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Exposure-Response Analysis of Cancer Mortality in a Cohort of Workers Exposed to Ethylene Oxide

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The authors previously reported results from the largest cohort mortality study of ethylene oxide-exposed workers that has been conducted to date. Here they extend their previous work by quantitatively examining the relation between cancer mortality and ethylene oxide exposure. This study included workers from 13 of the 14 geographically distinct facilities that were included in the previous investigation. These facilities began regularly using ethylene oxide to sterilize medical supplies or spices sometime between 1938 and 1969. Workers were followed from first exposure through December 31, 1987. Historical exposures to ethylene oxide were estimated using a regression model. Standard life-table analysis was used to examine cancer mortality in three categories of cumulative exposure to ethylene oxide. The Cox proportional hazards model was also used to examine cumulative and other measures of ethylene oxide exposure as predictors of cancer mortality. In both the life-table analysis and the Cox model, a positive trend was observed in all lymphatic and hematopoietic cancer mortality for cumulative ethylene oxide exposure. This trend was strengthened when ethylene oxide exposures 10 years prior to death were discounted (lagged) and when the analysis was restricted to neoplasms of lymphoid cell origin. Despite limitations discussed in this paper, the authors believe that these findings provide some support for the hypothesis that exposure to ethylene oxide increases the risk of mortality from lymphatic and hematopoietic neoplasms. The authors intend to continue follow-up of this relatively young cohort, which may allow more definitive conclusions to be drawn in the future. *Am J Epidemiol* 1993;138:787–98.

ethylene oxide; leukemia; mortality; neoplasms; occupational exposure

Ethylene oxide is a chemical of major commercial importance; with a US production of approximately 5 billion pounds (2.3 billion kg) in 1990 (1). It is widely used as a chemical intermediate and in the sterilization of medical devices and pharmaceuticals. The National Institute for Occupational Safety and Health estimates that approximately 270,000 US workers are exposed to ethylene oxide annually (2). Those with relatively high exposures include approximately 96,000 hospital workers and 21,000 workers exposed during the commercial sterilization of medical supplies, pharmaceuticals, and food products.

Ethylene oxide is a potent alkylating agent (3) and has been shown to cause mutations in a number of cellular test systems (4). An increased frequency of sister chromatid exchanges, chromosomal aberrations, or both has been reported in animals (5, 6) and workers (7–13).

The results from epidemiologic investi-

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Abbreviations: CI, confidence interval, ICD-9, *International Classification of Diseases*, Ninth Revision, SMR, standardized mortality ratio.

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gations of workers exposed to ethylene oxide have been somewhat contradictory, with some studies reporting an excess of leukemia and stomach cancer (14–17) and others failing to detect such an excess (18–23). Interpretation of these findings has been limited by the relatively small numbers of workers studied and by the presence of potentially confounding exposures.

Cancer incidence, particularly the incidence of brain cancer (5), leukemia (24, 25), and lymphoma (26), has been observed to increase with ethylene oxide exposure in inhalation studies of rodents exposed to ethylene oxide.

To further investigate the possible relation between ethylene oxide exposure and the risk of cancer, particularly lymphatic and hematopoietic (henceforth referred to as "hematopoietic") cancer and cancers of the stomach, brain, and pancreas, we conducted a retrospective cohort mortality study of approximately 18,000 workers employed in 14 US industrial facilities. The plants were primarily involved in the sterilization of medical products. The primary outcomes of concern were lymphomas and leukemias. As noted above, animal studies have implicated ethylene oxide in the occurrence of both of these neoplasms, while an association with leukemia has been reported in some human studies. All cancers of the white blood cells ultimately are derived from stem cells in the bone marrow, and in recent years the lines between lymphoma and leukemia have become more blurred (27). Some authors have suggested combining lymphocytic leukemia and non-Hodgkin's lymphoma into a single category for epidemiologic analysis (28).

