Cancer mortality in ethylene oxide workers

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Abstract

A cohort of 1971 chemical workers licenced to handle ethylene oxide was followed up retrospectively from 1940 to 1984 and the vital status of each subject was ascertained. No quantitative information on exposure was available and therefore cohort members were considered as presumably exposed to ethylene oxide. The cohort comprised 637 subjects allowed to handle only ethylene oxide and 1334 subjects who obtained a licence valid for ethylene oxide as well as other toxic gases. Potential confounding arising from the exposure to these other chemical agents was taken into consideration. Causes of death were found from death certificates and comparisons of mortality were made with the general population of the region where cohort members were resident. Seventy six deaths were reported whereas 98.8 were expected; the difference was statistically significant. The number of malignancies for any site exceeded the expected number (standardised mortality ratio (SMR) = 130; 43 observed deaths; 95% confidence interval (95% CI) 94-175) and approached statistical significance. For all considered cancer sites the SMRs were higher than 100 but the excess was only significant ($p < 0.05$, two sided test) for lymphosarcoma and reticulosarcoma (International Classification of Diseases—9th revision (ICD-9) = 200; SMR = 682; four observed deaths; 95% CI 186-1745). The excess of cases for all cancers of haematopoietic tissue (ICD-9 = 200-208) also approached statistical significance (SMR =

250; six observed deaths; 95% CI 91-544). Focusing the analysis on the subcohort of the ethylene oxide only licenced workers, who are likely to have experienced a more severe exposure to this gas, it became evident that all but one of the observed cases of haematopoietic tissue cancers in the cohort were confined to this subgroup, enhancing the relevant SMR to 700 (95% CI 237-1637) and the SMR of lymphosarcoma and reticulosarcoma to 1693 (95% CI 349-4953).

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Ethylene oxide is a gas often used in the chemical industry. It is an intermediate in the production of ethylene glycol, which is used in synthesis of antifreeze products, polyethylene fibres, and non-ionic surface active agents. Ethylene oxide is also used as a sterilant for heat sensitive products such as hospital equipment, pharmaceutical products, food-stuffs, etc. It is also a fungicide in the fumigation of books, leather, tobacco, clothing, furs, furniture and other goods. The world production of ethylene oxide exceeds 5.5 million tonnes per year.¹

Acute toxicity of this gas has been fully described,² as well as its mutagenicity *in vitro*,³ in laboratory animals,⁴ and in humans.⁵ Its carcinogenicity has been shown in animal species.^{6,7}

So far epidemiological evidence of carcinogenicity for ethylene oxide is contradictory. Four studies were published between 1979 and 1988 by Hogstedt *et al*⁸⁻¹¹ who followed up cohorts of workers exposed to ethylene oxide. An almost ninefold increase in mortality from leukaemia and a fivefold increase in mortality from gastric cancer were the overall estimates of risk inferred by these studies. Exposure to ethylene oxide was estimated to be in the range of 5 to 20 ppm and concomitant exposure to other known animal carcinogens could not be ruled out. Two negative studies were published, by Morgan *et al*¹² and by Thiess *et al*.¹³ Small sample size, poor information on exposure, and selection bias in the follow up affected the results of these studies. The potential cancer hazard of ethylene oxide became a matter of great controversy during the second half of the 1980s¹⁴⁻¹⁶ and in 1987 the International Agency for Research on Cancer (IARC) assigned ethylene

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oxide to the sub-group 2A, meaning that this gas is probably carcinogenic to humans, because the evidence of carcinogenicity is sufficient in experimental animals but limited in humans.¹⁷ Gardner *et al*¹⁸ reported a non-significant excess of mortality from leukaemia and non-Hodgkin's lymphoma in a cohort of chemical and hospital workers exposed to ethylene oxide (standardised mortality ratio (SMR) = 189; seven observed deaths; 95% confidence interval (95% CI) 76–390). In another cohort study of chemical workers at eight production plants in west Germany¹⁹ no difference in mortality from cancer of lymphatic and haematopoietic tissues was found between exposed and reference populations. An excess of mortality from leukaemia has been reported by Greenberg *et al*²⁰ in a recent cohort study of chemical workers at three facilities in West Virginia where ethylene oxide was manufactured. The authors reported, however, that this excess was limited to the subcohort of workers also exposed to ethylene chlorohydrin. Finally, Steenland *et al*²¹ published the results of a mortality study on the largest cohort of workers exposed to ethylene oxide studied so far. No cause of death had a statistically significant excess; nevertheless sex specific analysis showed that men had a significant increase of deaths from haematopoietic cancers (SMR = 155; 27 observed deaths) and lymphosarcoma and reticulosarcoma (ICD-9 = 200; SMR = 260; seven observed deaths).

