MORTALITY AMONG WORKERS EXPOSED TO ETHYLENE OXIDE

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Abstract *Background.* Ethylene oxide is a sterilant gas that causes leukemia and other cancers in animals. Studies in Sweden have shown an excess of leukemia and stomach cancer in humans exposed to ethylene oxide, but other studies have generally failed to confirm these findings.

Methods. We conducted a study of mortality in 18,254 U.S. workers exposed to ethylene oxide at 14 plants producing sterilized medical supplies and spices. The subjects averaged 4.9 years of exposure to the gas and 16 years of follow-up. The exposure levels in recent years averaged 4.3 ppm (eight-hour time-weighted adjusted exposure) for sterilizer operators and 2.0 ppm for other workers. The levels in earlier years are likely to have been several times higher. Mortality in this cohort was compared with that in the general U.S. population.

Results. Overall there was no significant increase in mortality from any cause in the study cohort. The standardized mortality ratios (SMRs) were 0.97 for leukemia (95 percent confidence interval, 0.52 to 1.67; 13 deaths observed), 1.06 for all hematopoietic cancers (95 percent confidence interval, 0.75 to 1.47; 36 deaths), and 0.94 for stomach cancer (95 percent confidence interval, 0.45 to 1.70; 11 deaths). Analyses according to job category and according to the duration of exposure showed no excess in cancers, as compared with the rate in the general population, but there was a significant trend toward increased mortality with increasing lengths of time since the first exposure for all hematopoietic cancers. The rate of death from hematopoietic cancer (especially non-Hodgkin's lymphoma) was significantly increased among men (SMR, 1.55; 27 deaths). Mortality from leukemia in recent years (1985 through 1987) was significantly increased among men (SMR, 3.45; 5 deaths).

Conclusions. For the entire cohort, there was no increase in mortality from hematopoietic cancer. There was a slight but significant increase among men, however. Among men and women combined, there was a trend toward an increased risk of death from hematopoietic cancer with increasing lengths of time since the first exposure to ethylene oxide. (N Engl J Med 1991; 324: 1402-7.)

ETHYLENE OXIDE is a gas used as a chemical intermediate; since the 1950s it has also been used to sterilize medical supplies and other materials. The National Institute for Occupational Safety and Health (NIOSH) estimates that approximately 270,000 workers in the United States are exposed to ethylene oxide.[1] Those with relatively high levels of exposure include approximately 96,000 exposed in hospitals and 21,000 exposed during the commercial sterilization of medical supplies, pharmaceutical products, and spices.

Ethylene oxide is a highly reactive epoxide and is a direct alkylating agent. Three inhalation studies in rodents have found that multiple cancers, particularly leukemia and brain cancer, are associated with exposure to ethylene oxide in a dose-related manner.[2-4] Numerous studies have indicated increased sister-chromatid exchange, chromosomal aberrations, or both in workers exposed to ethylene oxide.[5-11] The findings of epidemiologic studies of ethylene oxide and cancer have been contradictory, limited by the small numbers of cases, and sometimes difficult to interpret because of mixed exposures.

Hogstedt et al. studied 733 Swedish workers exposed to ethylene oxide at two production facilities and one facility using the gas.[12-15] As of 1988, the standardized mortality ratio (SMR) for leukemia was 9.21 (95 percent confidence interval, 3.51 to 18.03; 7 deaths observed) and that for stomach cancer was 5.46 (95 percent confidence interval, 2.66 to 10.22; 10 deaths). At all three facilities, there were other potential confounding exposures, including exposure to the known animal carcinogens ethylene chlorohydrin and ethylene dichloride at one of the production facilities. Historical ethylene oxide levels at the three facilities were estimated on the basis of limited sampling data to have been in the range of 5 to 20 ppm.