In a previously published article (29), we reported results from a life-table analysis of the mortality experience of this cohort. Overall, there was no significant increase in mortality from any cause of death in this study. However, an increase in mortality from all hematopoietic neoplasms (standardized mortality ratio (SMR) = 1.55, 95 percent confidence interval (CI) 1.02–2.26) was observed among males that was concentrated in the subcategories of lymphosarcoma-reticulosarcoma (SMR = 2.60, 95 percent CI 1.05–5.36) and non-Hodgkin's lymphoma (SMR = 2.16, 95 percent CI 0.87–4.45). Analyses by job category and duration of exposure showed no relation with any particular type of cancer, but a trend with time since first exposure was observed for all hematopoietic neoplasms. In this paper, we examine the relation between cancer mortality and individual estimates of ethylene oxide exposure derived from an industrial hygiene-based model.

MATERIALS AND METHODS

A complete description of the methods used to identify the study facilities and population was presented previously (29). Briefly, 14 US industrial plants were selected for the study following the completion of a feasibility study (30). Most of these facilities produced and sterilized medical supplies with ethylene oxide, although three plants treated spices with ethylene oxide and another manufactured and tested sterilizers with ethylene oxide. These facilities were selected for study on the basis of their contributing a minimum number (n = 400) of person-years at risk to the study, the adequacy of their personnel records, and the absence of any known confounding exposures (e.g., benzene). The year in which the study facilities first began regularly using ethylene oxide ranged from 1943 to 1969.

Industrial hygienists from the National Institute of Occupational Safety and Health, working with plant personnel, identified areas of the plant where workers were potentially exposed to ethylene oxide based on their knowledge of the industrial process or actual sampling data. Workers who had never been exposed to ethylene oxide or who had been exposed for less than 3 months were excluded from the study. Salaried workers were generally excluded from the study, because they frequently worked in nonexposed areas or because their work-history records had insufficient detail to in-

dicate where they had worked. Although workers from 14 facilities were included in our previous report, the analysis for this report was restricted to the 13 facilities that had adequate information for estimating historic exposures.

Ascertainment of workers' vital status was conducted through 1987 using a combination of records from the Social Security Administration, the National Death Index, the Internal Revenue Service, and local post offices. The end of follow-up was defined as the date on which each member of the cohort was last known to be alive. If a worker was known to have been alive before January 1, 1979 (when the National Death Index was created), and was not found in a search of the National Death Index, he or she was assumed to be alive at the end of follow-up (December 31, 1987).

Exposure estimation

An industrial hygiene-based regression model was utilized to estimate individual ethylene oxide exposures for the exposure-response analyses presented in this paper. This model facilitated the estimation of exposure levels for time periods, facilities, and operations for which industrial hygiene data were unavailable. The procedures used to construct this model have been previously reported (31). Briefly, the hygienic data consisted of 2,350 individual time-weighted exposure values acquired from 18 facilities between 1976 and 1985. After excluding passive diffusion monitoring data because of their higher variability, we calculated arithmetic mean exposure levels by facility, year, and exposure category. The exposure categories were based on grouping all sampled jobs into eight categories with similar potential for ethylene oxide exposure. (The eight exposure categories were sterilizer operator, chamber area, maintenance, production, warehouse, clean room, quarantine, and laboratory.) The data were then divided into one set for developing the regression model (205 mean exposure values from 12 plants) and another set for testing the model (46 mean exposure values from six other plants). The arithmetic means were logarithmically transformed, and weighted (inverse variance) linear regression models were fitted. Seven (exposure category, sterilizer volume, year, product age, product type, aeration of product, and presence of engineering controls) out of 23 independent variables tested for inclusion in the model were found to be significant predictors of ethylene oxide exposure and were included in our final model. The model predicted a remarkable 85 percent of the variation in average ethylene oxide exposure levels. The regression model also predicted the test data well, with an average bias of only −1.1 parts per million (ppm) (standard deviation = 3.7). In contrast, a panel of industrial hygienists familiar with the industry estimated the exposures for the same set of data with an average bias of −1.3 (standard deviation = 4.5).

