Mortality study of ethylene oxide workers in chemical manufacturing: a 10 year update

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Abstract

Men assigned to units producing ethylene oxide by the chlorohydrin or direct oxidation processes and to other departments using ethylene oxide in two chemical plants were followed up for mortality from 1940 to 1988 (n = 1896). Based on findings from a previous study of these workers to the end of 1978, which identified confounding exposures, workers assigned to one unit with low ethylene oxide exposure potential were excluded (n = 278). Average duration of exposure was over five years and average follow up was 27 years, with all subjects at least 10 years from first exposure. The data did not support associations of ethylene oxide with all cancer types combined, leukaemia, non-Hodgkin's lymphoma, or brain, pancreatic, or stomach cancers. There were also no duration-response trends. The standardised mortality ratio (SMR) for total cancer was 86 (95% confidence interval 71-104) and did not increase for those hired the earliest and with long duration assignments. The results of this 10 year update and those of other recent studies of ethylene oxide workers do not confirm findings from animal studies and are not consistent with the earliest results reported among ethylene oxide workers.

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Ethylene oxide is a reactive epoxide expressing genotoxic activity both in vivo and in vitro

systems, probably through the direct alkylation of macromolecules.¹ This epoxide has also exhibited carcinogenic activity in rodents.²⁻⁵ The reported effects in rats and mice include brain gliomas, lung adenomas, mononuclear cell leukaemia, lymphoma, and peritoneal mesothelioma. The potential for ethylene oxide to cause cancer in humans, however, has not been determined. Hogstedt *et al* have reported excesses of leukaemia among sterilant workers and of heart disease, cerebrovascular disease, leukaemia, and stomach cancer among employees of a chemical plant that produced ethylene oxide, its derivatives, and numerous other chlorinated products.⁶⁻⁹ Cohort mortality studies of several other working populations potentially exposed to ethylene oxide in the manufacturing setting do not support these findings.¹⁰⁻¹⁴ One of these studies, by Greenberg *et al*, included 2174 Union Carbide workers employed between 1940 and 1978 at either of two chemical plants in the Kanawha Valley of West Virginia and who were assigned to chemical manufacturing operations that produced ethylene oxide or used it in the production of derivatives.¹⁴ This study, with follow up from 1940 to the end of 1978, failed to show associations with ethylene oxide, but did find an excess of both leukaemia and pancreatic cancer among men assigned to the chlorohydrin unit, which primarily produced ethylene chlorohydrin. In this department, ethylene oxide was used intermittently and exposure was judged to have been low. There were no deaths due to leukaemia among men assigned to departments with intermediate or high exposure to ethylene oxide.

An ethylene oxide mortality study of over 18 000 male and female workers from 14 plants producing medical supplies and culinary spices also did not show the ethylene oxide related excesses of leukaemia, and brain, stomach, or pancreatic cancers suggested by previous animal and human studies.¹⁵ There was, however, a statistically significant increase in non-Hodgkin's lymphoma in male workers. The significance of this finding is uncertain because of a strong deficit of non-Hodgkin's lymphoma in the female workers, no independent association with duration of exposure in the men,

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and the absence of excess risk for this disease in published studies of male workers in ethylene oxide manufacture.

Because of increasing interest in the carcinogenicity of ethylene oxide in humans and the desire to increase the power of the study of Greenberg *et al.*, a 10 year update has been conducted. The objectives were to retest, with a larger set of observations and latency period, the lack of an association between ethylene oxide and leukaemia and to reexamine whether ethylene oxide in the manufacturing setting was associated with an increased risk for non-Hodgkin's lymphoma or other carcinogenic endpoints. Because exposure to the chlorohydrin unit confounds the study of ethylene oxide relations, the update for the 278 men assigned to this unit has been analysed and reported separately resulting in a sample size for this investigation of 1896.¹⁶

Methods

Company records and the National Death Index were used to update vital status for the population from 1 January 1979 to 31 December 1988. Vital status was complete for 99% of the study group and death certificates were obtained for 99% of the

431 decedents. The study population was assigned to ethylene oxide related departments for an average of 5.4 years with an average time since first assignment of 27.2 years. The update did not include additional work histories for study subjects or the addition of subjects first assigned to ethylene oxide units after 1978, the close of the previous study.¹⁴ As production of ethylene oxide at the two locations was discontinued before 1978, the 1978 work history cut off date did not affect duration of assignment relative to production units. The entire study group had completed at least 10 years from first assignment to an ethylene oxide unit.

