Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: a mortality study

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Abstract
A retrospective cohort study was conducted to examine the mortality experience of 2174 men employed between 1940 and 1978 by a large chemical company and who had been assigned to a chemical production department that used or produced ethylene oxide (EO). Comparisons were made with the general United States population, the regional population, and with a group of 26 965 unexposed men from the same plants. Comparisons with general United States death rates showed fewer deaths than expected in the EO group due to all causes and for total cancers. There was no statistically significant excess of deaths due to any cause. Seven deaths each due to leukaemia and pancreatic cancer were observed with 3·0 and 4·1 deaths expected. Among the subcohort of men who worked where both average and peak exposure levels were probably highest, however, one death due to pancreatic cancer (0·9 expected) and no deaths due to leukaemia were observed. Four of the seven who died from leukaemia and six of the seven who died from pancreatic cancer had been assigned to the chlorohydrin department where the potential for exposure to EO is judged to have been low. The relative risk of death due to each disease was strongly related to duration of assignments to that department. When men who worked in the chlorohydrin department were excluded, there was no evidence for an association of exposure to EO with pancreatic cancer or leukaemia. Together with the failure to show independent EO associations, the chlorohydrin department results suggest that leukaemia and pancreatic cancer may have

been associated primarily with production of ethylene chlorohydrin or propylene chlorohydrin, or both. These results emphasise the importance of examining additional concurrent/asynchronous exposures among human populations exposed to EO.

Ethylene oxide (EO) is a major industrial chemical with an annual production capacity in the United States in the range of six billion pounds.[1] Most EO produced is used to manufacture chemical derivatives, less than 0·5% is consumed by sterilant or fumigant users.

Because EO is flammable and highly reactive, process equipment in the manufacturing setting generally consists of tightly closed and highly automated systems. Currently, during routine operation, workers have minimal opportunity for exposure and levels in chemical manufacturing plants are typically low, usually less than 1 ppm, the current eight hour time weighted average (TWA8) standard.[2] Historical exposure levels are known to have been higher, however. In industries that use EO for sterilisation, the control of employee exposures may be more difficult due to the greater potential for workers to have physical contact with EO gas.

EO has been shown to be an alkylating agent, which may react directly (and irreversibly) with nucleophilic macromolecules (such as DNA, RNA, and proteins) without requiring metabolic activation.[3-5] It is genotoxic in a wide variety of biological systems and carcinogenic in rats and mice.[6-9]

Hogstedt *et al* have reported excesses of leukaemia among sterilant workers and leukaemia and stomach cancer among employees of a chemical production plant.[10-12] Mortality studies of several other occupational cohorts have been reported that do not support these findings.[13-15] Bisanti *et al* also did not observe an excess of leukaemia in Italian chemical workers but reported excesses of lymphosarcoma and cancers of the digestive system (L Bisanti *et al*, sixth international symposium of epidemiology in occupational health, Stockholm, 1988).

The present research is based on the follow up of

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2174 men who were employed between 1940 and 1978 at either of two Union Carbide Corporation (UCC) chemical production plants and who were assigned to chemical manufacturing operations that produced EO or used it in the production of derivatives.

Materials and methods

ETHYLENE OXIDE PRODUCTION AND USE
EO production at the South Charleston, West Virginia, plant began when the plant opened in 1925, using the chlorohydrin process exclusively. Chlorohydrin based EO production used crude ethylene chlorohydrin pumped in from the chlorohydrin department. In 1937 production of EO by the direct oxidation of ethylene gas went on line. By 1941, EO was being manufactured at South Charleston by three converters using the chlorohydrin method and by three more using direct oxidation. Chlorohydrin based EO production was shut down in 1957. Between 1948 and 1950, five direct oxidation EO converters were constructed and began production at UCC's Institute, West Virginia, plant.

In 1970 and 1971 EO manufacturing at the Institute and South Charleston facilities was phased out. EO for remaining production was shipped to Institute by rail and supplied to South Charleston from Institute by pipeline. The use of EO in Kanawha Valley derivatives operations remained substantial, however.

COHORT DESCRIPTION
The study cohort was drawn from a base file of 29 139 male employees of UCC who had ever been employed at any of the three UCC facilities in the Kanawha Valley (KV) of West Virginia (the two production plants and a technical centre) between 1940 and 1978. The mortality experience of this group has been previously reported.[16]

A detailed historical reconstruction of chemical processing at the two production facilities had been produced by veteran manufacturing personnel who reviewed available records and prepared chronological listings of substances present in each chemical processing department as far back as 1925.[17] Each production department was described in terms of start up and shut down dates and included an inventory of chemicals used and produced.