The regression model was used to predict exposure levels for the analysis in the following manner. Titles of jobs involving exposure and department titles from the personnel records for each facility were classified into one of the eight exposure categories used in the regression model. Ethylene oxide exposure was estimated for each exposure category, stratified by calendar year and facility, based on the values of the predictor variables used in the regression model and the associated regression coefficients. Information on the predictor variables was available for each facility, exposure category, and time period. Thus, an exposure matrix stratified by time and exposure category was constructed for each facility. We estimated cumulative exposure for each individual in the study by multiplying the estimated ethylene oxide exposure (ppm) for each job held by the duration of time (days) spent in that job, using the following formula:

$$\text{CUMEXP} = \sum_{i=1}^{n} (\text{ethylene oxide}_i \times \text{DUR}_i),$$

where CUMEXP represents cumulative exposure to ethylene oxide, "ethylene oxide" represents the estimated time-weighted exposure level (ppm), DUR represents the length of time (days) spent at that level, and i indexes the jobs held.

Although cumulative exposure is generally the exposure metric of primary interest in epidemiologic studies, estimates of duration of exposure, average time-weighted exposure level, and the maximum time-weighted exposure level were also evaluated in the analyses. The average exposure level was defined as the cumulative exposure divided by the duration of exposure. The maximum exposure level was defined as the highest time-weighted average ethylene oxide exposure that an individual had experienced over his or her work history. It was not possible to test the influence of short-term exposure peaks experienced during the course of a day, since real-time data on ethylene oxide exposure levels were not available for each individual in the study.

Summary statistics (mean, median, and range) for the exposure variables (cumulative, average, maximum, and duration) are presented in table 1. The mean and median exposure estimates differed substantially, indicating that the distributions of these measures were highly skewed. The range of the exposure measures spanned several orders of magnitude.

Statistical analysis

Exposure-response analyses were conducted for cancers of the kidney (*International Classification of Diseases,* Ninth Revision (ICD-9), codes 189.0–189.2), brain (ICD-9 codes 191 and 192), stomach (ICD-9 code 151), and pancreas (ICD-9 code 157); all hematopoietic neoplasms (ICD-9 codes 200–208); all leukemias (ICD-9 codes 204–208); non-Hodgkin's lymphoma (ICD-9 codes 200 and 202); and all other hematopoietic neoplasms (ICD-9 codes 201 and 203). In addition, Cox regression models were fitted to a combined category of lymphocytic leukemia (ICD-9 code 204) and non-Hodgkin's lymphoma, since it has been suggested that these neoplasms are closely related and should be combined for epidemiologic purposes (28).

TABLE 1. Summary statistics for ethylene oxide exposure in a cohort of US workers followed to December 31, 1987

	Exposure measure			
	Duration (years)	Average (ppm*)	Maximum (ppm)	Cumulative (ppm-years)
Mean	4.8	5.5	7.1	26 6
Median	2.2	3.2	4.5	5 6
Range				
Lowest	0.24	0.05	0.05	0 01
Highest	39.2	77.2	77.2	1,350 9

* ppm, parts per million.

A modified life-table program was used to compute expected numbers of deaths by multiplying cause-specific, 5-year age group-specific, and 5-year calendar time-, sex-, and race-specific mortality rates from the US population by the corresponding person-years distribution of the study population (32). Person-years at risk for each individual began only after 3 months of exposure was achieved. Person-years ended when the individual was lost to follow-up or died, or at the end of the study (December 31, 1987), whichever occurred first. For estimation of the SMR, the observed number of deaths for each cause of interest was divided by the expected number of deaths and multiplied by 100. Two-sided significance tests and 95 percent confidence intervals for the SMRs were estimated using Byar's method (33) when there were seven or more deaths observed; otherwise, exact tests were conducted and confidence intervals were computed. Tests for trend in the SMRs with cumulative ethylene oxide exposure were conducted using the method described by Breslow et al. (34).

The life-table analysis was stratified by race, sex, time since first exposure, and cumulative ethylene oxide exposure. Cutpoints for the cumulative exposure categories were chosen a priori with the goal of creating three categories ($<$1,200, 1,200–8,500, and $\geq$8,500 ppm-days) with approximately the same numbers of expected

deaths. For time since first exposure, cut-points of 10 and 20 years were chosen a priori on the basis of traditional epidemiologic practices.