Although these studies have shown an increased frequency of leukemia and stomach cancer among workers exposed to ethylene oxide, four other studies of a total of 5903 workers found no excess (the latter were limited by their small samples or by incomplete information on exposure).[16-19] Among these 5903 workers there were 6 cases of leukemia (as compared with 5.4 expected cases) and 23 cases of stomach cancer (as compared with 18.7 expected; one study did not report data on stomach cancer). A fifth study[20] of 2174 chemical-plant workers found 7 cases of leukemia, as compared with 3.0 expected, and 3 cases of stomach cancer, as compared with 3.7 expected. However, the excess cases of leukemia in this study were limited to workers using a particular process that entailed minimal exposure to ethylene oxide but higher exposures to ethylene chlorohydrin.[21]

In 1984, on the basis of the results of the animal studies and the Swedish studies, the Occupational Safety and Health Administration (OSHA) lowered the standard for eight-hour time-weighted exposure to ethylene oxide from 50 ppm to 1 ppm.[22] In 1987 the International Agency for Research on Cancer concluded, on the basis of what it considered sufficient evidence in animals and limited evidence from studies in humans, that ethylene oxide was a probable human carcinogen.[23]

To investigate further whether exposure to ethylene

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oxide increases the risk of cancer, particularly hematopoietic, stomach, brain, and pancreatic cancer, we studied mortality in approximately 18,000 workers exposed to ethylene oxide in 14 industrial plants. Most were exposed in the course of sterilizing medical supplies, although workers in three plants treated spices and those in another manufactured and tested sterilizers.

Methods

A feasibility study was conducted in which information was gathered on 75 facilities in the United States that had used ethylene oxide for sterilization.[24] Fourteen plants in 12 states were selected because they had adequate records on personnel and exposure and because their workers had at least 400 person-years at risk before 1978. Using their knowledge of the industrial process or actual sampling data, industrial hygienists from NIOSH and plant personnel worked together to determine in which areas of the plant workers were exposed to ethylene oxide. Since ethylene oxide in the air circulates freely, workers in any area sharing the same air with either the sterilizers or the recently sterilized product were likely to have had some exposure. Workers judged never to have been exposed to ethylene oxide were excluded from the study cohort. Similarly, salaried personnel were generally excluded from the cohort because they often worked in nonexposed areas or because their work-history records had insufficient detail to indicate where they had worked. Only workers with at least three months of exposure to ethylene oxide were included in the study. Separate analyses were conducted for workers first exposed before 1978, when many companies began to install engineering controls to lower workers' level of exposure (for example, increased ventilation and better door seals), after the initial reports of the carcinogenicity of ethylene oxide.

To validate our identification of the cohort from personnel records, alternative lists of employees were used. At two plants we used social security quarterly earnings reports, and at six other plants we used payroll lists. No information suitable for validation purposes was available at the remaining six plants.

The end of follow-up was defined as the date when each member of the cohort was last known to be alive, and it therefore varied among the workers. Vital-status follow-up was conducted through 1987 with use of a combination of data from the Social Security Administration, the National Death Index, the Internal Revenue Service, and the U.S. Postal Service. If a worker was known to have been alive after January 1, 1979 (when the records of the National Death Index begin), and was not found in a search of the index, he or she was assumed to have been alive at the end of follow-up (December 31, 1987). The National Death Index has been demonstrated to list 93 to 98 percent of all known deaths if reliable data (name, social security number, and birth date) are available for matching.[25]

Standard life-table analyses were conducted with use of the NIOSH life-table program.[26] The NIOSH life table groups deaths into 92 categories, according to the code in the *International Classification of Diseases* (revision at time of death) for the underlying cause of death. We calculated the number of person-years at risk for each worker beginning after three months of exposure and ending at the end of follow-up for each worker.

The U.S. population was used as the reference group. Death rates in the exposed cohort and the United States were stratified according to age, race, sex, and calendar year. Analyses were conducted for the total cohort and also according to the length of time since the first exposure, the duration of exposure, race, and sex. Cutoff points for the categories of duration of exposure were chosen before the analyses began, with the goal of creating three categories expected to include approximately equal numbers of deaths. For the length of time since the first exposure, cutoff points of 10 and 20 years were chosen on the basis of traditional epidemiologic practice. Tests for trends in SMRs were conducted as described by Breslow et al.[27] Confidence intervals for each SMR were computed by the method of Byar[28] when there were seven or more observed deaths; otherwise, exact tests were used. For simplicity's sake, we used two-sided significance tests (alpha = 0.05) and 95 percent confidence intervals for all outcomes, a conservative procedure for the outcomes suspected a priori. In other analyses (data not shown), exposure was also "lagged" by five years to discount exposure during the previous five years.[29]

