Occupational Exposure to Chloromethyl Ethers

A Retrospective Cohort Mortality Study (1948-1972)

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This industry-wide epidemiologic study to evaluate the human carcinogenicity of the chloromethyl ethers (CME) included 1827 CME-exposed workers and 8870 controls. Duration and relative intensity of exposure were classified by job description in the personnel records. This information permitted assigning relative magnitude of exposure scores for each job category at several plants, with allowance for temporal changes in the plant processes. Social security records were used for the ascertainment of deaths among separated employees. Death certificates were obtained for virtually all known deaths, and hospital pathology reports were obtained where possible for the cancer-related deaths. No differences in noncancer death rates were found. An increased risk of respiratory cancer death in CME-exposed workers was found at only one firm where high exposures are known to have occurred. A clear dose-response relationship with risk ratios exceeding ten for the longest duration and greatest exposure subgroups was demonstrated for this firm.

Chloromethyl-methyl ether (CMME) has been used for about 25 years by the chemical industry as a chemical intermediate in organic synthesis; e.g., as a crosslinking agent in the manufacture of ion-exchange resins. Commercial grades of CMME contain about 1-8% of bis-chloromethyl ether (BCME) as a contaminant, and we shall hereafter refer to the two of them as chloromethyl ethers (CME). Both CMME and BCME are alkylating agents and were shown to be mutagenic in bacterial test systems, and to be carcinogenic in skin application and inhalation studies by investigators at our Institute.[1-7] Under the auspices of the National Institute for Occupational Safety and Health (NIOSH), we initiated an industry-wide retrospective cohort study to evaluate the human carcinogenicity of these compounds. A preliminary report of this work has been published.[8] Here we will present the final report of the study based on ascertainment of vital status through December 31, 1972. (Note that Firm 1 in the preliminary report is called Firm 2 in this report and vice versa.)

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Methods

Sample Characteristics. — Records were obtained from six of the seven U.S. producers of CME on 1827 CME-exposed workers and 8870 non-CME-exposed ("controls") workers at the same firms during the same time period (1948-1972). The control workers entered the study on the date of first employment or the date at which CME was first used at the company, whichever was later. The number of studied workers at each firm is shown in Table 1 according to exposure group.

The duration of exposure was coded for all exposed workers, except for a small number of workers at one company (Firm 2) who were known to have filled in occasionally for others in CME work areas, but the frequency or dates of such CME exposure could not be determined from company records. Several companies had information by which the relative CME exposure intensities could be quantified for workers by job category. However, only one company had a large enough cohort of exposed workers to make it worthwhile to analyze mortality by weighted cumulative CME dose (i.e., Σ intensity x duration across all exposure periods).

Ascertainment of Vital Status. — Table 1 shows the status of the workers as of December 31, 1972, the termination date of the study, according to company records. Workers whose vital status was not definitely known by the companies (i.e., the separated employees) were followed by a variety of means to establish their mortality experience. The Social Security Administration (SSA) identified all the deaths known to them. In a sample of 300 known deaths sent to the SSA, 94% were detected by them, thus indicating that the sensitivity of this method is quite good.

The separated workers not identified as deceased by the SSA were further traced by a number of other vital status resources:

Table 1. — Status of CME-Exposed and Control Workers According to Company Records, by Firm.

Company Status	Total N	Total %	Firm 1 N	Firm 1 %	Firm 2 N	Firm 2 %	Firm 3 N	Firm 3 %	Firm 4 N	Firm 4 %	Firm 5 N	Firm 5 %	Firm 6 N	Firm 6 %
CME-Exposed														
Employed	833	46	146	72	401	56	120	93	26	12	100	20	40	60
Retired	93	5	14	7	30	4	3	2	1	1	44	9	1	2
Dead	133	7	7	3	82	11	3	2	5	2	35	7	1	2
Separated	768	42	36	18	208	29	3	2	183	85	313	64	25	37
Total	1827	100	203	100	721	100	129	99*	215	100	492	100	67	101
Control														
Employed	4821	54	3526	55	1021	56	150	52	0	—	12	15	112	40
Retired	1510	17	1346	21	83	5	72	25	0	—	2	2	7	3
Dead	1278	14	1040	16	178	10	49	17	0	—	6	7	5	2
Separated	1261	14	496	8	533	29	17	6	0	—	61	75	154	55
Total	8870	99	6408	100	1815	100	288	100	0	—	81	99	278	100