Cox proportional hazards models were fitted using the SAS program PROC PHGLM (35). This model allowed us to examine the ethylene oxide exposure variables (i.e., duration, average, maximum, and cumulative exposure) as continuous predictors of the cancer mortality (hazard) rate. For each death from the cause of interest (failure), a risk set was created of all individuals who had survived to at least the same age as the failure and who had met the criteria for entry into the cohort at that age. The values of the time-dependent covariates (i.e., the exposure variables and calendar time) were estimated at the age of the failure for each member of the risk sets. The analysis was performed by blocking (stratifying) on the risk sets; thus, the analysis tightly controlled for the potentially confounding effects of age. We also controlled for the potentially confounding effects of sex and race by stratifying on these variables. The potentially confounding effects of calendar time were controlled by including indicator variables in the models representing the time periods (at the age of failure) <1960, 1960–1969, and 1970–1987. We tested the proportional hazards assumption by fitting the models with and without a term representing the interaction between age and the exposure variables, and computing the log likelihood ratio statistic. Similarly, potential interactions between the exposure variables and the other covariates (i.e., calendar year, race, and sex) were assessed on the basis of the likelihood ratio statistic. We "lagged" exposures by 5, 10, 15, or 20 years to discount exposures occurring in previous years that might not be etiologically relevant (36).

RESULTS

Results from the life-table analysis, stratified by cumulative exposure to ethylene oxide, are presented in table 2. An elevated SMR (SMR = 124, 95 percent CI 66–213)

TABLE 2. Observed numbers of deaths and standardized mortality ratios for mortality due to all cancers and cancer at selected major sites, by cumulative exposure to ethylene oxide: US workers followed to December 31, 1987

Cancer site (ICD-9† code(s))	Cumulative exposure to ethylene oxide (ppm-days)												Trend test‡	
	<1,200			1,200–8,500			>8,500			Total				
	Obs†	SMR†	95% CI†	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	χ^2	p
All cancers	100	94	76–114	120	90	74–107	108	86	70–104	328	90*	80–100	0 10	0 66
Stomach (151)	5	174	57–407	4	124	29–260	1	23	1–132	10	90	43–166	4.31	0 04
Pancreas (157)	3	69	14–203	10	170	81–312	3	50	10–147	16	98	57–161	0 76	0.38
Brain (191 and 192)	0	0	0–102	4	99	27–253	2	59	7–212	6	54	20–118	0 63	0.43
Kidney (189 0–189.2)	1	52	1–292	8	322**	139–635	3	122	25–357	12	175	90–306	0 01	0.98
All hematopoietic cancers (200–208)	8	79	34–157	12	101	52–177	13	124	66–213	33	102	71–144	0 97	0.32
Leukemia/aleukemia (204–208)	4	99	27–252	4	85	23–219	3	75	15–218	11	86	43–154	0.13	0.72
Non-Hodgkin's lymphoma (200 and 202)	4	117	32–298	4	96	26–246	7	192	77–395	15	133	75–220	1 04	0 31
Other hematopoietic cancers (201 and 203)	0	0	0–147	4	134	36–343	3	111	23–325	7	85	34–176	1 26	0 26

* $p < 0.05$ (2-tailed); ** $p < 0.01$ (2-tailed)
† ICD-9, *International Classification of Diseases*, Ninth Revision, Obs, observed no of deaths, SMR, standardized mortality ratio, CI, confidence interval
‡ The midpoints of the first two categories were used as scores for the trend test For the last category, the score used was the lower bound of the category plus 50% (i e , 12,750 ppm-days)

was observed for all hematopoietic neoplasms in the highest cumulative exposure category, but the trend with cumulative exposure was weak ($\chi^2 = 0.97, p = 0.32$). A similar pattern was observed for non-Hodgkin's lymphoma, but no such patterns were observed for the other two subcategories (leukemia/aleukemia and other hematopoietic neoplasms). A negative trend with cumulative exposure was observed for all stomach cancer ($\chi^2 = 4.31, p = 0.04$). There was no evidence for a trend of increasing mortality with cumulative exposure for cancer at any of the other sites.

The results from the life-table analysis for all hematopoietic neoplasms, stratified by race, sex, and cumulative exposure, are presented in table 3. An excess (SMR = 196, 95 percent CI 101–343) was observed among males in the highest exposure category. There was a suggestive positive trend in the SMRs with exposure for males ($\chi^2 = 1.69$, $p = 0.19$), whereas a negative trend was observed among females ($\chi^2 = 1.01$, $p = 0.31$). The negative trend among females was based upon a small number of deaths, particularly in the highest exposure category.