Data from each plant included each worker's job title and department. In order to group workers at different plants into common exposure categories, we combined workers with these job titles and departments into six job categories: laboratory (quality-control) workers, workers in the sterilizer area who were not sterilizer operators, warehouse workers, production workers, sterilizer operators, and maintenance workers. Production workers could be expected to have been exposed to a more or less constant background level of ethylene oxide, whereas most other workers could be expected to have been exposed to the same background level and also to occasional peak levels. Separate analyses were conducted for these exposure categories. In these analyses, the number of person-years at risk began after the workers had had three months of exposure to ethylene oxide in any job category plus at least one day in the specific category of interest. Therefore, a single worker could be included in more than one of these analyses, if he or she had worked in more than one job category.

Air-sampling data (from personal samples and eight-hour time-weighted averages of samples collected with charcoal tubes) were available from most companies in the study after 1977, when companies first became aware of the potential carcinogenicity of ethylene oxide (13 of 14 plants in the study had sampling data). These data were used to quantify exposures in recent years.

Results

The characteristics of the study population and the plants are shown in Tables 1 and 2.

Comparison of the cohort identified through personnel files with alternative lists (payroll records or social security quarterly earnings reports) at

Table 1. Characteristics of the Study Population.

No. of workers	18,254
Job category — no. (%)*	
Sterilizer operator	1,222 (7)
In sterilizer area, not operator	2,301 (13)
Maintenance	1,937 (11)
Production	14,965 (82)
Laboratory	484 (3)
Warehouse	1,937 (11)
Employed before 1/1/78	15,750 (86)
No. of person-years at risk	
Total	286,787
With >7 years of exposure and >20 years of potential latency	12,734
With >7 years of exposure and >10 years of potential latency	46,350
Sex (% of cohort)	
Male	45
Female	55
Race (% of cohort)	
White	79
Black	16
Other	5
Vital status as of 12/31/87 — no. (%)	
Alive	16,242 (89.1)
Dead	
Death certificate received	1,137 (6.2)
Death certificate not received	40 (0.2)
Untraceable, vital status unknown	820 (4.5)
Average year of first exposure	1970
Average length of exposure (yr)	4.9
Average length of follow-up (yr)	16.1

*Workers are included in all categories in which they ever worked.

eight plants revealed that from 90 to 99 percent of the workers listed on the alternative lists were included in our cohort. At the plant with the least congruence (90 percent), the alternative list lacked social security numbers, and many mismatches probably resulted from discrepancies in the spelling of last names. At other plants, mismatches may have occurred because of incorrect recording of social security numbers, which were used to match workers in the two lists. In general, we found only a small number of workers missing from the personnel records from which we built our cohort. Although this type of evaluation was possible at only 8 of the 14 plants, personnel records appeared to have been maintained in a similar fashion at the remaining 6 plants, and there had been no known destruction of personnel records at these 6 plants.

The average level of exposure to ethylene oxide for sterilizer operators during the period from 1976 through 1985, calculated on the basis of 627 personal eight-hour samples obtained at 13 of the 14 study plants, was 4.3 ppm. The average level of exposure for other exposed workers, based on 1888 personal samples, was 2.0 ppm. These other exposed workers worked primarily in production, but also in the categories of maintenance, warehouse, and laboratory. Most of the samples were obtained in the 1980s, either during or just after the introduction of engineering controls designed to lower workers' level of exposure.

Table 2. Study Population According to Plant.

Plant No.	No. of Workers	Person-years at Risk	First Year of Regular Ethylene Oxide Use*
1	1,466	20,908	1966
2	2,023	26,716	1968
3	705	10,019	1958
4	1,895	33,314	1957
5	1,141	21,597	1943
6	450	6,617	1959
7	253	3,221	1969
8	760	10,758	1964
9	1,281	19,637	1960
10	1,355	19,754	1963
11	1,218	18,849	1966
12	1,536	27,057	1938†
13	1,835	29,865	1963
14	2,336	38,475	1962
Total	18,254	286,787	—

*At four plants there was some limited use of ethylene oxide, either intermittently or on an experimental basis, before the beginning of ethylene oxide use in full-scale production.