Work history records of all employees in the base file were searched and individuals were identified who had ever been assigned by 1979 to a chemical production department that was judged to have used or produced EO (study departments). Records of identified employees were further examined to ensure that their inclusion in the cohort was based on assignment during a period when EO was handled. Study members were not included based on main-

tenance assignments to EO departments, since their work history records did not typically provide department specific information. Eligible study subjects, however, may have also been assigned to maintenance jobs at some point in their employment.

ENVIRONMENTAL ASSESSMENT
Taken together, the study departments represented a diverse group of chemical manufacturing activities, ranging from the production of EO by two different methods (chlorohydrin process and direct oxidation) to its use in the production of numerous other chemicals. In some departments EO was used in the manufacture of virtually every product; in others it was used in small quantities, in a small minority of operations, or both. Study departments thus differed from one another not only on the basis of potential exposure to EO but also on the basis of exposures to other substances.

The first large scale environmental monitoring programme for EO began in 1976. Results indicated that TWA8 EO exposure levels in EO based chemical production departments averaged less than 1 ppm, although exposure levels as high as 66 ppm TWA8 had been observed. Exposure levels among maintenance employees were generally between 1 and 5 ppm TWA8. Although these data were useful in characterising ambient EO levels in departments operating at that time, they were of limited use for assessment of pre-1976 concentrations. An exposure categorisation scheme was therefore developed that did not rely on monitoring data, recognised the multiple agents in the environment as well as relative EO exposure levels, and reflected any changes that occurred over time (table 1). Department specific data on the factors affecting potential for exposures to EO and exposures to other substances were obtained by interviews and by reference to available records.

Three EO exposure levels were defined. EO production departments with one or more continuously operating EO converters and recovery systems were considered to have the highest potential for EO exposure, as a result of routine activities such as frequent sampling, maintenance of cycle machines, and EO compressors. Departments using EO were considered to be in the intermediate level if: (1) EO was routinely in use in systems that were indoors in the same building as the operators and there was no pressurised control room, (2) the department was developmental or the process tended to lose EO during routine operations, or (3) the department also produced EO but did not have its own recovery system and therefore was not considered to be a high exposure department. Remaining departments using EO were considered to have the lowest potential for exposure and were assigned to the low exposure category.

Table 1   Categorisation of study departments by work area and ethylene oxide exposure level

| | Work area | No of study departments at stated EO exposure level | | | Other substances commonly present in work area |
		Low	Int	High	
I	Oxide distribution, polymerisation, and aducts; glycol ethers and amines	10	10	2	Aliphatic and alkanolamines, aliphatic and aromatic alcohols, ammonia, caustic, glycol ethers, and inorganic acids
II	Chlorohydrin users and producers	5	1	2	Acetaldehyde, aliphatic alcohols and amines, allyl chloride, ammonia, bis-chloroethyl ether, caustic, chlorine, dichloroethane, dioxane, ethylene and propylene chlorohydrin, epichlorohydrin, glycol ethers, and inorganic acids
III	Specialty chemicals; oxide production; polyalkylene glycol ethers, diols, and triols	6	2	2	Acetonitrile, acrolein, acrylonitrile, aldehydes, aliphatic alcohols, aniline, benzene, butadiene, caustic, diethyl sulphate, epichlorohydrin, ethylene dichloride, formaldehyde, glycol ethers, methylene chloride, styrene, and toluidine

MEDICAL RECORD REVIEW

Because EO is acutely toxic, exposed employees often reported to the dispensary for examination or treatment. Beginning in 1950, an acute exposure log was maintained at the Institute plant dispensary. To test the consistency of the environmental characterisation, the frequencies of reported exposures were calculated by the EO exposure level (low, intermediate, high) of the departmental assignment at the time and by maintenance or distribution assignment.