The results of stratifying the life-table analysis for all hematopoietic neoplasms by time since first exposure and cumulative ethylene oxide exposure are presented in table 4. Overall, the greatest excess in hematopoietic neoplasms (SMR = 155, 95 percent CI 77–277) was observed among workers with more than 20 years since first exposure. However, no significant exposure-response trend was observed for the >20 years category or for any of the other categories.

The regression coefficients (β coefficients) and likelihood ratio tests (χ^2) from the Cox proportional hazards analyses are presented in table 5. Separate models were fitted for each cause of interest in this study and for each of the ethylene oxide exposure parameters (i.e., cumulative, average, and maximum). A highly significant exposure-response relation ($\beta = 9.0 \times 10^{-6}$; $\chi^2 =$

TABLE 3. Observed numbers of deaths and standardized mortality ratios for mortality due to all hematopoietic neoplasms, by sex and race, in a cohort of US workers exposed to ethylene oxide

Sex and race	Cumulative exposure to ethylene oxide (ppm-days)													
	<1,200			1,200–8,500			>8,500			Total			Trend test‡	
	Obs†	SMR†	95% CI†	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	χ^2	p
Male	4	95	26–243	8	143	62–283	12	196*	101–343	24	151	97–225	1 69	0 19
White	3	80	29–275	6	128	35–249	8	169	92–423	17	129	75–206	1.22	0.27
Nonwhite	1	214	5–1,191	2	226	27–818	4	291	79–745	7	257*	103–529	0.12	0 72
Female	4	69	19–176	4	64	17–163	1	23	1–128	9	55	25–104	1 01	0 31
White	4	75	20–192	4	70	19–179	0	0	0–95	8	53	23–106	2.54	0 11
Nonwhite	0	0	0–739	0	0	0–642	1	220	6–1,224	1	65	2–364	2 04	0.15

* $p < 0$ 05 (2-tailed)
† Obs, observed number of deaths, SMR, standardized mortality ratio, CI, confidence interval
‡ The midpoints of the first two categories were used as scores for the trend test. For the last category, the score used was the lower bound of the category plus 50% (i e , 12,750 ppm-days)

TABLE 4. Observed numbers of deaths and standardized mortality ratios for mortality due to all hematopoietic neoplasms, by time since first exposure to ethylene oxide: US workers followed to December 31, 1987

Years since first exposure	Cumulative exposure to ethylene oxide (ppm-days)									Total			Trend test‡	
	<1,200			1,200–8,500			>8,500							
	Obs†	SMR†	95% CI†	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	χ^2	p
0–10	4	85	23–219	2	44	5–162	3	238	26–369	9	78	36–148	0 31	0.58
10–20	3	75	15–219	4	78	21–200	6	130	48–283	13	95	50–162	0 83	0 36
>20	1	74	2–411	6	262	96–570	4	116	32–296	11	155	77–277	2.35	0 13

† Obs, observed number of deaths, SMR, standardized mortality ratio, CI, confidence interval.
‡ The midpoints of the first two categories were used as scores for the trend test. For the last category, the score used was the lower bound of the category plus 50% (i e , 12,750 ppm-days)

TABLE 5. Parameter coefficients (β) and chi-squares (χ^2) from fitting a Cox proportional hazards model to risk of cancer mortality, using different measures to represent ethylene oxide exposure: US workers followed to December 31, 1987†