Traditional standardised mortality ratio (SMR) analyses, as described previously, were conducted, with United States death rates for white males to the end of 1988 for calculation of expected deaths.¹⁴ Person-years were calculated from first assignment to an ethylene oxide department or 1 January 1940 if first assignment was before 1940, to the date last observed. The SMRs were examined by time since first exposure (0-4, 5-9, 10-14, 15-19, ≥ 20 years) and duration of assignment (<2, 2-9, 10-19, ≥ 20 years). Internal comparisons with workers from the Kanawha Valley plants not assigned to departments concerned with the production or use of ethylene oxide were conducted

Numbers of workers assigned to selected departments producing or using ethylene oxide, and other chemicals involved in these departments. The area exclusive of the circular regions represents the men assigned to departments using ethylene oxide, other than in the chlorohydrin unit (n = 1520).

for duration of assignment analyses. The ethylene oxide departments were classified into three qualitative exposure groups (high, intermediate, low), by the methodology developed for the previous study.¹⁴ Study subjects were also examined by assignment to these three department groups.

The figure describes the assignment distribution of the 2174 ethylene oxide workers to categories of units. It is also intended to clarify the distinction between the chlorohydrin unit, which primarily produced ethylene/propylene chlorohydrin and the unit that produced ethylene oxide by the chlorohydrin process. The area exclusive of the circular regions represents the 1520 men assigned to departments using ethylene oxide, other than the chlorohydrin unit.

Of the 278 men with assignments in the chlorohydrin unit who were excluded to avoid confounding, 40 had also been assigned to ethylene oxide production units by the chlorohydrin process and 15 to ethylene oxide production by direct oxidation. Six had worked in all three types of production units. The data were examined with and without men with overlapping assignments to the chlorohydrin unit.

EXPOSURE CONCENTRATIONS

Monitoring data were not systematically collected at company plants sites until 1976. Exposures since the monitoring programme began average less than

1 ppm eight hour time weighted average (8h TWA) in departments producing or using ethylene oxide. In the 1960s, estimated exposure in the units producing ethylene oxide by direct oxidation ranged from 3–20 ppm 8h TWA, with operator concentration estimated at between 5–10 ppm 8h TWA. Peaks of several hundred ppm were also reported. These estimates are based on an industrial hygiene survey conducted at another Union Carbide ethylene oxide production facility, that used the same process as that in place at the two Kanawha Valley facilities during the same period.¹⁷ Communications from the Kanawha Valley plant support the fact that 5–10 ppm 8h TWA exposure concentrations continued into the 1970s in the direct oxidation process units.

The earliest method for ethylene oxide production, the chlorohydrin process, operated from 1925 to 1957. Chlorohydrin based ethylene oxide production was in a closed building during the early years. Levels of exposure to ethylene oxide in this process would have been higher than in the direct oxidation production process because of start up difficulties, fewer engineering controls, less complex equipment, and the enclosed building. Numerous visits to the medical departments for exposures to ethylene oxide resulting in nausea, dizziness, and vomiting have been documented in the medical department and discussed in 1949 by Sexton and Henson, two plant physicians.¹⁸ Such

Table 1 Observed and expected deaths (1940–88) by selected causes for men assigned to departments producing or using ethylene oxide (*n* = 1896)