Skin and eye contact were the most frequently reported exposures to EO. Most were reported by men assigned to producing EO where the calculated frequency of such exposures was 31·5/1000 person-years (PY) of assignment. The frequency of these exposures among men assigned to intermediate and low EO levels were 6·0 and 6·4/1000 PY, respectively, and they were least frequent for men assigned to maintenance or distribution departments (2·3/1000 PY). Inhalation exposures resulting in nausea and vomiting were also most frequently reported among men assigned to EO production (6·9/1000 PY). Exposure frequencies decreased with decreasing EO level (intermediate 2·0/1000 PY; low 1·2/1000 PY) and were lowest for the maintenance/distribution subgroup (0·2/1000 PY).

ANALYSIS

Traditional standardised mortality ratio (SMR) analyses were used to examine the mortality experience of the total study cohort and subgroups of interest compared with that of the general United States population or the regional population of Kanawha and Putnam counties. Comparisons were performed using a modified life table approach and white male death rates for the general United States population.[18] Regional comparisons used rates developed by the University of Pittsburgh.

Person-years were accumulated into five year age and calendar year specific intervals beginning with the date of hire or 1 January 1940, whichever was later. Cohort members continued to contribute PY until lost to follow up (in which case they were withdrawn alive on the date last observed), death, or 31 December 1978, whichever occurred first. Ninety five per cent confidence limits were computed using the programs of Rothman and Boice.[19]

Mantel-Haenszel extension analyses for a cohort study were used to evaluate trends in the relative risk for hypothesised cause specific mortality over levels of duration of EO assignments.[20 21] The non-EO exposed KV population was used as an internal comparison group. Analyses were stratified by age, calendar year, and interval since hire. Level specific relative risk estimates were standardised to the referent level and 95% confidence intervals were calculated using the variance estimator described by Robins *et al*.[22] Trend analyses were also performed after incorporating a series of lags (5, 10, or 20 years) into the calculation of the exposure variable. In these analyses the dose-response relation (where duration of assignment was used as a surrogate for dose) was tested using the methodology developed by Pasternack and Shore.[23]

Results

The vital and employment status of the 2174 men in the study cohort is summarised in table 2. At the end of 1978, 37% were employed; 48% had left employment with UCC in the KV and were known to be alive; 14% had died and the vital status of less than 2% was unknown. Death certificates were collected for all but five of the 297 known decedents.

Slightly over 10% of the cohort had been first assigned to a study department before 1940. Their inclusion in the study occurred because they remained on the payroll as of 1 January 1940. Almost two thirds of the deaths occurred among men hired before or during the 1940s. Thus the overall study results largely reflect the mortality patterns of men

Table 2   Vital and employment status of the ethylene oxide (EO) cohort by decade of first EO assignment and total duration of assignments to EO using/producing departments as of 31 December 1978

Decade of first EO assignment and duration of EO employment	Known alive			Dead (n = 297)	Vital status unknown (n = 39)
	Total (n = 2174)	Actively employed (n = 804)	Left (n = 1034)		
First assignment before 1940:					
Total	223	0	108	111	4
< 1 year	28	0	14	14	0
1–4 years	54	0	0	31	1
5–9 years	42	0	23	18	1
10–19 years	40	0	16	22	2
20–29 years	40	0	21	19	0
⩾ 30 years	19	0	12	7	0
First assignment 1940–9:					
Total	400	61	249	84	6
< 1 year	78	6	52	18	2
1–4 years	83	10	49	23	1
5–9 years	69	13	45	10	1
10–19 years	89	12	54	22	1
20–29 years	66	17	37	11	1
⩾ 30 years	15	3	12	0	0
First assignment 1950–9:					
Total	481	192	235	39	15
< 1 year	108	23	67	10	8
1–4 years	148	39	92	15	2
5–9 years	88	40	42	3	3
10–19 years	115	72	32	9	2
20–29 years	22	18	2	2	0
First assignment 1960–9:					
Total	760	332	357	57	14
< 1 year	253	59	176	13	5
1–4 years	315	135	139	33	8
5–9 years	122	80	31	10	1
10–19 years	70	58	11	1	0
First assignment ⩾ 1970:					
Total	310	219	85	6	0
< 1 year	157	87	66	4	0
1–4 years	135	116	17	2	0
5–9 years	18	16	2	0	0

who were first assigned to study departments before 1950. The cohort was followed up for an average of 20 years per man.