The purpose of the present study was to investigate mortality from cancer among ethylene oxide workers in Italy, focusing in particular on cancer of lymphatic and haematopoietic tissue.

Population and methods

The adopted study design is a prospective non-concurrent cohort study. All chemical workers who obtained a temporary licence for handling ethylene oxide in the period 1938–84 were considered. This source of enrolment into the cohort was selected partly to overcome difficulties related to the usually small sample size of the workforce in the chemical industries. Ethylene oxide belongs to a group of toxic gases for which a licence is compulsory by Italian law for all workers whose job entails the handling of one or more of the listed toxic gases (table 1). This law has been in effect since 1927; the licence is valid for a five year period and must be renewed if use is continued. A special commission is appointed to ascertain that the worker applying for the licence is in good physical condition and has an adequate knowledge of the specific hazards and current safety rules related to the toxic gases.

In this study being licenced for ethylene oxide is assumed to be a surrogate of exposure.

In two regions of northern Italy (Lombardia and Piemonte) complete rosters of licenced workers from

Table 1 List of toxic gases for which a licence is compulsory by Italian Law if handling them. The year of inclusion in the law and, for those evaluated for carcinogenicity, the IARC classifications are indicated

Gas	Year of inclusion in the law	IARC group
Hydrocyanic acid	1927	
Ammonia (anhydrous)	1927	
Sulphur dioxide	1927	
Gasoline	1927	
Alkalic cyanides	1927	
Chlorine	1927	
Chloropicrin	1927	
Cyanogen	1927	
Cyanocarbon ether	1927	
Phosgene	1927	
Isocyanocarbons	1927	
Ethylene oxide	1927	2A
Tetraethyl lead	1927	3
Carbon disulphide	1927	
Phosphine	1939	
Tetramethyl lead	1961	3
Dimethyl sulphate	1965	2A
Methyl chloride	1965	3
Hydrofluoric acid	1969	
Boron trifluoride	1972	
Methyl bromide	1973	3
Methylmercaptan	1974	
Tetrahydrothiophene	1978	
Ethylmercaptan	1978	
Diethyl sulphide	1978	
Dimethyl sulphide	1978	
Ethyl isopropyl sulphide	1978	

1938 are available. Through these rosters it was possible to identify 2292 workers (1988 from Lombardia and 304 from Piemonte) who were licenced for ethylene oxide sometime between 1938 and 1984. Only male workers were considered and, among them, only subjects who had had a licence for at least one year were included. Thus 1971 subjects were admitted to the cohort; 637 of them obtained a licence for ethylene oxide only and 1334 obtained a licence valid for ethylene oxide as well as for other toxic gases. The observation period lasted from 1 January 1940 to 31 May 1984.

Vital status of each cohort member at the end of follow up was assessed through the census office of the places of residence. Only 16 persons (0.8%) were lost to follow up. For the computation of mortality figures, they were considered as still living at the end of the follow up period. The computation of the number of person-years at risk for each worker started one year after the licence was obtained.

Seventy six deceased subjects were identified, and their death certificates were obtained from the census offices of the respective place of residence. The International Classification of Diseases—9th revision (ICD code) of the underlying cause of death was gathered from the records of the Istituto Centrale di Statistica (ISTAT) for the 61 cohort members who died after 1969. The ICD code for the 15 deaths that occurred before that period was assigned by a qualified nosologist, strictly with the criteria in use at

Table 2 Distribution of total person-years contributed by cohort members by age, time since the first exposure (latency), duration of exposure, and calendar period

Age		Latency		Exposure	Calendar period	
< 25	581	6839	< 5	6839	1940-4	29
25-34	6002	5280	5- 9	8393	1945-9	49
35-44	6996	3431	10-14	2496	1950-4	103
45-54	4069	2090	15-19	1181	1955-9	385
55-64	1326	1098	20-24	294	1960-4	1123
65-74	279	379	25-29	65	1965-9	2104
≥ 75	15	151	30->	—	1970-4	3357
					1975-9	4946
					1980-4	7172
Total	19268	19268		19268		19268

ISTAT. This is a common practice in Italy, where individual death records on tape are available only from 1969. Nevertheless to check the consistency of this procedure, the underlying causes of deaths that occurred in the 1969-84 period were also blindly coded by the same nosologist and the respective codes compared with those assigned by ISTAT. No cancer death was coded as non-cancer or vice versa, but three (none of them was a haematopoietic cancer) out of 29 cancer deaths received different ICD codes.