Cause of death	Observed/expected† deaths	SMR‡ (95% CI)
All causes	431/547.73	79** (71–87)
Malignant neoplasms, total	110/128.14	86 (71–104)
Digestive organs and peritoneum	32/32.63	98 (67–138)
Oesophagus	1/3.63	(1–178)
Stomach	8/5.00	160 (69–315)
Intestine except rectum	12/11.52	104 (54–182)
Rectum	2/2.99	- (8–242)
Liver unspecified and primary	5/2.84	176 (57–411)
Pancreas	4/6.57	61 (17–156)
Respiratory system	44/48.80	90 (66–121)
Male genital organs	7/8.24	85 (34–175)
Kidney	2/3.27	- (7–221)
Bladder and other urinary organs	1/3.11	- (1–179)
Skin	2/2.62	- (9–276)
Brain and other parts of nervous system	6/4.00	150 (55–327)
Lymphatic and haematopoietic tissue	7/11.82	59 (24–122)
Lymphosarcoma and reticulosarcoma	2/2.03	- (12–356)
Leukaemia and aleukaemia	5/4.70	106 (35–248)
Hodgkin's disease	0/1.16	- (0–318)
Other lymphatic and haematopoietic tissue	0/3.93	- (0–94)
Benign neoplasms of the brain	0/0.25	- (0–1476)
Heart disease	187/217.10	86** (74–99)
Cerebrovascular disease	22/27.16	81 (51–123)
Other	112/175.08	64** (53–77)
Unable to locate death certificates	4	

***p* < 0.01.

†Expected deaths based on white male death rates, 1940–88, in the United States.

‡SMR not calculated when both observed and expected numbers of deaths are both less than five.

acute effects are known to occur in humans at several hundred ppm.¹ Hogstedt *et al* estimated average concentrations of about 14 ppm during the 1940s, for the Swedish chlorohydrin based ethylene oxide production unit, which was also in an enclosed building.⁷

These concentrations would likely be similar to those in the United States during the same period and less than concentrations occurring during the first 15 years of ethylene oxide production in the United States (1925–40). The estimated exposure ranges for units producing or using ethylene oxide during the period covered by this investigation are: 1925–39 >14 ppm; 1940–56 14 ppm; 1957–73 5–10 ppm; and 1974–88 <1 ppm, with frequent peaks of several hundred ppm in the earliest period and some peaks of similar intensity in the 1940s to mid 1950s.

Results

Based on comparisons with the general United States population, the study group showed lower death rates from all causes and from total cancers with SMRs of 79 (95% confidence interval (95% CI) 71–87) and 86 (95% CI 71–104) respectively (table 1). There were no statistically significant excesses of any specific causes of death. In the overall category of lymphatic and haematopoietic tissue cancers, there were seven observed and 11.8 expected deaths (95% CI 24–122). The SMR for leukaemia was 106 (95% CI 35–248), based on five observed and 4.7 expected deaths. No deaths were identified due to Hodgkin's disease (1.2 expected) or in the category of other lymphatic and haematopoietic tissue cancers (3.9 expected). There were non-significant excesses of deaths due to malignant and benign neoplasms of the brain

(six observed, 4.3 expected, SMR = 141) and stomach cancer (8 observed, 5.0 expected, SMR = 160) and a deficit of deaths from pancreatic cancer (4 observed, 6.6 expected). No deaths due to peritoneal mesothelioma were identified. Death rates for heart disease were 14% lower than those in the general United States population. Cerebrovascular disease rates were 19% lower. Among those assigned for 20 or more years to ethylene oxide units, the SMR for heart disease was 94 (95% CI 57–147) and the SMR for cerebrovascular disease was 222 (95% CI 81–483). There were deficits of deaths due to the last cause at all other duration of assignment categories.

The data were also examined for those who spent two or more years in high, intermediate, and low exposure departments. There were no excesses for the outcomes of interest among the men in high exposure departments. The observed number of deaths due to brain tumours, stomach cancer, and leukaemia was one death each in this group. Men in the intermediate exposure departments had significantly low overall and respiratory cancer death rates (SMRs 59 and 32 respectively) and a borderline significant excess of stomach cancer mortality with four observed and 1.1 expected deaths (95% CI 102–957). The low exposure group had a similar pattern for stomach cancer with four observed and 1.8 expected deaths (95% CI 61–575).