*Percents may not total 100 because of rounding error.

motor vehicle bureaus, post office address confirmations, Internal Revenue Service records, voter registration records, alumni associations and telephone directories. No one resource is entirely accurate; therefore, several were usually tried. Table 2 summarizes the number of follow-up resources which successfully verified the vital status of the separated workers by exposure group and company. One company (Firm 4) did not permit us to obtain identifying information on their workers, so follow-up other than through the SSA was not possible at that company. If this company is deleted from the tabulations, then of the separated workers, 99% of the CME-exposed and 98% of the controls had at least one verification of vital status. Similarly, 66% of separated CME-exposed workers and 71% of controls had at least two verifications of vital status.

For the five companies with follow-up, 99.8% of the CME-exposed and 99.7% of the controls had vital status known from either company records, SSA death records, or at least one verification on follow-up. If Firm 4 is also included, then the corresponding figures are 89.8% of CME-exposed and 99.7% of controls. If the SSA system is considered to be 90% efficient in detecting deaths (a reasonable assumption in view of the 94% efficiency we found in a sample of deaths), then only about 10% of the deaths among the 10.2% of workers not verified in the CME-exposed group would have been missed. Thus it can be estimated that only about 1% of deaths were missed.

Death Certificate Ascertainment and Coding. — Ninety percent of the death certificates were obtained for the CME-exposed group and 99% for the control group. (However, of the 13 deaths without death certificates in the exposed group, ten were from Firm 5; death certificates were, therefore, obtained for 97% of the deceased among the CME-exposed at other companies.) Table 4 details the follow-up experience for deceased persons. After it became apparent that many hospitals were uncooperative or charged large fees for medical records, the hospital verification attempts were restricted to cases in which cancer was listed anywhere on the death certificate. (In addition, it was generally not possible to obtain hospital information on deaths at Firm 1.) Very little change occurred in the coding of primary cause of death because of the hospital information. Table 5 presents a tabulation of detailed causes of death according to the primary cause of death on the death certificate, and according to adjusted cause: assigning the cause as cancer whenever it was listed anywhere on the death certificate or hospital record, and with corrected cause whenever the hospital record differed from the death certificate as to primary cancer site. Presented in Table 5 are the frequencies, and proportional mortality rates (PMR = the proportion of total verified deaths attributable to a particular cause). The table shows that there are no substantial differences between the CME-exposed and control groups in causes of death, except respiratory cancer.

Table 2. — Number of Sources Successfully Verifying the Vital Status of Separated Employees.

No. of Sources	Total* N	Total* %	Firm 1 N	Firm 1 %	Firm 2 N	Firm 2 %	Firm 3 N	Firm 3 %	Firm 4 N	Firm 4 %	Firm 5 N	Firm 5 %	Firm 6 N	Firm 6 %
CME-Exposed														
0	4	1	2	6	1	0	0	0	183	100	1	0	0	0
1	192	33	13	36	37	18	1	33	0	0	132	42	9	36
2	318	54	4	11	151	73	2	67	0	0	157	50	4	16
3	68	12	17	47	16	8	0	0	0	0	23	7	12	48
4	3	1	0	0	3	1	0	0	0	0	0	0	0	0
Total	585	101†	36	100	208	100	3	100	183	100	313	99	25	100
Control														
0	28	2	20	4	3	1	0	0	0	—	0	0	5	3
1	338	27	131	26	89	17	4	24	0	—	30	49	84	55
2	514	41	63	13	390	73	13	76	0	—	27	44	21	14
3	365	29	282	57	35	7	0	0	0	—	4	7	44	29
4	16	1	0	0	16	3	0	0	0	—	0	0	0	0
Total	1261	100	496	100	533	101	17	100	0	—	61	100	154	101

*Total column excludes Firm 4, for which follow-up could not be done.
†Percents may not total 100 because of rounding error.