For the full cohort the SMR for all causes was 79 (p < 0·05) and for total cancers the SMR was 81 (not significant (NS)) (table 3). No statistically significant rises were observed for any cause of death category. Significant deficits were seen for deaths due to diseases of the respiratory system and suicide. Non-significantly raised SMRs were observed for deaths due to brain cancer, leukaemia, liver cancer, and cancer of the pancreas. Using regional rates, the mortality patterns of the study group were essentially unchanged, suggesting that regional factors were relatively unimportant.

Mortality patterns for the subcohort assigned to study departments for at least two years were similar to those of the full cohort. To focus on those men with the greatest potential for exposure, the remaining SMR tables are restricted to this subcohort. Only six of the 211 observed deaths in the subcohort were observed among men who were hired into salaried jobs. Consequently, the mortality patterns of the total subcohort primarily reflect the experience of the hourly subset.

Table 4 shows the cause specific mortality for the ⩾ 2 years group by EO exposure level. For each level, follow up started on the day two years of assignments to departments at that level had occurred, or 1 January 1940, whichever was later. The three subcohorts were not mutually exclusive as cohort members may have been assigned for two years to departments at more than one level. There were no statistically raised SMRs for any cause of death for the subcohort assigned to departments with the highest exposure to EO. The SMR for all cancers was 78 (NS) and there were no deaths due to stomach cancer, brain cancer, or leukaemia. For the subcohort at the intermediate exposure level, there were no statistically significant excesses in any cause of death category and there were no observed deaths due to brain cancer or leukaemia. There were raised SMRs observed for stomach and pancreatic cancers. Among men in the lowest exposure subcohort, there were significantly more deaths than expected for cancer of the pancreas and for lymphatic and haematopoietic

Table 3   Observed and expected deaths (1940–78) by selected causes for men ever assigned to EO using/producing departments

Cause of death category	Obs/Exp	SMR†	(95% CL)
All causes:	297/375·9	79*	(70, 89)
Malignant neoplasms, total:	60/74·6	81	(62,104)
Digestive organs & peritoneum:	20/20·3	98	(60,152)
Oesophagus	1/1·8	(56)	(3,276)
Stomach	3/3·7	(81)	(16,237)
Intestine except rectum	3/6·4	(93)	(34,203)
Rectum	0/2·3	—	(0,164)
Liver unspecified and primary	3/1·8	(170)	(33,498)
Pancreas	7/4·1	(171)	(69,353)
Respiratory system	19/26·7	71	(43,111)
Male genital organs	2/3·8	(53)	(4,190)
Kidney	1/2·0	(51)	(2,255)
Bladder and other urinary organs	0/1·9	—	(0,199)
Skin	1/1·5	(65)	(3,312)
Brain and other parts of nervous system	4/2·8	(141)	(38,362)
Lymphatic and haematopoietic tissue:	9/7·5	120	(55,228)
Leukaemia and aleukaemia	7/3·0	232	(94,478)
Non-Hodgkin's lymphoma	2/2·4	(82)	(6,293)
Multiple myeloma	0/0·9	—	(0,404)
Diabetes mellitus	1/5·2	(19)	(1,109)
Vascular lesions affecting CNS	14/19·9	70	(39,118)
Unable to locate death certificate	5		

*SMR is statistically different from 100 (p < 0·05, two tailed).
†Parenthetical values in the SMR column indicate observed to expected ratios for which the numerator or denominator or both is less than 5.

malignancies, which were attributable to an excess of leukaemia. There were non-significantly raised SMRs for cancer of the brain and non-Hodgkin's lymphoma. Additional analyses performed to pinpoint a more specific subcohort from which these excesses arose identified the group of men who had been assigned to the chlorohydrin department.

Table 5 shows the results of the SMR analysis of this group. Statistically significant excess mortality was observed for pancreatic cancer (6 obs/0·7 exp) and leukaemia (3 obs/0·4 exp). For the remainder of the cohort never assigned to the chlorohydrin department, there was one death from pancreatic cancer (2·2 exp) and three from leukaemia (1·5 exp). These

findings were supported by trends with duration of assignment to the chlorohydrin department (table 6). Compared with the non-EO group, the relative risks for pancreatic cancer and leukaemia were 14 and 8·7-fold, respectively, for those with 10 or more years of chlorohydrin department assignments. Lagged analyses by duration of chlorohydrin assignments performed for these diseases showed trends that grew steeper and remained highly significant as the assumed induction period increased from 0 to 20 years. No trends for mortality due to either stomach or brain cancer were observed with duration in all study departments or specifically in the chlorohydrin department.