Both national and regional (Lombardia) populations were used as reference groups but only comparisons with the regional population are presented since the results were similar adopting either reference group. (Data on the comparisons with the national population are available from the authors on request.)

The expected number of deaths was calculated by multiplying the person-years of observation within

each five year age group during the respective calendar years of the study by the cause, sex and age specific death rates of Lombardia. The National Institute of Safety and Health life-table analysis system,²² adapted to the population of Lombardia, was used for the analyses. The 95% CIs of the SMRs were calculated assuming a Poisson distribution. Two sided significance tests were used for comparisons, to adopt a conservative procedure. Tests for trend in SMRs were conducted with the procedure described by Breslow and Day.²³

Results

The total cohort contributed 19 268 person-years. Table 2 shows the distribution by age, duration of exposure, time since the first exposure, and calendar period. Duration of exposure was estimated by the duration of the period during which the licence was

Table 3 Cause specific mortality in 1971 ethylene oxide licenced cohort members (1940-84): observed and expected deaths, SMRs standardised by sex, age, and calendar period on regional (Lombardia) population, and 95% CIs

Cause of death	ICD-9	Obs	Exp	SMR	(95% CI)
All causes	1-999	76	98.8	76*	(60-96)
All cancers	140-208	43	33.0	130	(94-175)
All haematopoietic cancers	200-208	6	2.4	250	(91-545)
Leukaemia-aleukaemia	204-208	2	1.0	193	(23-699)
Lymphosarcoma, reticulosarcoma	200	4	0.6	682*	(186-1745)
All digestive cancers	140-149	14	10.1	138	(76-233)
Stomach	151	5	4.1	122	(40-287)
Intestine	152-153	3	1.7	171	(35-500)
Rectum	154	1	0.8	126	(3-704)
Liver	155	2	1.0	190	(23-686)
Pancreas	157	3	1.2	254	(52-744)
All respiratory cancers	160-165	15	12.6	119	(67-197)
Larynx	161	3	1.7	176	(36-515)
Lung	162	11	10.5	104	(52-187)
Pleura	163	1	0.3	313	(8-1740)
All urinary cancers	185-189	4	1.4	291	(79-746)
Kidney	188	1	0.6	161	(4-895)
Bladder	189	3	0.7	399	(82-1169)
Melanoma	172	1	0.3	359	(9-2000)
Other cancers	195	3	2.9	103	(21-303)
Nervous system diseases	320-389	1	1.1	87	(2-487)
Respiratory system diseases	460-519	4	5.3	75	(15-200)
Circulatory system diseases	390-459	18	30.7	58*	(35-93)
Digestive system diseases	520-579	2	12.1	16**	(2-60)
Accidents	800-999	7	12.4	56	(22-116)
Unknown causes	799	1	0.6	159	(4-888)

*p < 0.05; **p < 0.001.

Table 4 Distribution of SMRs and number of observed deaths (parentheses) for selected causes of death and cancer site by duration of exposure to ethylene oxide

Cause of death	Duration of exposure (y)		
	< 5	5-9	≥ 10
All deaths	84 (14)	79 (36)	71 (26)
All non-cancer deaths	50 (6)	60 (18)	38 (9)
All cardiovascular diseases	24 (1)	84 (12)	40 (5)
All cancers	169 (8)	119 (18)	130 (17)
All digestive cancers	224 (3)	107 (5)	147 (6)
Stomach	380 (2)	53 (1)	121 (2)
Intestine	399 (1)	248 (2)	— (0)
Pancreas	— (0)	— (0)	629 (3)
All respiratory cancers	124 (2)	121 (7)	116 (6)
Larynx	444 (1)	127 (1)	144 (1)
Lung	75 (1)	103 (5)	114 (5)
All haematopoietic cancers	542 (3)	277 (3)	— (0)
Lymphosarcoma and reticulosarcoma	781 (1)	1131 (3)	— (0)
Leukaemia-aleukaemia	818 (2)	— (0)	— (0)

kept. Almost 50% of the cohort members entered the cohort after 1975 and therefore a large proportion of total person-years are distributed in exposure and latency periods shorter than 10 years.