Table 2 presents the results of the internal comparisons for examining trends with duration of assignment, adjusting for age, calendar year, and time since first assignment. There were no statistically significant trends for all cancer, leukaemia, or pancreatic, brain, or stomach cancers. The relative risk (RR) estimate for stomach cancer among those assigned 2–9 years was statistically significant (RR = 2.77; 95% CI 1.11–6.93). Because intensity of

Table 2 Observed deaths, RR estimates, and 95% CIs for selected causes by cumulative duration in departments using or producing ethylene oxide

Cause of death category	Duration of assignments to ethylene oxide departments. (y)					Test for trend (p value)
	Never assigned RR†(obs)	<2 RR†(obs) (95% CI)	2–9 RR†(obs) (95% CI)	10–20 RR†(obs) (95% CI)	≥ 20 RR†(obs) (95% CI)	
Total malignancies	1 (1944)	0.88 (36) (0.63–1.23)	0.88 (47) (0.66–1.18)	0.84 (18) (0.52–1.33)	0.74 (9) (0.38–1.42)	0.12
Pancreatic cancer	1 (89)	0 (0)	1.29 (3) (0.41–4.09)	1.07 (1) (0.15–7.75)	0(0)	0.65
Stomach cancer	1 (79)	0.64 (1) (0.09–4.64)	2.77* (5) (1.11–6.93)	2.62 (2) (0.63–10.82)	0(0)	0.13
Leukaemia and aleukaemia	1 (75)	0 (0)	1.11 (2) (0.27–4.50)	2.57 (2) (0.63–10.57)	2.50(1) (0.34–18.15)	0.28
Cancer of brain and other nervous system	1 (38)	2.48 (2) (0.77–7.96)	1.41 (2) (0.34 5.85)	0 (0)	3.26(1) (0.44–23.91)	0.33

*p < 0.05.

†Estimates of RR with the non-exposed level as baseline adjusted for age, calendar period, and interval since assignment.

Obs = Observed.

exposure varies by period and would be expected to be greater in the early years of plant operations, SMRs were also examined for those first exposed before or after 1940. Those with long duration assignment to EO units (≥ 10 years) and long time since first assignment (≥ 20 years) had total cancer SMRs of 88, if first assigned before 1940 and 92, if first assigned between 1940 and 1968. One of the workers who died from stomach cancer was first assigned before 1940 (0.8 expected) and seven (4.2 expected) were first assigned after 1939.

Two of the eight subjects who died from stomach cancer worked in ethylene oxide production by direct oxidation (one for three months and one for five years). The remaining cases worked in the production of propylene oxide (one) and ethylene oxide derivatives (five). One worker who died from leukaemia worked in ethylene oxide production (21 years, direct oxidation process). None worked in production by the chlorohydrin process.

Among the 118 workers assigned to ethylene oxide production by the chlorohydrin process, including the 40 men who also worked in the chlorohydrin unit, there were no deaths due to lymphopoeitic tissue cancers (1.5 expected) and one death due to stomach cancer (0.9 expected). This worker spent one year in this process.

Discussion

Occupational cohort studies are often limited by insufficient follow up, dilution effects, multiple comparisons, confounding by other exposures, and the healthy worker effect due to comparisons with the general population. An attempt was made to minimise such difficulties in this update of an earlier investigation. It represents 49 years of follow up of 1896 men, 23% of whom are deceased. At least 10 years has elapsed since first exposure for all study subjects, whose average period of observation is 27 years and whose average duration of exposure is over five years. External comparisons with the United States white male population were supplemented with internal comparisons with the workforce from which the study group was drawn, for the causes of death of a priori interest. Confounding by assignment to the chlorohydrin unit was removed and this exposure was considered separately.¹⁶

The mortality from all cancers combined was 14% lower for the ethylene oxide workers than that of the general population. Among those assigned 10 years or more to ethylene oxide units and who were 20 or more years from first exposure, the SMR for cancer was 88 (95% CI 57–130). There were no statistically significant excesses of any specific types of cancer. In particular, the data do not support associations of ethylene oxide with heart disease,

cerebrovascular disease or brain or pancreatic cancers.