Neoplasm	Measure of ethylene oxide exposure							
	Duration (days)		Average (ppm)		Maximum (ppm)		Cumulative (ppm-days)	
	β	χ^2	β	χ^2	β	χ^2	β	χ^2
All hematopoietic cancers	$3\,6 \times 10^{-5}$	0 28	$1\,6 \times 10^{-2}$	0.87	$1\,3 \times 10^{-2}$	0 88	$6\,4 \times 10^{-6}$*	3 81
Leukemia	7.8×10^{-6}	0 44	$-6\,7 \times 10^{-3}$	0 02	2.3×10^{-3}	0.00	6.9×10^{-6}	1 47
Non-Hodgkin's lymphoma	$1\,9 \times 10^{-5}$	0 04	$2\,1 \times 10^{-2}$	0.76	$1\,8 \times 10^{-2}$	0 89	$7\,7 \times 10^{-6}$	3 32
Lymphoid‡	5.2×10^{-5}	0.43	$2\,2 \times 10^{-2}$	1 02	$2\,2 \times 10^{-2}$	1 67	9.0×10^{-6}**	6 80
Other hematopoietic cancers	$1\,4 \times 10^{-5}$	0 01	2.8×10^{-2}	0 67	1.5×10^{-2}	0.25	$-7\,7 \times 10^{-6}$	0 21
Stomach	-1.5×10^{-4}	1.08	$-2\,2 \times 10^{-1}$*	4.91	$-1\,5 \times 10^{-1}$*	4 08	-7.2×10^{-5}*	4 41
Pancreas	$-6\,5 \times 10^{-5}$	0 45	$5\,5 \times 10^{-4}$	0 00	-2.4×10^{-3}	0 01	$-6\,0 \times 10^{-6}$	0 43
Brain	$1\,4 \times 10^{-4}$	1 12	$-4\,3 \times 10^{-2}$	0.61	$-3\,7 \times 10^{-2}$	0.65	-1.2×10^{-5}	0.58
Kidney	$-1\,7 \times 10^{-4}$	2 00	$1\,3 \times 10^{-2}$	0 18	1.2×10^{-2}	0 21	-1.5×10^{-5}	1 81

* $p < 0\,05$ (2-tailed), ** $p < 0\,01$ (2-tailed) based on the log likelihood ratio test.
† Results from all models were controlled for calendar year, age at risk, sex, and race (except for the category "Other hematopoietic," for which we could not provide solutions for the calendar year variables)
‡ Combined category of lymphocytic leukemia (*International Classification of Diseases*, Ninth Revision (ICD-9), code 204) and non-Hodgkin's lymphoma (ICD-9 codes 200 and 202)

6.80, $p < 0.01$) was observed between cumulative ethylene oxide exposure and the combined lymphocytic leukemia and non-Hodgkin's lymphoma category ("lymphoid" neoplasms). A weaker exposure-response relation was observed for all hematopoietic neoplasms ($\beta = 6.4 \times 10^{-6}$; $\chi^2 = 3.81, p = 0.05$) and for non-Hodgkin's lymphoma ($\beta = 7.7 \times 10^{-6}$; $\chi^2 = 3.32, p = 0.07$) and cumulative ethylene oxide exposure. The exposure-response relation between cumulative ethylene oxide exposure and leukemia was positive but statistically nonsignificant ($\beta = 6.9 \times 10^{-6}$; $\chi^2 = 1.47$, $p = 0.23$). Negative coefficients were observed for cumulative ethylene oxide exposure in the models for other hematopoietic neoplasms and stomach, pancreatic, kidney, and brain cancers. The coefficients for duration, average, and maximum exposure were either weakly positive or negative in all of the models evaluated for these sites. No evidence of a significant interaction between the exposure variables and either age, sex, race, or calendar year was observed in any of the models.

The results from the best-fitting models, assuming a lag period for the lymphatic and hematopoietic neoplasm categories, are presented in table 6. The model likelihood was maximized for the "lymphoid" category with a 5-year lag period, and for leukemia, non-Hodgkin's lymphoma, and all hematopoietic neoplasms with a 10-

TABLE 6. Results from Cox proportional hazards models for mortality due to lymphatic and hematopoietic neoplasms in which cumulative exposures to ethylene oxide were lagged†,‡

Neoplasm	Lag period (years)	β	SE§	χ^2	Rate ratio for 45 ppm-years‖	95% CI§,¶
All hematopoietic cancers	10	1.12×10^{-5}	4.24×10^{-6}	4.96	1.20	1.05–1.38
Leukemia	10	1.29×10^{-5}	7.73×10^{-6}	2.07	1.24	0.96–1.58
Non-Hodgkin's lymphoma	10	1.29×10^{-5}	5.36×10^{-6}	3.98	1.24	1.04–1.47
Lymphoid	5	1.20×10^{-5}	3.31×10^{-6}	8.44	1.22	1.09–1.35

† Results presented are those from the models which used a lag period that maximized the goodness of fit (i.e., minimized the −2 log-likelihood)