Table 4   Observed and expected deaths (1940–78) by selected causes for men assigned to EO using/producing departments for two years or more

Cause of death category	Assigned for ⩾ 2 years to low exposure depts		Assigned for ⩾ 2 years to int exposure depts		Assigned for ⩾ 2 years to high exposure depts	
	Obs/Exp	SMR*	Obs/Exp	SMR*	Obs/Exp	SMR†
All causes	118/150·5	78†	69/78·2	88	58/83·7	69¶
Malignant neoplasms, total:	31/31·4	99	10/15·7	64	13/16·8	78
Digestive organs and peritoneum:	12/8·6	140	8/4·4	(182)	4/4·6	(87)
Stomach	1/1·5	(66)	3/0·8	(364)	0/0·9	—
Pancreas	7/1·8	(400)‡	2/0·9	(229)	1/0·9	(109)
Respiratory system	8/11·6	69	1/5·6	(18)	7/6·0	116
Brain and other parts of NS	2/1·1	(184)	0/0·6	—	0/0·6	—
Lymphatic and haematopoietic tissue:	8/2·9	(275)§	1/1·5	(67)	0/1·7	—
Leukaemia and aleukaemia	6/1·2	(517)‖	0/0·6	—	0/0·7	—
Non-Hodgkin's lymphoma	2/1·0	(204)	1/0·5	(203)	0/0·6	—
Multiple myeloma	0/0·4	—	0/0·2	—	0/0·2	—
Unable to locate death certificate	1		1		1	

*Parenthetical values in the SMR column indicate observed to expected ratios for which the numerator or denominator or both is less than 5.
95% Confidence limits: †(65, 94), ‡(164, 817), §(120, 541), ‖(196, 1107), ¶(53, 89).

Table 5 Observed and expected deaths (1940–78) by selected causes and by assignments to the chlorohydrin department among men assigned for two years or more to EO using/producing departments

Cause of death category	Assigned for ⩾ 2 years to chlorohydrin dept			Assigned for ⩾ 2 years to EO, never to chlorohydrin dept		
	Obs/Exp	SMR†	95% CL	Obs/Exp	SMR†	95% CL
All causes	61/59·5	103	(79, 132)	140/191·8	73*	(62, 86)
Malignant neoplasms, total:	18/11·7	153	(91, 242)	25/39·1	64*	(41, 94)
Digestive organs and peritoneum:	8/3·4	(233)*	(102, 459)	9/10·5	85	(39, 162)
Stomach	0/0·7	—	(0, 549)	3/1·9	(161)	(31, 470)
Pancreas	6/0·7	(911)*	(355, 1898)	1/2·2	(46)	(2, 237)
Respiratory system	4/4·1	(99)	(26, 253)	9/14·4	63	(29, 119)
Brain and other parts of NS	1/0·4	(263)	(13, 1394)	1/1·5	(67)	(3, 319)
Lymphatic and haematopoietic tissue:	4/1·1	(376)*	(103, 958)	4/3·9	(104)	(28, 266)
Leukaemia and aleukaemia	3/0·4	(668)*	(139, 1895)	3/1·5	(197)	(38, 576)
Non-Hodgkin's lymphoma	1/0·3	(291)	(14, 1564)	1/1·3	(78)	(4, 362)
Multiple myeloma	0/0·1	—	(0, 2564)	0/0·5	—	(0, 761)
Unable to locate death certificate	1			0		

*SMR is statistically different from 100 (p < 0·05, two tailed).
†Parenthetical values in the SMR column indicate observed to expected ratios for which the numerator or denominator or both is less than 5.

CASE SUMMARIES

Table 7 shows exposure summaries for men who died of pancreatic cancer or leukaemia. Four of the seven men who died from leukaemia had been assigned to the chlorohydrin department (0·7 exp). Causes of death on the death certificate were listed as acute leukaemia, acute myeloblastic leukaemia, and chronic myelogenous leukemin (2). Their average duration of assignments to the department was nine years and ranged from less than one to 16 years. No one was first assigned after 1937 and no one had ever been assigned to a department classified as intermediate or high exposure to EO. They died between 18 and 39 years after their first assignment to the department. ·

All of the EO assignments of the three remaining leukaemia decedents were in the lowest exposure departments and no two were assigned to the same department. The case who had the longest exposure died of chronic myelogenous leukaemia at age 53, 29 years after his first EO related assignment. The other two men died of myelogenous leukaemia and acute myeloblastic leukaemia. They spent under three years in assignments to departments with potential exposure to EO and died less than four years after those assignments started.

