemia. Even if this was counted as an AML, the SMR would be increased to only 68·7.

Discussion

We studied by far the largest cohort of workers exposed to EO to date, and, therefore, had the highest statistical power in detecting increases in cause specific mortality. Furthermore, because only those plants without any major confounding occupational exposures were chosen, some of the limitations due to confounding exposures encountered in previous studies were not applicable to this study. Thus the study provided the best available data to consider the question of human cancer risk from occupational exposure to EO.

The all causes SMR was only 73·3, a significant reduction from the expected on the basis of United States mortality statistics, showing the presence of the healthy worker effect. The overall cancer mortality and several site specific cancer mortalities were also significantly lower than the expected.

Table 4 Non-Hodgkin's lymphoma mortality analysis for entire cohort

Group	Observed deaths	Expected deaths	SMR	(95% CI)
All cohort members	18	12·74	141·3	(83·6–223·2)
Men	16	6·47	247·3**	(141·3–401·5)
Women	2	6·27	31·9	(3·9–115·2

**p < 0·01.

The primary objective of this study was to determine whether exposure to EO would increase mortality from leukaemia in this cohort of workers. The data clearly indicated no increase in such mortality. In fact, a slight reduction occurred in the total cohort (14 observed *v* 16·17 expected). The absence of an increased risk of leukaemia was seen in both sexes. The consistency of the data was further strengthened by the lack of an upward trend in the exposure response analyses based on duration of employment and latency.

Analysis by leukaemia cell type was also performed to determine if there was an increased risk for cell type specific leukaemia. For example, exposure to benzene above a certain level over an extended period can increase risk of leukaemia, but epidemiological data indicate that the particular cell type affected is acute myeloid leukaemia. Thus an overall analysis of leukaemia could mask or underestimate the risk in a specific cell type. Table 6 presents the leukaemia analysis by cell type. Clearly there was no increased mortality from leukaemia for any of the cell types.

For "all lymphopoietic cancer," there was no increase in the total cohort (43 observed *v* 42·05 expected). There was a non-significant increase in men, primarily due to the increase in non-Hodgkin's lymphoma. On the other hand, there was a significant deficit in mortality from all lymphopoietic cancer in the women. Furthermore, there was no upward trend in the analysis by duration of employment.

In a previous study, Hogstedt *et al*[2] reported an increase of stomach cancer (based on only three deaths) in a group of 89 employees exposed to EO and other chemicals. In our study, there was no indication of an increase of stomach cancer or digestive cancer in the total cohort or in either sex.

Because our study did not find any increase in cancer sites of interest based on previous studies, a consideration of statistical power is important. For all cancers, the study had adequate power (80% at the 0·05 level) to detect an SMR as small as 112, or an increase of 12%, if indeed such a risk existed. For leukaemia, the minimum detectable SMR was 171 (80% power at the 0·05 level). To put this into perspective, Hogstedt *et al*[1] reported an SMR for a leukaemia of about 1500 (based on three deaths) in their study. Clearly, such a leukaemia risk did not exist in our cohort.

Among the men, 16 deaths were due to non-Hodgkin's lymphoma, whereas only 6·47 were expected. The corresponding SMR of 247·3 among the men was statistically significant, but when we examined the data by duration of employment as a surrogate for duration of exposure, there was no obvious upward trend. We also examined in detail the work histories of those who died from non-

Table 5 SMR (observed deaths) for non-Hodgkin's lymphoma by duration of employment and latency

	Entire cohort		Men		Women	
	SMR	Obs	SMR	Obs	SMR	Obs
Duration of employment (y):						
<1	52·4	(1)	94·9	(1)	0	(0)
1– 4	148·5	(5)	232·1	(4)	60·9	(1)
5– 9	230·8	(5)	396·0*	(4)	86·5	(1)
10–19	158·2	(5)	335·3*	(5)	0	(0)
⩾20	93·7	(2)	168·2	(2)	0	(0)
Total	141·3	(18)	247·3**	(16)	31·9	(2)
Latency (y):						
<10	124·4	(4)	173·2	(3)	67·4	(1)
10–19	119·6	(6)	203·2	(5)	39·1	(1)
20–29	193·5	(6)	413·4**	(6)	0	(0)
⩾30	142·4	(2)	242·8	(2)	0	(0)
Total	141·3	(18)	247·3**	(16)	31·9	(2)

*p < 0·05; **p < 0·01.

Table 6 Leukaemia mortality analysis by cell type for the entire cohort

Leukaemia cell type	*Observed deaths*	*Expected deaths*	*SMR*	*(95% CI)*
All cell types combined	14	16·17	86·6	(47·3–135·3)
Acute lymphatic leukaemia	1	1·18	84·7	(2·1–470·5)
Acute myeloid leukaemia	3	5·82	51·5	(10·6–150·6)
Chronic lymphatic leukaemia	2	1·99	100·5	(12·2–362·8)
Chronic myeloid leukaemia	2	2·47	80·8	(9·8–291·7)
Others	6	4·71	127·4	(46·7–283·1)

Hodgkin's lymphoma. No specific job categories seemed responsible for the increase in the men. Furthermore, the women had a deficit in mortality from non-Hodgkin's lymphoma. In our study there was no major difference in exposure between the sexes. This inconsistency in non-Hodgkin's lymphoma risk was puzzling, as there is no indication based on either human or animal data that the carcinogenic effect, if any, of EO is sex specific. Thus although non-Hodgkin's lymphoma was statistically increased among the men, an interpretation of this being related to exposure to EO did not meet two important criteria for determining causation in chronic diseases—namely, a dose-response relation and consistency.