Haematopoietic tissue cancers, in particular leukaemia, and stomach cancer have been reported to be associated with ethylene oxide, based on rodent data and the worker studies of Hogstedt *et al.*^{2,9} The present study found a deficit of all haematopoietic tissue cancers (SMR = 59). The number of deaths due to leukaemia (five) was similar to that expected (4.70). There was no duration response trend or association with high exposure departments. One leukaemia case worked in ethylene oxide production by direct oxidation and none was ever assigned to chlorohydrin based ethylene oxide production. These leukaemia data are consistent with those reported by Gardner *et al*, Kiesselbach *et al*, and Steenland *et al*, which combined included 19 observed leukaemia deaths *v* 19.2 expected (SMR = 99; 95% CI 60–155).^{10 11 15} One other death due to non-Hodgkin's lymphoma occurred during the update period. There were two deaths due to lymphosarcoma and reticulosarcoma (2.0 expected) and no deaths in the category of other lymphopoeitic tissue cancers (3.9 expected) in the study group from 1940–88.

Our investigation showed a statistically non-significant excess of stomach cancer, based on eight observed and 5.0 expected deaths. The excess in the 2–9 year duration group was significant although no duration-response trend was seen. The five men in this group had assignment durations of 6, 5, 5, 3, and 3 years, almost exclusively in the low and intermediate exposure departments. Hogstedt *et al* reported nine deaths from stomach cancer (1.2 expected) among 167 men who worked in chlorohydrin based ethylene oxide production in an old processing plant in Sweden.⁷ None of the eight workers who died in the present investigation had assignments in chlorohydrin based ethylene oxide production. There was another death due to this cause (1.4 expected) in a 78 year old man in the chlorohydrin unit cohort removed from this analysis. He also spent 17 years in ethylene oxide production by direct oxidation and one year in ethylene oxide production by the chlorohydrin process.¹⁶ The plant studied by Hogstedt *et al* also produced many chlorinated products, including chloroform, chlorinated acetals, chloral, and DDT and ethylene oxide derivatives. It was noted that other chemical exposures may be involved in the stomach cancer excess, which was not seen in other ethylene oxide cohorts studied by these investigators.⁹

A relation between ethylene oxide and stomach cancer is not supported by the combined data from the studies of Gardner *et al*, Kiesselbach *et al*, and Steenland *et al*, which include 30 observed deaths from stomach cancer *v* 28.43 expected (SMR =

106; 95% CI 71–151).^{10 11 15} Chance or chemical exposures other than to ethylene oxide in longer term assignments may be the explanation in the present study, although there did not seem to be a cluster of similar assignments among our cases.

With an addition of 10 years of follow up, these ethylene oxide workers do not show evidence of excess risk for cancers of haematopoietic tissue, including leukaemia and non-Hodgkin's lymphoma, and brain or pancreatic cancers. A non-significant excess of stomach cancer occurred in men with shorter term assignments mainly to ethylene oxide derivative units. This is by contrast with the large excess reported in one study of men in chlorohydrin based ethylene oxide production.⁹

The 278 men with assignments in the chlorohydrin unit, which mainly produced ethylene chlorohydrin and involved ethylene dichloride (1,2 dichloroethane) and bis-chloroethyl ether as byproducts, did not experience such a favourable mortality pattern. Benson and Teta report large excesses of pancreatic and haematopoietic tissue cancers and statistically significant duration-response trends, but no excess of stomach cancer.¹⁶ Separate analyses of assignments to the chlorohydrin unit were possible, as this production unit was distinct from the unit producing ethylene oxide by the chlorohydrin process. This was not the case in the Swedish production plant studied by Hogstedt *et al.*, which used a single production unit and the same workers for both processes.

Schulte *et al.* reported that exposure to low average concentrations of ethylene oxide (<1 ppm 8 h TWA) over a four month period results in increased frequency of haemoglobin adducts and sister chromatid exchanges.¹⁹ Although these measures are indicators of possible exposure, the health significance of the biochemical and biological changes found is unknown. The data from this investigation suggest that these indicators are not predictive of increased risk for cancer. In the present study, 96% of the deaths occurred in men first assigned to ethylene oxide units before 1970, when the exposures ranged from about 5 ppm to greater than 14 ppm, well above the concentrations shown to impact biological indices. Experimental studies of mechanisms of action are needed to better clarify these relations.

Two of us carried out our work as consultants to Union Carbide Corporation.

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