ORIGINAL ARTICLE

Mortality of workers exposed to ethylene oxide: extended follow up of a British cohort

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Aims: To obtain further information about the risks of cancer associated with occupational exposure to ethylene oxide

Methods: Follow up was extended by 13 years for a cohort of 2876 men and women with definite or potential exposure to ethylene oxide in the chemical industry or in hospital sterilising units. Subjects were traced through National Health Service and social security records, and their mortality was compared with that expected from rates in the national population by the person-years method.

Results: Analysis was based on 565 deaths, of which 339 had occurred during the additional period of follow up. Mortality was close to or below expectation for all causes (565 deaths *v* 607.6 expected), all cancers (188 *v* 184.2), and for all specific categories of malignancy including stomach cancer (10 *v* 11.6), breast cancer (11 *v* 13.2), non-Hodgkin's lymphoma (7 *v* 4.8), and leukaemia (5 *v* 4.6). All five deaths from leukaemia occurred in the subset of subjects with greatest potential for exposure to ethylene oxide, but even in this group the excess of deaths was small (2.6 expected).

Conclusions: The balance of evidence from this and other epidemiological investigations indicates that any risk of human cancer from ethylene oxide is low, particularly at the levels of occupational exposure that have occurred in Britain over recent decades. This may reflect the capacity of human cells to repair DNA damage caused by the chemical, which is a potent genotoxin and animal carcinogen.

Ethylene oxide is an important chemical intermediate in the manufacture of products such as ethylene glycol antifreeze and non-ionic detergents.[1] It is also used as a fumigant, and in the sterilisation of medical equipment and cosmetics. It is a reactive chemical with the capacity to form adducts with DNA and proteins, mutagenic both in vitro and in vivo, and clastogenic in a wide range of species.[1–3] In particular, an increased frequency of chromosomal aberrations and sister chromatid exchanges has been shown repeatedly in studies of exposed workers.[1 4] Consistent with this genotoxicity, it is a proven animal carcinogen, causing malignant tumours at various sites in rats and mice exposed by oral administration, inhalation, and subcutaneous injection.[1]

Early epidemiological studies from Sweden indicated an increased risk of gastric cancer and leukaemia among workers employed in the manufacture of ethylene oxide or in its use as a sterilant.[5 6] More recent investigations, including a cohort study conducted by our group,[7] have failed to confirm these findings,[2 8–15] but they have not excluded an increased risk of lymphatic and haematopoietic cancer, particularly at higher exposures; and despite the limited epidemiological evidence, the International Agency for Research on Cancer (IARC), taking into account positive findings from human cytogenetic studies, has classified ethylene oxide as carcinogenic to humans.[1]

In addition to the possible hazard of lymphatic and haematopoietic cancer, one more recent study has suggested an increased rate of breast cancer in female workers exposed to ethylene oxide.[16] However, because most epidemiological investigations to date have focused largely on men, this remains an area of uncertainty.

As the potential hazard from ethylene oxide has become clearer, controls on exposure in the workplace have been made tighter. Nevertheless, there is a need to confirm that current limits on exposure are adequate. Also, clarification of the risk of human cancer from ethylene oxide could have important implications for the assessment of chemical hazards of cancer more generally. If, despite its strong genotoxicity, ethylene oxide carries only a relatively low risk of cancer in humans, it would be helpful to establish the explanation, since it might also be relevant to other substances.

To provide further information on the risks of cancer associated with occupational exposure to ethylene oxide, we have updated the follow up of our cohort.

METHODS

The study focused on three factories that had manufactured ethylene oxide and derivative compounds such as polyethylene glycols and ethoxylates, one that produced alkoxides from ethylene oxide that had been bought in, and eight hospitals with ethylene oxide sterilising units (table 1). Employees at these facilities (all of which were located in England or Wales) were eligible for inclusion in the cohort if they had worked in a job with likely exposure to ethylene oxide at a time for which employment records were thought to be complete. (At some facilities records were no longer retained for the period in which ethylene oxide was first used. The dates from which records were complete were provided by managers at the factories and hospitals, and were checked by review of the earliest recorded dates of leaving employment for cohort members at each facility.)

Subjects who met these criteria were identified, and the jobs listed in their employment files were classified according to their potential exposure to ethylene oxide. At the chemical factories we distinguished jobs with definite exposure (workers assigned specifically to ethylene oxide plants), probable exposure (mainly maintenance engineers who worked on several plants including the ethylene oxide area), and unknown exposure (poorly described, but possibly involving contact with ethylene oxide). Jobs at the hospital were classed as having continual exposure (people who worked continuously in the sterilising room), intermittent

Main messages

- Any risk of human cancer from ethylene oxide at the levels of exposure which have occurred in British industry over recent decades is low.