Table 3 presents the distribution of the 76 observed deaths by groups of causes. A healthy worker effect is evident, particularly if cancer deaths in large excess are not considered. This effect seems to be mainly due to the deficit of deaths from heart diseases and non-malignant diseases of the digestive system (in particular liver cirrhosis: two observed and 9.7 expected deaths). The observed number of deaths exceeded the expected at any considered cancer site. This excess approached statistical significance for all haematopoietic cancers (six observed

and 2.4 expected deaths) and reached statistical significance only for lymphosarcoma and reticulosarcoma (four observed and 0.6 expected deaths).

The trend of the SMRs by increasing duration of exposure (table 4) does not show a clear pattern; it is negative for all deaths and respiratory cancers, positive for lung cancer, and contradictory for most of the considered causes of death. Surprisingly, the trend of the SMRs by increasing time since the first exposure to ethylene oxide (table 5) is clearly negative for most of the considered causes of death.

Because two thirds of cohort members were holders of a licence valid for ethylene oxide as well as for other toxic gases, the possible confounding role of these agents was investigated by analysing the mor-

Table 5 Distribution of SMRs and number of observed deaths (parentheses) for selected causes of death and cancer site by time since first exposure to ethylene oxide

Causes of death	Latency (y)		
	< 10	10-19	≥ 20
All deaths	91 (32)	76 (27)	60 (17)
All non-cancer deaths	115 (12)	98 (12)	88 (9)
All cardiovascular diseases	54 (5)	72 (8)	48 (5)
All cancers	192 (20)	122 (15)	78 (8)
All digestive cancers	232 (7)	107 (4)	90 (3)
Stomach	248 (3)	132 (2)	— (0)
Intestine	550 (3)	— (0)	— (0)
Pancreas	— (0)	224 (1)	534 (2)
All respiratory cancers	191 (7)	144 (7)	25 (1)
Larynx	193 (1)	296 (2)	— (0)
Lung	165 (5)	123 (5)	29 (1)
All haematopoietic cancers	464 (5)	123 (1)	— (0)
Lymphosarcoma and reticulosarcoma	1188 (3)	489 (1)	— (0)
Leukaemia-aleukaemia	427 (2)	— (0)	— (0)

Table 6 Cause specific mortality in 637 ethylene oxide only licenced cohort members (1940–84): observed (Obs) and expected (Exp) deaths, SMRs standardised by sex, age, and calendar period on regional (Lombardia) population, and 95% CIs

Cause of death	ICD-9	Obs	Exp	SMR	(95% CI)
All causes	1–999	27	30.1	87	(57–127)
All cancers	140–208	15	10.5	142	(79–234)
All haematopoietic cancers	200–208	5	0.7	700*	(227–1637)
Leukaemia-leukaemia	204–208	2	0.3	650	(79–2349)
Lymphosarcoma, reticulosarcoma	200	3	0.2	1693**	(349–4953)
All digestive cancers	140–149	3	3.2	92	(19–271)
Stomach	151	1	1.3	76	(2–426)
Intestine	152–153	1	0.5	179	(4–999)
Rectum	154	1	0.2	397	(10–2208)
All respiratory cancers	160–165	5	4.1	122	(39–286)
Lung	162	4	3.4	116	(32–298)
Pleura	163	1	0.1	990	(25–5500)
Bladder cancer	189	1	0.2	406	(10–2259)
Other cancer	195	1	0.9	111	(3–618)
Nervous system diseases	320–389	1	0.3	289	(7–1610)
Circulatory system diseases	390–459	7	9.8	71	(29–147)
Accidents	800–999	4	3.5	114	(31–293)

*p < 0.05; **p < 0.001.

tality data of all subcohorts of workers licenced for any but one of the listed toxic gases. This iterative procedure showed that site specific SMRs fluctuate in each subcohort but were consistent with those calculated for the entire cohort. (Detailed results of these analyses are available on request.)