Analyses of non-Hodgkin's lymphoma based on death certificates are limited by a number of factors: inconsistent use of the term by different groups of health researchers (for example epidemiologists *v* pathologists), inconsistent classification of the disease in published work, and the various changes in the ICD revisions over time. Although non-Hodgkin's lymphoma is defined generally as neoplasms of the lymphoreticular system, the classification encompasses a heterogeneous group of tumours including reticulosarcoma, lymphosarcoma, and other neoplasms of lymphoid tissue. Table 7 shows the individual ICD-8 codes for the deaths from non-Hodgkin's lymphoma based on the NCI classification.[12] Some of the deaths (for example, from mycosis fungoides and Burkitt's lymphoma) may not be included as non-Hodgkin's lymphoma in some other classifications.

Table 7 Distribution of deaths from non-Hodgkin's lymphoma by ICD Code

Disease	*ICDA-8 code**	*Number of deaths*
Lymphosarcoma	200·0	4
Reticulosarcoma	200·1	5
Mycosis fungoides	202·1	1
Lymphoma (NOS)	202·2	5
Burkitt's lymphoma	202·2	1
Large cell lymphoma	202·2	1
Non-Hodgkin's lymphoma	202·2	1
Total		18

*International classification of diseases adapted (8th revision); NOS = not otherwise specified.

There are several known risk factors for non-Hodgkin's lymphoma or its subtypes. According to a review article by Green,[11] known risk factors include familial aggregation, primary immunodeficiency syndromes, therapeutic immunosuppression, acquired disorders of immunity, genetics, radiation, certain medications or drugs, certain infectious agents, and diet. For occupational exposures, some studies have reported an increased risk in anaesthesiologists, chemists, farmers, and herbicide applicators.

In recent years, disproportionally more patients with acquired immunodeficiency syndrome (AIDS) have died from non-Hodgkin's lymphoma. For example, in a San Francisco study, Harnly *et al*[15] reported that non-Hodgkin's lymphoma was significantly higher among never married men aged 25–44 years in census tracts with high incidence of AIDS than those in other census tracts. In a New York City study, Kristal *et al*[16] reported that in neighbourhoods with the highest mortality from AIDS, incidence of non-Hodgkin's lymphoma increased an average 37·8% annually and mortality increased 65·2% biannually; whereas there were no changes in incidence or mortality in areas with low AIDS mortality. In a study on non-Hodgkin's lymphoma and dioxins conducted by the Centers for Disease Control, a substantial number of non-Hodgkin's lymphoma cases were AIDS related, and these cases were excluded from the study.[17] In our study, as the increase of mortality from non-Hodgkin's lymphoma was limited to men, the issue of AIDS related non-Hodgkin's lymphoma could be a major potential confounder. Because of the nature of the data in this study, however, this issue could not be considered. In general, an examination of non-occupational risk factors is beyond the scope of the present study.

A few other causes of death were found to be increased in some of the previous studies—namely, pancreatic cancer, brain cancer, and diseases of the circulatory system. No increased mortality from these diseases occurred in our cohort.

Our study has some limitations. We did not code detailed employment histories, and, as a result, we were not able to analyse data by quantitative exposure. Instead we used duration of employment as a surrogate for exposure. For some employees, information on race was not available. In our analysis, we relied on the mortalities for white

persons for comparison. Because of the small percentage of non-white subjects in the cohort and the nature of diseases of interest, this assumption would not have introduced any significant impact on the results. Being a mortality study based entirely on death certificates, the diagnostic information might not be accurate for certain diseases. This limitation was somewhat compensated for by the fact that the comparison was also based on death certificate information in the general population.

On the other hand, this study has several strengths. Firstly, the cohort was the largest studied to date. It had adequate statistical power to detect a modest increase in risk for most causes of death. In particular, for the cancer sites of interest, the study had excellent power to detect a risk of less than twofold. Secondly, in terms of confounding exposures, a problem in many previous studies, only facilities without known leukemogens were included. Thirdly, the study had adequate follow up information; less than 5% of deaths were without death certificates. Fourthly, analyses based on duration of employment allowed an examination of the data for any dose-response relation.

In conclusion, this cohort of workers potentially exposed to EO experienced a more favourable mortality than the general population. Their overall mortality was 27% less than the expected, primarily due to significant deficits in circulatory and other non-malignant diseases. No excess mortality risk from leukaemia was found, a major concern based on some of the previous studies. The absence of such risk was further supported by a lack of an upward trend based on an analysis of duration of employment. Similarly, there were no increases in mortality from cancers of the stomach, pancreas, or brain and central nervous system. There was an increased mortality from non-Hodgkin's lymphoma among the men but not among the women. Because of the lack of a dose-response relation and the inconsistency between the two sexes, the increase in non-Hodgkin's lymphoma among the men did not seem to be related to exposure to EO. Without an examination of some of the major risk factors for non-Hodgkin's lymphoma (both occupational and lifestyle) among the male cohort members, no definite aetiological agent for the increased mortality from non-Hodgkin's lymphoma among the men can be identified at this point. More data, including lifestyle risk factors, are needed for clarification.

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