Policy implications

- The findings of this study do not suggest any need to modify the current UK occupational exposure limit for ethylene oxide of 5 ppm.

exposure (porters and others who spent only part of their working day in the sterilising room) and unknown exposure (poorly described, but most would have involved some contact with ethylene oxide).

Environmental and personal monitoring carried out since 1977 indicated time weighted average exposures of less than 5 ppm in almost all jobs, but with occasional peaks of up to several hundred ppm because of operating difficulties in the chemical plants and when sterilisers were loaded and unloaded in hospitals. In earlier years, exposures were probably somewhat higher, and peak exposures above the odour threshold of 700 ppm were reported both at factories and hospitals. Other potentially confounding exposures at the chemical factories included chlorhydrin, propylene oxide, styrene, and benzene. Some hospital workers would have experienced occasional low level exposure to formaldehyde and carbon tetrachloride.

The cohort was followed to 31 December 2000 through the National Health Service Central Register (NHSCR), in some cases with supplementary information from records held by the Department of Health and Social Security (DHSS) for the period up to 1987. On this basis, subjects were classed as untraced, alive, deceased, or otherwise lost to follow up. For those who had died, the underlying cause of death was ascertained from the death certificate, and coded to the ninth revision of the International Classification of Diseases (ICD-9).

The mortality of the cohort was analysed by the person-years method with expected numbers of deaths derived from five-year age, calendar period, and sex specific rates in the national (England and Wales) population. The results were summarised by standardised mortality ratios (SMRs) with 95% confidence intervals (CIs) based on the Poisson distribution.

RESULTS

As in our previous report,[7] analysis was based on 2876 subjects (1864 men and 1012 women). A further 16 workers met the criteria for inclusion in the cohort, but were excluded because information was missing about one or more of their sex, date of birth, or date of first potential exposure to ethylene oxide. Among the 2876 subjects analysed, 1471 had been employed at chemical manufacturers (all but one male), including 887 with definite exposure to ethylene oxide, 356 with probable exposure, and 228 with unknown exposure. Of the 1405 men and women who had worked at hospitals, 714 were classed as having continual exposure, 149 intermittent, and 542 unknown.

By 31 December 2000, 565 members of the cohort were known to have died (including two for whom the underlying cause of death was not available). This represented an additional 339 deaths since our earlier analysis. Fifty one subjects (1.8%) could not be traced at NHSCR or DHSS, and for these men and women, follow up was censored at the last known date of employment. The number of ''no traces'' was higher than reported previously because of corrections to the classification of 13 subjects. A further 206 subjects (7.2%) had emigrated or otherwise been lost to follow up since leaving the factories and hospitals under study, and for these, follow up was censored at the date when they were last known to be alive. The remaining 2054 were still alive.

Table 2 compares mortality in the cohort with that in the national population. Overall, there were fewer deaths than expected, both in the chemical workers and in the hospital employees. Small excesses of deaths were observed among the chemical manufacturers for circulatory disease (SMR 1.04) and cancer (SMR 1.11), but these were not statistically significant. Mortality from cancer in the hospital workers was less than would be expected from national rates.

Table 3 summarises the distribution of mortality from specific cancers. There was no statistically significant increase in deaths from any category of tumour, either in the cohort as a whole, or in the chemical workers and hospital employees when analysed separately. In particular, the numbers of deaths from leukaemia (5 *v* 4.6 expected), non-Hodgkin's lymphoma (7 *v* 4.8), stomach cancer (10 *v* 11.6), and female breast cancer (11 *v* 13.1) were close to expectation.

Table 4 shows mortality from selected cancers of a priori interest, for different categories of exposure to ethylene oxide. Among the chemical manufacturers, the risk of lymphatic and haematopoietic malignancies was somewhat higher in those with definite exposure, but there was no excess mortality from these cancers among the hospital workers with continual exposure.

Table 1 Composition of cohort

Workforce	Activity*	Period in which exposure to ethylene oxide occurred	Period for which cohort was ascertained
A	Manufacture of ethylene oxide and derivatives	1950–	01.01.1956–31.12.1978
B	Manufacture of ethylene oxide and derivatives	1955–	01.07.1976–30.04.1985
C	Manufacture of ethylene oxide and derivatives	1960–	01.05.1960–30.06.1985
D	Manufacture of derivatives from ethylene oxide produced elsewhere	1959–	01.01.1963–31.10.1985
E	Hospital sterilising unit	1962–	01.06.1964–10.12.1984
F	Hospital sterilising unit	1972–84	01.07.1972–30.06.1984
G	Hospital sterilising unit	1965–84	01.07.1975–31.12.1984
H	Hospital sterilising unit	1969–	01.07.1969–31.08.1985
I	Hospital sterilising unit	1971–	01.07.1971–30.09.1985
J	Hospital sterilising unit	1971–	01.09.1974–30.09.1985
K	Hospital sterilising unit	1968–82	01.09.1968–31.07.1980
L	Hospital sterilising unit	1965–	01.07.1965–30.09.1986