†Person-years at plant 12 were calculated beginning in 1967 because personnel records were unavailable for employees who left the plant before that year.

Table 3. Mortality According to Cause of Death for All Plants Combined.*

Cause of Death	Deaths		SMR	95% CI	SMR 1978
	Observed	Expected			
All causes	1177	1454.3	0.81	0.76–0.86	0.81
All cancers	343	380.3	0.90	0.81–1.00	0.89
All hematopoietic cancers†	36	33.8	1.06	0.75–1.47	1.06
Lymphosarcoma–reticulosarcoma	8	5.3	1.52	0.65–3.00	1.55
Hodgkin's disease	4	3.5	1.14	0.31–2.92	1.18
Leukemia–aleukemia	13	13.5	0.97	0.52–1.67	1.01
Others	11	11.7	0.93	0.47–1.68	0.88
Non-Hodgkin's lymphoma	8	6.7	1.20	0.57–2.37	1.25
Myeloma	3	5.1	0.59	0.12–1.73	0.40
Brain–nervous system cancer	6	11.6	0.52	0.19–1.13	0.53
All digestive cancers	80	85.6	0.93	0.74–1.16	0.93
Stomach	11	11.6	0.95	0.45–1.70	0.97
Esophagus	8	7.7	1.04	0.44–2.06	1.07
Pancreas	16	16.9	0.95	0.54–1.53	0.96
Respiratory system cancer	96	101.7	0.94	0.76–1.15	0.92
Breast cancer	42	49.6	0.85	0.61–1.14	0.82
Urinary-organ cancer	17	12.4	1.37	0.80–2.19	1.39
Kidney	13	7.2	1.80	0.96–3.08	1.84
Bladder	4	5.2	0.77	0.21–1.96	0.77
Heart disease	358	430.0	0.83	0.75–0.92	0.84
Nonmalignant respiratory disease	61	76.4	0.80	0.61–1.03	0.81
Nonmalignant digestive disease	48	79.4	0.60	0.44–0.80	0.60
Nonmalignant genitourinary disease	12	18.8	0.64	0.33–1.12	0.65

*SMR denotes standardized mortality ratio, CI confidence interval, and SMR 1978 the SMR for workers first exposed to ethylene oxide before January 1, 1978 (86 percent of the cohort).

†Includes the following diseases designated by the codes indicated in the *International Classification of Diseases*, 9th revision: lymphosarcoma–reticulosarcoma (200), Hodgkin's disease (201), leukemia (204–208), and other hematopoietic cancers (202, 203), divided in this table into non-Hodgkin's lymphoma (202) and myeloma (203).

Table 3 shows the numbers and causes of death for all 14 plants combined, with increased detail for the cancers. No category had a significantly increased number of deaths, as compared with the general population. Mortality was lower for all causes, heart disease, and nonmalignant digestive diseases, probably largely because of the healthy-worker effect.[30] The only type of cancer for which the increase in mortality approached statistical significance was kidney cancer, for which there was no a priori hypothesis in this study.

Engineering controls and new work practices were generally adopted by ethylene oxide users in 1978 and 1979, when the first reports of carcinogenesis appeared. Table 3 shows the mortality from cancer for those first exposed to ethylene oxide before 1978 (86 percent of the cohort). The results for this subgroup were virtually identical to those for the entire cohort, and no further analyses of this subgroup are presented here.

Table 4 shows the mortality according to the duration of exposure and for selected cancers as well as for all cancers. There were no significant trends in mortality with increased duration of exposure. In analyses in which exposure lagged by five years, this pattern did not change (data not shown). As Table 5 shows, we found trends toward increased SMRs with increasing lengths of time since the first exposure to ethylene

Table 4. Standardized Mortality Ratios (SMRs) and Numbers of Observed Deaths for Selected Cancers, According to Duration of Exposure to Ethylene Oxide.