‡ Results from all models were controlled for calendar year, age at risk, sex, and race

§ SE, standard error; CI, confidence interval

‖ Rate ratios for a particular exposure level were estimated by using the following formula $\exp(\beta X)$, where X is the cumulative exposure in ppm-days. For example, the rate ratio for all hematopoietic neoplasms corresponding to 45 years of exposure at 1 ppm is $\exp[(1.2 \times 10^{-5})\ (45\ \text{ppm-years})\ (365\ \text{days/year})]$

¶ Confidence intervals for the rate ratios were estimated by computing the upper and lower bound estimates of the regression coefficients ($\beta \pm$ SE) and substituting those bounds into the rate ratio formula described above

year lag period. Rate ratios and 95 percent confidence intervals corresponding to a working lifetime (45 years) of exposure at the current Occupational Safety and Health Administration standard level for ethylene oxide (1 ppm) are also presented in table 6. It is apparent that all of the lagged models for lymphatic and hematopoietic neoplasms produced similar rate ratio estimates of about 1.2 at the current standard level. The rate ratio estimate for leukemia was the least stable, as reflected by the width of the confidence interval for this category. None of the regression coefficients for the other cancer sites and exposure measures presented in table 5 were statistically significant when different lag periods were assumed.

DISCUSSION

In addition to being the largest epidemiologic study of workers exposed to ethylene oxide conducted to date, this study is the only study in which it has been possible to quantitatively estimate past and present ethylene oxide exposure levels. Previous evaluation of this cohort (29) did not include a detailed assessment of exposure. The availability of this exposure information has provided us with a unique opportunity to more carefully examine the relation between level of ethylene oxide exposure and cancer mortality. We observed a strong relation ($p = 0.004$) between cumulative exposure to ethylene oxide and mortality from neoplasms of lymphoid cell line origin in the Cox regression analysis. A weaker relation was also observed between cumulative exposure to ethylene oxide and mortality from all hematopoietic neoplasms ($p = 0.03$) and non-Hodgkin's lymphoma ($p = 0.046$) when a 10-year lag period was assumed.

A negative (inverse) exposure-response relation was observed between cumulative ethylene oxide exposure and cancers of the stomach, pancreas, brain, and kidney. A protective effect of ethylene oxide exposure for stomach, pancreas, and brain cancer is contrary to our a priori hypotheses for this study and is inconsistent with previous studies. Kidney cancer was not truly an a priori hypothesis in our study, and these results suggest that this excess is unrelated to ethylene oxide exposure.

Our findings of an increase in lymphocytic leukemia and non-Hodgkin's lymphoma combined (e.g., "lymphoid" neoplasms) need to be carefully examined in light of the histopathologic characteristics of these neoplasms and of results from the previous toxicologic and epidemiologic studies. We combined lymphocytic leukemias and non-Hodgkin's lymphomas on the basis of ontogenic considerations, since these neoplasms may represent different expres-

sions of the same underlying disease process (28, 37).

The observed excess incidence of lymphocytic leukemia and non-Hodgkin's lymphoma may be viewed as reasonably consistent with the results from experimental studies of animals exposed to ethylene oxide. An excess of malignant lymphomas was observed in the National Toxicology Program study among female mice, but not among male mice exposed to ethylene oxide (26). Mononuclear-cell leukemia was found to be elevated in the inhalation studies of Fischer 344 rats exposed to ethylene oxide (5, 24). Stromberg (38) has emphasized that the mononuclear-cell neoplasms observed in Fischer 344 rats may be a useful model for human T-cell chronic lymphocytic leukemias and non-Hodgkin's lymphomas.

Our findings for leukemia may be viewed as not being wholly consistent with the excess of leukemia that was reported in studies by Hogstedt et al. of Swedish workers exposed to ethylene oxide (14–17). We only observed a weak relation ($p = 0.15$) between cumulative ethylene oxide exposure and leukemias as a group, although we did observe a strong exposure-response relation ($p = 0.003$) with a category combining lymphocytic leukemia and non-Hodgkin's lymphoma. Given the clinical and pathologic interrelations between these neoplasms, it may be unrealistic to expect complete consistency between epidemiologic mortality studies in the results for the subcategories of hematopoietic neoplasms.