To shed more light on the specificity of the association of exposure to ethylene oxide and mortality from cancer, a separate analysis of cohort members licenced for ethylene oxide only was conducted. Table 6 shows that the standardised mortality ratios of this subcohort were generally higher than those in the general cohort with the exception of the SMRs for all digestive cancers and stomach cancer. Five out of six observed cancers of lymphatic and haematopoietic tissue in the entire cohort were confined to the ethylene oxide only subcohort producing large SMRs, in particular for lymphoma and reticulosarcoma. Table 7 shows some characteristics of men who died from leukaemia and lymphosarcoma or reticulosarcoma. The mean age at death was 41.3 years, the mean duration of exposure was five years, and the mean time since first exposure was 5.5 years. Causes of death on the death certificates were centrally coded as: reticulosarcoma (three cases), lymphosarcoma, unspecified lymphoid leukaemia, and acute leukaemia of unspecified cell type.

Discussion

Two thirds of cohort members were holders of a

licence valid for ethylene oxide as well as for other toxic gases. Nevertheless, we believe that the increased risk for cancer among the cohort members is less likely to be attributed to these other gases, although some interaction of the effects of these substances with ethylene oxide cannot be ruled out. These gases, indeed, are known to produce severe manifestations of acute toxicity but not to act as cancer causing agents. The International Agency for Research on Cancer evaluated the carcinogenicity of six gases out of the 27 listed in Italian law (table 1) and only ethylene oxide and dimethyl sulphate were considered as probably being carcinogenic to humans. Exposure to dimethyl sulphate was associated with lung cancer²⁴ and with melanoma²⁵ but not with cancer of lymphatic and haematopoietic tissue.

The finding that five out of six cases of cancer of lymphatic and haematopoietic tissue were confined to the subcohort of ethylene oxide only licenced workers provides indirect evidence of the postulated higher risk of cancer in subjects occupationally exposed to ethylene oxide. Indeed, even though documentation is lacking, it is likely that among the total ethylene oxide cohort, the workers who required and obtained a licence for handling ethylene oxide only had a job title primarily related to the production or use of this gas; on the other hand, the workers who kept a licence valid for a number of gases, including ethylene oxide, had a job title not specifically related to this gas but, rather, with

Table 7 Characteristics of cohort members who died from lymphatic and haematopoietic tissue cancers

ICD-9	Year of birth	Time of first exposure to ethylene oxide		Duration of exposure (y)	Latency (y)	Age at death (y)
		Year	Age (y)			
208-0	1926	1958	32	2	2	34
200-0	1937	1962	25	4	4	29
200-0*	1933	1962	29	10	13	42
200-1	1928	1968	40	5	5	45
204-9	1936	1978	42	4	4	46
200-0	1931	1978	47	5	5	52

*The licence of this subject was valid for ethylene oxide and carbon disulphide. The other five subjects were licenced for ethylene oxide only.

various chemical agents. In this sense it has been assumed that: (1) a higher proportion of workers actually exposed to ethylene oxide was present in the first compared with the second subgroup and (2) the former group registered higher values of cumulative exposure to ethylene oxide.

The chemical workers in the ethylene oxide cohort were also exposed to cancer inducing agents other than the gases considered so far. Unfortunately, information on a quantitative basis is not available. It can be argued that the ethylene oxide only licenced workers experienced an actual exposure to this toxic agent whereas their exposure to other carcinogenic chemicals simply cannot be ruled out. On the contrary, the remaining cohort (those workers who kept a licence for several toxic gases, including ethylene oxide) presumably had a less severe and more intermittent exposure to ethylene oxide whereas their exposure to other carcinogenic chemical substances is more likely.

The reported excess of deaths in almost all cancer sites together with the large deficit of deaths in non-malignant disease groups can hardly be attributed to a biased codification of death certificates for three reasons: (1) only a small proportion of ICD codes was not retrieved from the ISTAT mortality registry; (2) the validity of the code provided by an external nosologist was checked, and (3) the excess of cancer deaths from all sites is a common finding in mortality studies of chemical workers.

The distribution of site specific cancer deaths by duration of exposure and by time since the first exposure did not show any positive trend. It is disputable, however, whether the duration of licence use is a meaningful estimate of dose. Moreover, the absence of a dose response relation is important but not crucial to the determination of a causality of an association.²⁶ Chance could be responsible for the negative trend of cancer SMR by latency, and a prolonged study period will shed more light on this point.