Type or Site of Cancer	Duration of Exposure		
	<1 yr*	1–7 yr	>7 yr
	SMR (no. of deaths)		
All cancers	0.88 (65)	0.97 (152)	0.83 (126)†
All hematopoietic	0.69 (5)	1.25 (18)	1.07 (13)
Leukemia–aleukemia	0.98 (3)	0.87 (5)	1.09 (5)
Hodgkin's disease	0.00 (0)	2.40 (4)	0.00 (0)
Lymphosarcoma–reticulosarcoma	1.81 (2)	1.29 (3)	1.63 (3)
Other	0.00 (0)	1.28 (6)	1.03 (5)
Non-Hodgkin's lymphoma	0.00 (0)	1.50 (4)	1.52 (4)
Myeloma	0.00 (0)	1.00 (2)	0.45 (1)
Kidney	2.23 (3)	1.71 (5)	1.68 (5)
Brain	0.00 (0)	0.59 (3)	0.76 (3)
Stomach	0.00 (0)	1.47 (7)	0.82 (4)
Pancreas	1.38 (4)	1.18 (8)	0.55 (4)

*Only subjects with at least three months of exposure are included.
†Significantly different from 1.00 at the P = 0.05 level.

oxide (potential latency) for all cancers (P = 0.04) and for hematopoietic cancers (P = 0.03). The SMR for hematopoietic cancer among those with more than 20 years of latency approached statistical significance (SMR, 1.76; 95 percent confidence interval, 0.94 to 3.01). The excess mortality from kidney cancer among the workers with the longest latency period was significant (SMR, 3.27; six deaths). When we restricted the analysis to the workers in the categories with the longest duration of exposure and the longest time since the first exposure (those with more than 7 years of exposure and more than 20 years since the first exposure), the SMR was 1.88 (95 percent confidence interval, 0.86 to 3.56; nine deaths) for all hematopoietic cancers.

Table 6 shows the SMRs for the cancers of interest in our a priori hypothesis, as well as for kidney cancer and all cancers combined, among workers who were ever employed in particular job categories. Sterilizer operators, who were likely to have had the highest exposure, had some increase in deaths from all hematopoietic cancers (especially leukemia and lymphosarcoma–reticulosarcoma), but these results are based on small numbers of deaths and are not statistically significant.

Plant-specific analyses were also performed for all 14 plants, but the results are not presented here. The numbers of observed deaths for each plant were small. For the principal cancers of interest (hematopoietic cancers and cancers of the brain, stomach, and pancreas) only one SMR (for "other hematopoietic cancers") at one plant (three deaths) was significantly increased.

Sex-specific analyses showed that men had an elevated rate of death from all hematopoietic cancers, as compared with the general population, whereas women had a lower rate (Table 7). For all hematopoietic cancers combined, mortality among men was significantly elevated (SMR, 1.55; 95 percent confidence interval, 1.02 to 2.27) and was concentrated in the categories of lymphosarcoma–reticulosarcoma and non-Hodgkin's lymphoma. There were no significant positive trends in mortality with duration of exposure among men, but there were significant upward trends with increasing lengths of time since the first exposure among men both for all hematopoietic cancers and for leukemia. Among the men with the longest time since the first exposure (>20 years) and the longest duration of exposure (>7 years), the SMR for all hematopoietic cancers was 2.63 (95 percent confidence interval, 1.05 to 5.42). Five of the seven men who died of leukemia died in the most recent calendar period (1985 through 1987), generating a statistically significant excess mortality for those years (SMR, 3.45; 95 percent confidence interval, 1.11 to 8.06).

Further analyses according to race (data not shown) indicated that although mortality from hematopoietic cancer was increased in men of both racial groups, such cancers were more common among nonwhites (SMR, 2.54; 95 percent confidence interval, 1.02 to 5.25; 7 deaths) than among whites (SMR, 1.37; 95 percent confidence interval, 0.84 to 2.12; 20 deaths). Among white and nonwhite men, the greatest excesses in mortality from hematopoietic cancer were for non-Hodgkin's lymphomas. Among women, both whites and nonwhites had similar decreases in mortality from all hematopoietic cancers as compared with the general population (SMR, 0.53 for whites and 0.65 for nonwhites).