Aside from cumulative ethylene oxide exposure, none of the other measures of exposure (i.e., duration, average, and maximum) were found to be predictors for mortality due to all hematopoietic neoplasms or mortality from any of the other cancers examined in our study. The lack of a relation with duration of exposure appears to attest to the increased power gained from using the quantitative exposure matrix to estimate historic exposures in our investigation.

The average exposure (or "exposure rate") examined in this investigation was not found to be a predictor of mortality from hematopoietic neoplasms. This lack of a dose-rate effect is consistent with the results from an experimental study of sister chromatid exchanges and histidine hemoglobin adduct changes in rabbit lymphocytes (39), but is inconsistent with the results of a mouse dominant-lethal study (40).

Although the highest cumulative ethylene oxide exposure category did show a slightly elevated risk (SMR = 124) for all hematopoietic neoplasms in the life-table analysis, the trend with cumulative exposure was not statistically significant, as it was in the Cox model. The discrepancy in results from these analytic approaches may be readily explained by the increase in statistical power resulting from the treatment of ethylene oxide exposure as a continuous variable in the Cox model as opposed to the categorical treatment of exposure in the life-table analysis. Thus, greater weight should probably be given to the results from our Cox proportional hazards analysis.

The results from the Cox regression analyses were quite dependent on the inclusion of those cases with very high cumulative ethylene oxide exposures. For example, dropping the case with the highest cumulative exposure (352,465 ppm-days) from the Cox regression model for the combined lymphocytic leukemia and non-Hodgkin's lymphoma category had little effect on the magnitude of the cumulative ethylene oxide exposure coefficient; however, it did eliminate its statistical significance ($\chi^2 = 2.91$, $p = 0.09$). There is no known reason for deleting this case or any of the other cases from the analysis. However, the fact that the inclusion of just one case would have such a large influence indicates that our findings were not "robust." This problem might be expected in an analysis based on only 19 cases.

The results from the life-table analysis suggested a positive exposure-response relation with cumulative ethylene oxide ex-

posure and all hematopoietic neoplasms among males, but a negative relation for females. To some extent, this same phenomenon was also reflected in the Cox regression results. Although the regression coefficient for the interaction between sex and cumulative ethylene oxide exposure (lagged 10 years) was not quite statistically significant ($\chi^2 = 2.95, p = 0.09$), the direction of the coefficient representing the exposure-sex interaction was indicative of a positive exposure-response relation for males and a negative relation for females. There is little evidence from previous toxicologic or epidemiologic studies to indicate that the relation between ethylene oxide exposure and mortality from hematopoietic neoplasms should be modified by sex.

Although the exposure information available for our study was superior to the type of exposure data often used in occupational mortality studies, the potential for exposure misclassification should be clearly recognized. Our exposure matrix was created without knowledge of the exposure status of the cases. Thus, any errors made in the exposure classification were expected to be nondifferential with respect to disease status. Random errors in classification of exposures may result in bias either towards or away from the null hypothesis when log-linear models (e.g., the Cox model) are used (41).

In summary, we observed a positive trend between cumulative ethylene oxide exposure and mortality from lymphatic and hematopoietic neoplasms in both the life-table and Cox proportional hazards model analyses. This trend was the strongest when cumulative ethylene oxide exposure was lagged 10 years, and when the analysis was restricted to neoplasms of lymphoid cell origin. Our findings do not provide evidence for a positive association between exposure to ethylene oxide and cancers of the stomach, brain, pancreas, and kidney, and leukemias as a group. Interpretation of our positive findings is limited by 1) the lack of evidence for an exposure-response relation among females, 2) the finding in the Cox regression analysis that the statistical significance but not the magnitude of the coefficient for cumulative ethylene oxide exposure was sensitive to the deletion of a single case with high exposure to ethylene oxide, and 3) the lack of definite evidence for an effect on leukemia as a group, which had previously been observed epidemiologically. Despite the above limitations, we believe that our findings do provide some support for the hypothesis that cumulative exposure to ethylene oxide increases the risk of mortality from hematopoietic neoplasms, particularly neoplasms of lymphoid cell origin. We intend to continue follow-up of this relatively young cohort, which may allow us to draw more definitive conclusions in the future.

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