The occurrence of all cases of lymphatic and haematopoietic cancers within 10 years of latency is consistent with the tendency of this kind of tumour to appear in a shorter period compared with solid tumours, after the exposure to the causative agent. Assuming that carcinogenicity of ethylene oxide has a radiomimetic pattern, the excess of lymphatic and haematopoietic cancers should be evident within 10 years of initial exposure.²⁷

In 1983, on the basis of the results of Swedish epidemiological studies, the Italian government lowered the standard for eight hour time weighted average exposure to ethylene oxide from 50 ppm to 3 ppm. Before that time, given the ignorance of long term effects of this gas, exposures to ethylene oxide are known to have exceeded the standard value. All cases of leukaemia and lymphosarcoma found in this study had had first exposure to ethylene oxide (obtained licence for the first time) by 1978 (table 7);

Table 8 Distribution of observed (Obs) and expected (Exp) deaths and SMRs by calendar period

Calendar period	All causes			All cancer			All non-cancer			Circulatory		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
1939-44	0	0.0	—	0	0.0	—	0	0.0	—	0	0.0	—
1945-9	0	0.0	—	0	0.0	—	0	0.0	—	0	0.0	—
1950-4	1	0.4	244	1	0.1	862	0	0.3	—	0	0.1	—
1955-9	0	1.4	—	0	0.4	—	0	1.0	—	0	0.4	—
1960-4	5	4.1	122	3	1.2	257	2	2.9	68	0	1.1	—
1965-9	8	8.7	92	7	2.5	277	1	6.2	16	0	2.5	—
1970-4	13	16.3	79	5	4.8	103	8	11.4	70	4	4.8	82
1975-9	21	27.8	75	14	9.2	151	7	18.6	38	4	9.1	44
1980-4	28	40.1	69	13	14.7	88	15	25.4	59	10	12.6	79
1939-84	76	98.8	76	43	33.0	130	33	65.8	50	18	30.7	58

thus it is plausible that they have been severely exposed to ethylene oxide since that time or even earlier and this could provide an explanation of the short latency associated with these cases. Even though the law that makes the licence compulsory has been active since 1927 ethylene oxide workers have been pushed to submit for the licence when attention was paid to the possible carcinogenicity of this gas. Consequently, it is likely that a proportion of workers obtained the licence for the first time when the actual exposure had already started. It provides a further explanation of the short latency period.

The time distribution of person-years at risk (table 2) and cancer SMR by latency (table 5) could suggest some sort of bias. Removal of deceased workers from the registries and/or removal of workers licensed at an early stage of the observation period could account for both the small number of person-years during the 1940s and 1950s and the negative trend of SMR by latency. Actually it is unlikely that such a bias affected the study because the registries are filled in successively when the licence is issued and the record is fully independent of the future vital status of the worker. Furthermore five or more records are listed on each page of the registries and each record has a sequential identification code. Under these circumstances no removal of records could occur unnoticed. Production and use of ethylene oxide by the Italian chemical industries has had an exponential growth in the past decade. Only a few chemical workers were licensed during the 1940s and 1950s but some thousands were licensed later during the 1970s and 1980s. This seems to be the most plausible explanation of the time distribution of person-years in this study.

As a systematic removal of old or "dead" records from the registries would correspond to very low SMRs in the early stage of the study period, the SMR of selected causes of death by calendar period were examined (table 8). Very high values for SMRs have been found in the early five year periods of observation when few deaths occurred but a low number of events was expected.

Mortality data have not been adjusted for smoking habits, because the relevant information was not available. It is worth noting, however, that this variable has not yet been reported as strongly associated with lymphosarcomas and leukaemia. Moreover, the cancer excess found could hardly be explained by an unlikely larger proportion of smokers among cohort members than in the general population.^{28 29}

Results of our study favour the suggested hypothesis of a higher risk of cancer in occupational exposure to ethylene oxide. In particular, we emphasise that the excess of cancers of lymphatic and haematopoietic tissue, statistically significant in this study, has been consistently found in most previous studies.

Nevertheless, given the adopted definition of exposure to ethylene oxide and the lack of information on the exposure to other industrial chemicals, our findings are not conclusive.

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