Discussion

Ethylene oxide is a potent mutagen and animal carcinogen. The data on the relation of ethylene oxide exposure to human cancer have been contradictory. Hogstedt et al. found a ninefold excess of leukemia and a fivefold excess of stomach cancer among workers in Sweden exposed to ethylene oxide.[15] Some of these workers, however, were also exposed to other

Table 5. Standardized Mortality Ratios (SMRs) and Numbers of Observed Deaths for Selected Cancers, According to Length of Time Since the First Exposure to Ethylene Oxide (Potential Latency).

Type or Site of Cancer	Potential Latency		
	<10 yr*	10–20 yr	>20 yr
	SMR (no. of deaths)		
All cancers*	0.77 (90)†	0.91 (157)	1.03 (96)
All hematopoietic*	0.71 (9)	0.98 (14)	1.76 (13)
Leukemia–aleukemia	0.40 (2)	1.07 (6)	1.79 (5)
Hodgkin's disease	0.49 (1)	1.74 (2)	2.97 (1)
Lymphosarcoma–reticulosarcoma	1.31 (3)	1.91 (4)	1.10 (1)
Other	1.06 (3)	0.36 (2)	1.77 (6)
Non-Hodgkin's lymphoma	1.30 (2)	0.31 (1)	1.92 (5)
Myeloma	0.80 (1)	0.42 (1)	0.68 (1)
Kidney	0.95 (2)	1.52 (5)	3.27 (6)†
Brain	0.44 (2)	0.19 (1)	1.39 (3)
Stomach	0.80 (3)	0.99 (5)	1.06 (3)
Pancreas	1.31 (6)	0.77 (6)	0.86 (4)

*The test for trend for SMRs was significant for all cancers (P = 0.04) and for hematopoietic cancers (P = 0.03).
†Significantly different from 1.00 at the P = 0.05 level.

Table 6. Standardized Mortality Ratios (SMRs) and Numbers of Observed Deaths for Selected Cancers, According to Job Category.

Type or Site of Cancer	Job Category*				
	Sterilizer Operator	In Sterilizer Area	Maintenance	Warehouse	Production
	SMR (no. of deaths)				
All cancers	1.08 (22)	0.87 (44)	0.99 (49)	0.93 (34)	0.86 (265)†
All hematopoietic	1.80 (4)	0.94 (4)	1.31 (6)	0.89 (3)	0.96 (26)
Leukemia	2.78 (2)	1.22 (2)	1.12 (2)	1.49 (2)	0.83 (9)
Hodgkin's disease	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)	1.42 (4)
Lymphosarcoma–reticulosarcoma	6.68 (2)	1.37 (1)	1.39 (1)	0.00 (0)	1.32 (6)
Other	0.00 (0)	0.68 (1)	1.85 (3)	0.91 (1)	0.78 (7)
Kidney	2.77 (1)	3.62 (3)	2.44 (3)	1.32 (1)	1.81 (10)
Brain	1.64 (1)	0.00 (0)	0.63 (1)	0.90 (1)	0.54 (5)
Stomach	0.00 (0)	1.47 (2)	0.54 (1)	0.77 (1)	0.96 (9)
Pancreas	0.00 (0)	2.21 (1)	0.00 (0)	0.59 (1)	1.10 (15)

*Workers contributed person-years at risk to a category if they had ever worked in it. They could have worked in more than one category and hence have contributed both person-years and observed deaths to more than one category. The calculation of person-years at risk for any worker began when he or she entered the category in question. Results for laboratory workers are not presented here because there were very few deaths in this group; laboratory workers made up only 3 percent of the study population.

†Significantly different from 1.00 at the P = 0.05 level.

carcinogens. Other studies in humans, although limited by small numbers and by uncertainties about exposure, have not shown an increased risk.

This is the largest cohort of workers exposed to ethylene oxide studied to date. The study population had documented exposure to ethylene oxide and no evidence of confounding exposure to other occupational carcinogens. Exposure levels have been relatively low since the late 1970s (averaging 1 to 2 ppm for production workers and 5 ppm for sterilizer operators). Exposure levels are likely to have been higher, however, before the installation of engineering controls, when the OSHA standard was 50 ppm instead of the present 1 ppm.