*Further details of the processes carried out by the chemical companies (workforces A–D) have been reported previously.[7]

Table 2 Mortality from major causes of death by place of employment

Cause of death (ICD-9 code)	Chemical manufacturers				Hospitals				All places of employment			
	Deaths observed	Deaths expected	SMR	(95% CI)	Deaths observed	Deaths expected	SMR	(95% CI)	Deaths observed	Deaths expected	SMR	(95% CI)
All cancer (140–208)	120	108.6	1.11	(0.92 to 1.32)	68	75.6	0.90	(0.70 to 1.14)	188	184.2	1.02	(0.88 to 1.18)
Circulatory disease (390–459)	174	167.6	1.04	(0.89 to 1.20)	77	97.5	0.79	(0.62 to 0.99)	251	265.0	0.95	(0.83 to 1.07)
Respiratory disease (460–519)	31	36.5	0.85	(0.58 to 1.20)	21	26.6	0.79	(0.49 to 1.21)	52	63.1	0.82	(0.61 to 1.08)
Digestive disease (008–009, 520–579)	6	11.4	0.53	(0.19 to 1.15)	7	8.8	0.80	(0.32 to 1.64)	13	20.2	0.64	(0.34 to 1.10)
Injury and poisoning (800–999)	14	19.3	0.73	(0.40 to 1.22)	8	10.2	0.79	(0.34 to 1.55)	22	29.4	0.75	(0.47 to 1.13)
All causes	366	366.9	1.00	(0.90 to 1.11)	199	240.7	0.83	(0.72 to 0.95)	565	607.6	0.93	(0.85 to 1.01)

Table 3 Mortality from cancer by place of employment

Cancer (ICD-9 code)	Chemical manufacturers				Hospitals				All places of employment			
	Deaths observed	Deaths expected	SMR	(95% CI)	Deaths observed	Deaths expected	SMR	(95% CI)	Deaths observed	Deaths expected	SMR	(95% CI)
Oesophagus (150)	5	4.8	1.04	(0.34 to 2.43)	3	2.3	1.32	(0.27 to 3.84)	8	7.1	1.13	(0.49 to 2.23)
Stomach (151)	5	8.0	0.62	(0.20 to 1.46)	5	3.6	1.40	(0.46 to 3.28)	10	11.6	0.86	(0.41 to 1.59)
Large intestine (153)	5	7.2	0.69	(0.22 to 1.61)	5	5.6	0.90	(0.29 to 2.09)	10	12.8	0.78	(0.37 to 1.43)
Rectum (154)	2	4.6	0.43	(0.05 to 1.56)	2	2.6	0.78	(0.09 to 2.82)	4	7.2	0.56	(0.15 to 1.42)
Liver* (155.0, 155.1)	3	1.1	2.62	(0.54 to 7.65)	0	0.6	0	(0 to 6.22)	3	1.7	1.72	(0.36 to 5.04)
Pancreas (157)	8	4.7	1.72	(0.74 to 3.38)	3	3.2	0.95	(0.20 to 2.78)	11	7.8	1.41	(0.70 to 2.52)
Lung (162)	43	36.5	1.18	(0.85 to 1.59)	16	15.3	1.04	(0.60 to 1.70)	59	51.8	1.14	(0.87 to 1.47)
Female breast (174)	–	–	–	–	11	13.1	0.84	(0.42 to 1.51)	11	13.1	0.84	(0.42 to 1.50)
Prostate (185)	5	6.9	0.72	(0.23 to 1.68)	2	1.1	1.82	(0.22 to 6.56)	7	8.0	0.87	(0.35 to 1.80)
Bladder (188)	7	3.8	1.85	(0.74 to 3.82)	1	1.6	0.63	(0.02 to 3.50)	8	5.4	1.49	(0.64 to 2.94)
Kidney (189)	6	2.6	2.33	(0.85 to 5.07)	1	1.2	0.81	(0.02 to 4.50)	7	3.8	1.83	(0.74 to 3.78)
Brain and nervous system (191–2)	1	3.4	0.30	(0.01 to 1.65)	2	1.9	1.05	(0.13 to 3.78)	3	5.3	0.57	(0.12 to 1.66)
Hodgkin's disease (201)	1	0.7	1.40	(0.04 to 7.82)	1	0.3	2.98	(0.08 to 16.62)	2	1.0	1.91	(0.23 to 6.89)
Non-Hodgkin's lymphoma (200, 202)	4	2.9	1.38	(0.38 to 3.53)	3	1.9	1.59	(0.33 to 4.66)	7	4.8	1.46	(0.59 to 3.02)
Multiple myeloma (203.0)	3	1.5	2.03	(0.42 to 5.94)	0	1.0	0	(0 to 3.57)	3	2.5	1.20	(0.25 to 3.49)
Leukaemia (204–8)	4	2.8	1.41	(0.39 to 3.62)	1	1.8	0.55	(0.01 to 3.06)	5	4.6	1.08	(0.35 to 2.51)