Table 3. — Use of Various Agencies and Resources to Verify the Vital Status of Separated Workers.

Resource	CME-Exposed (768) % Verified	Controls (1261) % Verified
Motor Vehicle Bureau	59	64
Post Office address	46	67
Internal Revenue Service	99	95
Other sources	21	19

Results

Comparison of Mortality Experience with U.S. General Population. — The mortality experience in the CME-exposed and control groups was compared to that in the U.S. white male population, using mortality rates generated from the annual *Vital Statistics of the United States*. The rates were specific to cause, race, sex, and quinquennia of age and calendar year. The standardized mortality ratios (SMR = 100 x observed/expected deaths) for the CME-exposed and control groups were calculated separately by company and summed across all companies. Table 6 gives a summary of observed and expected deaths and SMR's for 21 causes. As is typical of occupational cohorts, the total mortality was less than expected from U.S. rates, the SMR being about 60. Ninety-five percent confidence limits[9] on the SMR's showed that the only elevated death rates in the CME-exposed group were for respiratory cancer at Firm 2 and at all companies, plus all malignant neoplasms at Firm 2. These three elevated rates are all attributable to excess respiratory cancer at Firm 2. No SMR's were significantly elevated in the control group.

Detailed tabulations of mortality experience by five-year intervals since the onset of CME exposure (entry into the study) were also obtained but are not presented here. There were no time periods with excess mortality for any diseases except respiratory cancer. The respiratory cancer rate at Firm 2 was elevated in the CME-exposed group throughout the period 6-25 years after the onset of exposure.

Internal Comparisons of Mortality Experience. — Each man-year contributed by CME-exposed (and control) workers was characterized by duration of CME exposure, attained age and elapsed years since first exposure (entry into study). Thus the man-years of a given worker could be distributed among several exposure categories. Analyses were then performed by duration of CME exposure using an adaptation of the Mantel-Haenszel combination chi-square procedure[10] controlling for age (strata of: <35, 35-44, 45-54, 55-64, 65-74, 75+), five-year intervals since onset of exposure, and company. Since the man-years at risk of a given worker were shifted into appropriate exposure categories, the analyses are based on comparisons among exposure categories with equivalent times since onset of exposure. This results in eliminating the bias in estimating exposure-response relationships which are inherent in other methods of analysis.[11] The test for a linear trend in the exposure duration-response relationship was by the method of Tarone.[12] Analyses were performed for respiratory cancer, digestive cancer, other cancer, diseases of the circulatory system, all other diseases, and accidental and traumatic deaths. The results are shown in Table 7.

For respiratory cancer there is a highly significant difference between groups, reflecting a strong linear trend with duration of exposure. However, for the other causes of death in Table 7 there is no systematic difference by exposure duration. (The significant combination chi-square for heart disease does not reflect a systematic trend by duration of exposure.)

Analyses of respiratory cancer by duration of exposure and by weighted cumulative exposure were performed for the data at Firm 2, controlling for interval since onset of exposure by single year and age by decade. Man-years at risk were again shifted to appropriate exposure categories as described above. These results are presented in Tables 8 and 9. Both tables show a highly significant CME exposure-response relationship, which further substan-

Table 4. — Verification of Cause of Death by Exposure Group.

Verification	CME-Exposed N	CME-Exposed %	Control N	Control %
Hospital records & death certificate	73	55	155	12
Death certificate	47	35	1107	87
No verification	13	10	16	1
Total	133	100	1278	100

Table 5. — Frequency of Death and Proportional Mortality for Selected Causes of Death in the CME-Exposed (E) and Control (C) Groups.