We did not find the same excess mortality from leukemia or stomach cancer that was found in the Swedish studies. However, we did find an excess of hematopoietic cancers that approached statistical significance among workers in the longest latency category. We also found a significant excess of hematopoietic cancers among men (SMR, 1.55), concentrated in the subcategories of lymphosarcoma–reticulosarcoma (SMR, 2.60) and non-Hodgkin's lymphoma (SMR, 2.16) (these diseases might be combined into a broader category of non-Hodgkin's lymphomas). Women, in contrast, had a lower rate of mortality from hematopoietic cancers than the general U.S. population. Such differences between the sexes were not observed for other types of cancer. There is little evidence in the literature of a sex-specific carcinogenic effect of ethylene oxide in either animals or humans. It is possible that the men were more heavily exposed; we found some evidence, based on small numbers, that workers in more highly exposed job categories (such as sterilizer operators) had a higher risk. Men have historically predominated in jobs with higher levels of exposure, whereas women have most often been employed in general production. The average calendar year of first exposure was similar for men and women, indicating similar potential latency. Although the men are likely to have smoked more than women, hematopoietic cancers in general are not strongly related to smoking, and confounding by smoking is unlikely to explain the differences in the risk of hematopoietic cancer between men and women.[31] The SMRs for lung cancer among men and women (0.93 and 0.89) indicate that smoking habits in both groups differed little from those in the general U.S. population.

Table 7. Standardized Mortality Ratios (SMRs) and Numbers of Observed Deaths for Selected Cancers, According to Sex.

Type or Site of Cancer	Men	Women
	SMR (no. of deaths)	
All cancers	0.99 (175)	0.82 (168)
All hematopoietic	1.55 (27)*	0.54 (9)
Leukemia–aleukemia	1.16 (8)	0.77 (5)
Hodgkin's disease	1.98 (4)	0.00 (0)
Lymphosarcoma–reticulosarcoma	2.60 (7)*	0.38 (1)
Other	1.38 (8)	0.50 (3)
Non-Hodgkin's lymphoma	2.16 (7)	0.29 (1)
Myeloma	0.40 (1)	0.78 (2)
Kidney	2.11 (9)	1.34 (4)
Brain	0.86 (5)	0.17 (1)*
Stomach	0.56 (4)	1.54 (7)
Pancreas	0.69 (6)	1.21 (10)

*Significantly different from 1.00 at the P = 0.05 level.

The large size of our study cohort meant that we could exclude high risks with a reasonable degree of confidence. For example, for the entire cohort the SMR for leukemia was 0.97 with an upper 95 percent confidence bound of 1.67. When subgroups with presumably higher exposure levels were examined, however, the upper bounds were considerably higher. For example, for the combined category of sterilizer operators and others who worked in the sterilizer area, the SMR was 1.46 with an upper confidence bound of 4.28.

It is possible that we have studied a cohort with an insufficient length of exposure or potential latency period for disease to appear. When we restricted our analysis to those with the longest duration of exposure and the longest time since the first exposure, we found an excess of all hematopoietic cancers that was not statistically significant (SMR, 1.68; 95 percent confidence interval, 0.73 to 3.32; eight deaths). Among men, however, the increase in the SMR was statistically significant (SMR, 2.63; 95 percent confidence interval, 1.05 to 5.42; seven deaths). On the basis of data on radiation-induced leukemia,

excess leukemia caused by ethylene oxide might be expected to be evident within 10 years of the initial exposure,[32] although chemical-induced leukemia could have a longer latency period. Our cohort averaged 16 years of potential latency, and 86 percent of the cohort had at least 9 years. On the other hand, only 8 percent of the cohort had at least 20 years of potential latency.

Although our study is the largest to date of workers exposed to ethylene oxide, the results for the relatively rare cancers of a priori interest are still limited by the small numbers of cases and perhaps limited by the short follow-up. Our findings are therefore not conclusive.

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