In addition to the cancers listed above, deaths were recorded from cancer of the tongue (1), mouth (1), small intestine (2), larynx (1), pleura (1), thymus (1), cervix (1), body of uterus (1), ovary (2), testis (1), penis (1), and unspecified sites (17).
*Because of changes in disease classification, the earliest follow up for cancer of the liver was from 1958.

Table 4 Mortality from selected cancers by exposure category

Exposure category	Cancer of stomach			Cancer of female breast			Leukaemia			All lymphatic and haematopoietic cancers		
	Deaths observed	Deaths expected	SMR	Deaths observed	Deaths expected	SMR	Deaths observed	Deaths expected	SMR	Deaths observed	Deaths expected	SMR
Chemical manufacturers												
Definite	4	5.1	0.78	–	–	–	4	1.7	2.29	9	4.9	1.84
Probable	1	1.8	0.57	–	–	–	0	0.7	0	2	1.9	1.07
Unknown	0	1.1	0	–	–	–	0	0.4	0	1	1.2	0.82
Hospitals												
Continual	5	1.8	2.73	5	7.2	0.70	1	0.9	1.08	1	2.6	0.38
Intermittent	0	0.4	0	0	0.7	0	0	0.2	0	1	0.5	2.09
Unknown	0	1.4	0	6	5.2	1.16	0	0.7	0	3	2.0	1.48

DISCUSSION

Over the 13 additional years of follow up included in this analysis, the observed number of deaths in the cohort more than doubled, substantially increasing the power of the investigation. Nevertheless, we found no statistically significant increase in mortality from cancer overall, or from any specific category of tumour.

The main suspicion a priori related to lymphatic and haematopoietic cancer, and especially to leukaemia. The early Swedish findings which had suggested an increased risk of leukaemia were based on only a small number of cases,[5 6] and later studies found much smaller excesses or none at all.[8–15] Thus, a meta-analysis published in 1999, and based on 10 cohorts, found an overall SMR for leukaemia of 1.08 (95% CI 0.61 to 1.93) and concluded that the evidence for a hazard was inconclusive.[2] However, more detailed analysis for the largest single component cohort did indicate a positive trend in mortality from lymphatic and haematopoietic cancer with higher cumulative exposure to ethylene oxide.[17] In our study, deaths from lymphatic and haematopoietic cancer were increased in chemical manufacturers with definite exposure (9 observed *v* 4.9 expected), as were deaths from leukaemia specifically (4 *v* 1.7). However, no excess was observed among hospital workers with continual exposure. Although only limited occupational hygiene data were available, it seems unlikely that exposures to ethylene oxide (both peak and average) were markedly higher in the chemical operatives than in the hospital workers.

The much higher risk estimates in the Swedish studies are unlikely to be explained by bias in the selection of the subjects or ascertainment of disease outcome. They could, in part, reflect a confounding effect of other chemical exposures in some manufacturing plants—for example, to epichlorhydrin. Also, it is possible that exposures in the Swedish cohorts were higher than in many of the other populations studied. In addition, some of the discrepancy between studies may be attributable to chance.

The Swedish investigations also suggested that ethylene oxide causes stomach cancer.[5 6] However, our findings do not support this. A small excess of deaths was observed among the hospital workers with continual exposure, but there was a deficit in the manufacturers with definite exposure, and in total, the number of deaths from gastric cancer in the cohort was fewer than expected. When the results from other cohort studies are taken into account, the overall evidence for a hazard of stomach cancer from ethylene oxide is weak.[2]

One study of female employees at a sterilising plant in New York State has suggested an increased risk of breast cancer.[16] Again, however, our results give no support to this hypothesis. Nor was there an excess of breast cancer in a large study of employees at 14 other sterilising plants in the United States.[10] It should be noted, however, that levels of exposure were relatively high in the New York plant.[16]

In accord with the balance of evidence from other epidemiological investigations, our findings indicate that any risk of human cancer from ethylene oxide is low, particularly at the levels of occupational exposure which have been the norm in recent decades. This is perhaps surprising, given its clear genotoxicity, animal carcinogenicity, and capacity to cause chromosomal damage in exposed workers, and there is a need to understand better why risks are not higher. It is possible that the explanation lies in the capacity of human cells to repair the DNA damage caused by ethylene oxide, which also occurs naturally through the action of endogenously formed ethylene oxide.[3]

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