Cause of Death	Primary Cause on Death Certificate Freq E	Freq C	PMR† E	PMR† C	Adjusted Causes* Freq E	Freq C	PMR† E	PMR† C
Cancer								
Buccal, pharynx	0	1	0	0.1	0	3	0	0.2
Esophagus, stomach	0	23	0	1.9	0	23	0	1.9
Colorectal	2	26	1.7	2.1	2	28	1.7	2.3
Liver	0	4	0	0.3	2	4	1.7	0.3
Pancreas	1	22	0.9	1.8	1	23	0.9	1.9
Other digestive	1	15	0.9	1.2	1	17	0.9	1.4
Respiratory	26	115	22.2	9.3	27	119	23.1	9.6
Bone, connective tissue, skin	0	5	0	0.4	0	5	0	0.4
Prostate	3	15	2.6	1.2	3	19	2.6	1.5
Bladder	1	5	0.9	0.4	1	7	0.9	0.6
Other genitourinary	0	10	0	0.8	0	11	0	0.9
Central nervous system	1	15	0.9	1.2	0	15	0	1.2
Endocrine	0	1	0	0.1	0	1	0	0.1
Lymphomas	0	14	0	1.1	0	15	0	1.2
Leukemias	0	11	0	0.9	0	15	0	1.2
Other hematopoietic	0	7	0	0.6	0	7	0	0.6
Other and unknown sites	2	20	1.7	1.6	1	19	0.9	1.5
Non-Neoplastic								
Infections	0	5	0	0.5	0	6	0	0.5
Endocrine, metabolic	0	14	0	1.1	0	13	0	1.1
Circulatory system	46	665	39.3	53.8	45	651	38.5	52.7
Emphysema, COPD	2	22	1.7	1.8	2	21	1.7	1.7
Other respiratory	2	31	1.7	2.5	2	26	1.7	2.1
Cirrhosis	3	14	2.6	1.1	3	14	2.6	1.1
Renal disease	0	9	0	0.7	0	9	0	0.7
Sudden death and unknown disease	4	12	3.4	1.0	4	12	3.4	1.0
Miscellaneous disease	3	49	2.6	4.0	3	48	2.6	3.9
Vehicular accidents	8	37	6.8	3.0	8	37	6.8	3.0
Accidental poisoning	0	3	0	0.2	0	3	0	0.2
Suicide	4	28	3.4	2.3	4	28	3.4	2.3
Homicide	1	4	0.9	0.3	1	4	0.9	0.3
Other external causes	7	32	6.0	2.6	7	32	6.0	2.6

*Adjusted causes = Cancer if listed anywhere on death certificate or hospital record, with corrected cause whenever the hospital record differed from the death certificate on primary cancer site; otherwise the primary cause of death on the death certificate.

†PMR (proportional mortality rate) = percent of total verified deaths attributable to a given cause.

Table 6. — Observed (O) and Expected (E) Deaths and Standardized Mortality Ratios (SMR) for Selected Diseases in the CME-Exposed (CME) and Control (Cont) Groups, by Firm.