Risk for pancreatic cancer was not among the a priori hypotheses, yet seven men died of this disease (4·1 exp). Their death certificate diagnoses were: carcinoma of the pancreas (5), carcinoma, head of pancreas (1), and metastatic carcinoma, probably pancreas (1). Six of these men had been assigned to the chlorohydrin department. Their dates of first assignment ranged from September 1929 to September 1944. The cumulative duration of assignments to the department ranged from two (the "probable pancreatic cancer") to 30 years and averaged 12 years. They died between 26 and 48 years after their first chlorohydrin assignment.

A pathological review of the cases of pancreatic

Table 6 Observed and expected deaths, relative risk estimates, and 95% confidence limits for selected causes by cumulative duration in the chlorohydrin department

Cause of death category	Never assigned to EO depts	Duration of assignments to chlorohydrin dept (y)				
		0–2	2–10	10–20	>20	
	RR† (deaths)	RR† (obs/exp) (95% CL)	RR† (obs/exp) (95% CL)	RR† (obs/exp) (95% CL)	RR† (obs/exp) (95% CL)	
Total malignancies	1 (1023)	0·66 (4/6·45) (0·25, 1·76)	1·10 (7/6·45) (0·52, 2·31)	2·07 (7/3·43) (0·98, 4·38)	2·68 (4/1·52) (0·99, 7·21)	p < 0·05
Pancreatic cancer	1 (52)	— (0/0·35)	6·44* (2/0·35) (1·55, 26·8)	18·0* (3/0·19) (5·51, 58·6)	12·9* (1/0·09) (1·74, 95·2)	p < 0·01
Leukaemia and aleukaemia	1 (47)	4·08 (1/0·28) (0·54, 31·0)	3·97 (1/0·29) (0·54, 29·4)	13·6* (2/0·17) (3·24, 57·2)	— (0/0·06)	p < 0·01
Cancer of brain and other NS	1 (24)	— (0/0·20)	— (0/0·21)	11·5* (1/0·09) (1·53, 86·1)	— (0/0·04)	p > 0·10

*p < 0·05.
†Relative risk estimates using the non-exposed level as baseline. Expected deaths are adjusted for age, calendar period, and interval since hire.

Table 7 Characteristics of decedents from pancreatic cancer and leukaemia and aleukaemia among men in the EO cohort, 1940–78

Cause code	ICDA rev	Birth year	Age at		Duration (y)					Highest EO	Latency (y)		Age at death
			First EO	First Chlor	EO	Chlor	EO level				EO	Chlor	
							Low	Int	High				
Pancreatic cancer													
157·0	8	1905	23	23	25	9	22	0	2	High	48	48	71
157·9	8	1903	26	26	24	19	19	5	0	Int	43	43	68
157·0	7	1907	26	26	34	11	11	23	0	Int	34	34	60
157·0	7	1904	30	30	30	30	30	0	0	Low	31	31	61
157·9	8	1908	51	—	4	0	4	0	0	Low	15	—	66
157·9	8	1914	26	29	20	18	20	0	0	High*	29	26	56
157·9	8	1913	29	29	2	2	2	0	0	Low	33	33	62
Leukaemia and aleukaemia													
204·1	6	1898	33	33	1	1	1	0	0	Low	18	18	52
205·1	8	1908	26	26	8	7	8	0	0	Low	36	36	62
207·0	8	1891	44	44	16	16	16	0	0	Low	39	39	82
205·0	8	1908	29	29	11	11	11	0	0	Low	34	34	63
205·0	8	1922	45	—	3	0	3	0	0	Low	4	—	49
204·1	6	1908	46	—	3	0	3	0	0	Low	3	—	49
205·1	8	1925	24	—	13	0	13	0	0	Low	29	—	53

*Employee spent less than 0·5 years in a "high" EO department. Duration in "high" is 0 due to rounding.

cancer and leukaemia based on hospital records confirmed the death certificate diagnoses for all but two individuals. The primary cancer site was judged unknown for one case of pancreatic cancer and the medical record for one case of leukaemia could not be obtained.

Discussion

The study was originally conceived as an integral component of the cohort mortality study of UCC's three facilities in the Kanawha Valley of West Virginia that was conducted in collaboration with the National Institute for Occupational Safety and Health (NIOSH). It was agreed to perform certain chemical and process specific retrospective cohort studies once follow up for the entire population was complete and sufficient information on chemical production departments had been compiled. The present study represents the first complete exposure specific research using the database.

Study departments were ranked according to relative potential for exposure according to the nature of their routine production practices determined using the best available evidence. Medical records of acute exposures to EO support the ranking scheme with respect to the frequency of inhalation and dermal exposures. The ranking scheme is also supported by industrial hygiene surveys of these and other UCC facilities. Based on estimates of operators' TWA8 EO exposures at the UCC Texas City, Texas, plant, exposure levels in direct oxidation EO production were probably in the range of 10–20 ppm.[24] Levels in EO production using the chlorohydrin process were probably somewhat higher, since (1) the technology, construction materials, and

work practices were from an earlier era, (2) there was no control room, and (3) the production equipment was indoors. Based on breathing zone samples collected from 1976 to 1978 at the South Charleston and Institute plants, continuous exposure levels in departments using EO were in the order of <1–3 ppm (possibly an order of magnitude lower than those in production departments).

There were no observed associations of stomach or brain cancer mortality with duration of assignments to study departments. In addition, the risk of death due to leukaemia was not raised in the subcohort exposed to the highest EO levels or in the entire cohort after removal of the chlorohydrin group. Supplementary analyses by level of "integral EO exposure" (level of exposure (high = 3, intermediate = 2, low = 1) × duration) were also conducted and yielded similar results. The relative risks of both leukaemia and pancreatic cancer, however, were shown to be strongly associated with duration of assignment to the chlorohydrin department, even after the incorporation of appropriate latent intervals.

Results of proportional hazards modelling were consistent with those of the categorical analyses.[25] No index of EO exposure was statistically significant when present in a model containing a term for chlorohydrin department duration, whereas the chlorohydrin duration variable was highly significant and remained so for all induction periods examined (0, 5, 10, and 20 years).

The chlorohydrin department started up in November 1925. Until September 1931 the department produced ethylene chlorohydrin exclusively. The crude ethylene chlorohydrin was pumped to the

EO production department and used for EO production (chlorohydrin process). After that time, three of the seven reaction towers were made available for "special production" of propylene chlorohydrin until sometime between the late 1930s and early 1940s. The equipment was then infrequently used to manufacture bis-chloroethyl ether (BCEE) and dichloroethane or concentrated ethylene chlorohydrin. Both processes used EO and according to the best available information, they were run only sporadically and production volumes were small. These processes represented the sole uses of EO in the chlorohydrin department. The only other opportunity for exposure to EO was the result of fugitive emissions from other EO departments in the same building. Ethylene chlorohydrin production ceased in 1957.

Four of the seven leukaemia decedents and six of the seven pancreatic cancer decedents in the EO cohort had been assigned to the chlorohydrin department. All four leukaemia decedents were first assigned in the 1930s. The six men in the chlorohydrin subcohort who died of pancreatic cancer were first assigned to the department before 1945. Nine of the 10 decedents with leukaemia and pancreatic cancer worked in the chlorohydrin department between 1935 and 1945 and only three of the ten had additional work experience in that department after ethylene chlorohydrin production ceased.

Because the chlorohydrin department had been operating for over 15 years by the beginning of study follow up, there was ample opportunity for selection out of the cohort. Given the distribution of deaths by chlorohydrin duration and that selection out was most likely among men with shorter assignments, it is unlikely that bias could have artificially created the observed trends with duration of chlorohydrin assignments.

The conditions of EO use in the chlorohydrin department were probably not unique, as ad hoc small volume "special production" occurred in many study departments. Thus the possibility that the chlorohydrin results were due to any special circumstances of exposure to EO in that department seems remote. The relative risk of leukaemia (and pancreatic cancer) mortality was found not to be associated with assignment to EO production units or with duration or "integral EO exposure" among the 1896 men in the cohort never assigned to the chlorohydrin department. Inferences from the results in this subgroup to similarly exposed groups are limited by the small cohort size. This is partially offset by the long average period of observation (almost 20 years). Omitting the chlorohydrin subcohort from the total study population and allowing for a latency period (time from first EO related assignment) of ten years, the leukaemia SMR was 65 (1 obs/1·5 exp, 95% CL = 3, 310) or 140 (3 obs/2·1

exp, 95% CL = 27, 409) if the latency requirement is dropped.

During the relevant period, the opportunity for exposure in the chlorohydrin department was greatest for substances related to the production of ethylene chlorohydrin, including the byproducts, dichloroethane and BCEE. Ethylene chlorohydrin has not been found to be carcinogenic when administered to rats by gavage or by dermal application to rats or mice.[26][27] It was only inconsistently carcinogenic by subcutaneous injection.[26][28] On the other hand, the carcinogenicity of dichloroethane has been shown in rats and mice of both sexes.[29][30] Oral dosing of mice with BCEE has produced an increased incidence of hepatomas[31] but this result has been questioned as a reliable indication of true carcinogenic potential.[32] Other studies using both rats and mice have shown no evidence of carcinogenicity.[33-37]

The results of this study are best viewed in the context of the existing published epidemiological studies of EO exposed populations. Hogstedt *et al* reported the first putative excess of leukaemia associated with EO among a group employed in a factory in which a mixture of EO and methyl formate was used as a sterilant.[10] This was actually the report of a cluster and factors other than exposure to EO do not appear to have been evaluated. The second excess of leukaemia, also reported by Hogstedt *et al*, occurred among a population employed as operators in a chemical production facility that manufactured EO by the chlorohydrin process.[11] Numerous chemicals were present in this chlorohydrin based EO production unit and in other chemical production at the plant. These EO workers were reported to have spent more than one hour per shift in the chlorohydrin room and, furthermore, were reported to have tasted the chemical reaction product to assess the result of EO synthesis. Three of the remaining EO production cohorts studied by other investigators included plants that produced EO by the chlorohydrin process.[13][15] The findings from these studies are not consistent with those reported by Hogstedt *et al*. The observed and expected numbers of deaths from leukaemia were 1 *v* 0·2 (A M Thiess *et al*, international symposium for the prevention of occupational cancer, Helsinki, 1982), 2 *v* 2·4 (N Kiesselbach *et al*, Stockholm, 1988) and 3 *v* 2·1.[15] The three cases from the Gardner study did not occur among men assigned to EO production (by either process). Nor did these individuals work in ethylene chlorohydrin production.

In the present study no deaths from leukaemia were observed among men assigned to EO production. With the exception of ingestion of the reaction mixture, the exposure conditions described by Hogstedt *et al* are, at least qualitatively, similar to those in the South Charleston plant.[11] The inter-

pretation of the leukaemia-chlorohydrin results, however, is further complicated by the fact that the decedents from leukaemia were first assigned to the chlorohydrin department between 1931 and 1937. This finding could have been due to chance or it could result from qualitatively or quantitatively different pre versus post 1940 exposures, or both.

As to stomach cancer, Hogstedt's findings may have been related to the ingestions of the EO reaction mixture, which would have contained EO, ethylene glycol, ethylene chlorohydrin, dichloroethane, BCEE, and other substances. Dunkelberg has shown cancer of the forestomach in rats exposed to EO by gavage.[38]

Pancreatic cancer was not found in Hogstedt's cohorts but it was raised in the EO cohorts studied by Morgan et al.[14] In the former study EO was produced by direct oxidation only. Both pancreatic cancer and pancreatitis have been observed in cohorts exposed to short chain chlorinated hydrocarbons.[39-41] There is also limited and inconsistent epidemiological evidence concerning pancreatic cancer and employment in the dry cleaning industry.[42-44]

Together with the failure to support independent EO associations, the chlorohydrin department results suggest that the observed excesses of leukaemia and pancreatic cancer were primarily associated with the production of ethylene chlorohydrin or propylene chlorohydrin, or both. These results emphasise the importance of examining additional concurrent/asynchronous exposures among EO exposed (or other) occupational populations.

The prediction of human risk related to EO is problematical. The mutagenicity, genotoxicity, and carcinogenicity of EO have been clearly shown in experimental studies. Yet overall, epidemiological publications do not show an independent EO effect. Inconsistencies of the human and experimental data would be better understood if the pharmacokinetics of EO were known.

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From 1 July 1985 articles submitted for publication will not be returned. Authors whose papers are rejected will be advised of the decision and the manuscripts will be kept under security for three months to deal with any inquiries and then destroyed.