Cause of Death*		Total	Firm 1	Firm 2	Firm 3	Firm 4	Firm 5	Firm 6
	CME	(23130)†	(2768)	(11155)	(1865)	(1784)	(4975)	(583)
	O	114	7	78	0	3	25	1
	E	171.7	15.3	81.1	10.0	4.6	58.6	2.1
Total	SMR	66‡	45‡	96	—	65	43‡	47
mortality	Cont	(172667)†	(136645)	(27672)	(5232)	(0)	(876)	(2242)
(000-999)	O	1232	1021	170	32	0	6	3
	E	2054.9	1702.1	253.5	78.1	0.0	7.8	13.5
	SMR	60‡	60‡	67‡	41‡	—	77	22‡
	CME							
	O	37	2	29	0	0	6	0
	E	30.0	2.7	14.3	1.7	0.6	10.3	0.3
All malignant	SMR	123	75	203‡	—	—	58	—
neoplasms	Cont							
(140-209)	O	309	258	39	10	0	1	1
	E	378.7	315.9	44.1	14.9	0.0	1.4	2.4
	SMR	82‡	82‡	89	67	—	73	41
	CME							
	O	4	0	3	0	0	1	0
	E	8.4	0.7	4.0	0.4	0.1	3.1	0.1
Cancer of the	SMR	47	—	75	—	—	32	—
digestive tract	Cont							
(150-159)	O	90	82	6	2	0	0	0
	E	113.6	95.0	13.1	4.4	0.0	0.4	0.6
	SMR	79‡	86	46‡	45	—	—	—
	CME							
	O	26	1	23	0	0	2	0
	E	9.3	0.9	4.5	0.6	0.1	3.1	0.1
All respiratory	SMR	278‡	116	506‡	—	—	64	—
cancer	Cont							
(160-163)	O	115	93	18	4	0	0	0
	E	119.1	99.9	13.2	4.9	0.0	0.4	0.8
	SMR	97	93	137	82	—	—	—
	CME							
	O	7	1	3	0	0	3	0
	E	12.2	1.1	5.8	0.7	0.3	4.1	0.2
All other	SMR	57	91	52	—	—	73	—
cancer	Cont							
(140-149,	O	104	83	15	4	0	1	1
170-209)	E	146.0	121.1	17.8	5.6	0.0	0.6	1.0
	SMR	71‡	69‡	84	72	—	179	103
	CME							
	O	44	3	27	0	1	12	1
	E	68.2	5.7	32.2	3.7	1.0	25.0	0.6
Heart	SMR	65‡	53	84	—	101	48‡	154
disease	Cont							
(391-429)	O	663	541	101	18	0	2	1
	E	884.0	737.1	104.0	34.7	0.0	3.2	5.0
	SMR	75‡	73‡	97	52‡	—	63	20
	CME							
	O	4	0	1	0	0	3	0
All respiratory	E	9.7	0.8	4.6	0.5	0.2	3.6	0.1
disease except	SMR	41	—	22	—	—	82	—
cancer	Cont							
(010-012,	O	52	43	7	2	0	0	0
460-519)	E	128.5	107.0	15.3	4.9	0.0	0.5	0.7
	SMR	40‡	40‡	46‡	41	—	—	—
	CME							
	O	14	2	10	0	0	2	0
All	E	18.4	2.1	8.7	1.3	1.4	4.3	0.4
accidents	SMR	76	94	115	—	—	46	—
(E800-E949,	Cont							
E980-E999)	O	63	61	2	0	0	0	0
	E	144.8	114.5	23.4	4.3	0.0	0.7	1.9
	SMR	44‡	53‡	9‡	—	—	—	—
Other known and	CME							
ill-defined causes	O	11	0	7	0	2	2	0
(0-9, 13-136,	E	43.5	4.9	20.4	2.5	1.4	14.7	0.6
210-315, 320-	SMR	25‡	—‡	34‡	—	148	14‡	—
390, 430-458,	Cont							
520-794,	O	121	102	14	2	0	3	0
E950-	E	498.3	410.5	64.0	18.5	0.0	2.0	3.3
E978)	SMR	24‡	25‡	22‡	11‡	—	152	—

*International Classification of Diseases, Eighth Revision, World Health Organization, 1967.
†Man years-at-risk.
‡$P < 0.05$.

Table 7. — Deaths from Respiratory Cancer, Digestive Cancer, Other Cancer, Heart and Circulatory Disease, All Other Desease, and External Causes by Duration of CME Exposure at All Firms.

	Duration of CME Exposure (Yr.)					Combination X^2, 4 d.f.*	Linear Trend X^2, 1 d.f.*
	10-20	5-9.9	2-4.9	0.1-1.9	Control		
Respiratory Cancer							
Observed deaths	3	9	11	4	119	39.3	19.8
Expected deaths*	1.8	2.9	3.4	8.4	129.5	(p <.0001)	(p = .00001)
Relative risk	1.8	3.4	3.5	0.5	1.0		
Digestive Cancer							
Observed deaths	1	0	0	5	95	3.2	0.5
Expected deaths*	1.0	1.0	1.2	3.2	94.7	(p > .10)	(p > .10)
Relative risk	1.0	—	—	1.6	1.0		
Other Cancer							
Observed deaths	2	1	1	1	117	6.6	0.1
Expected deaths*	0.9	1.6	1.8	5.1	112.6	(p > .10)	(p > .10)
Relative risk	2.3	0.7	0.6	0.2	1.0		
Heart and Circulatory Disease							
Observed deaths	2	10	13	19	651	11.7	3.9
Expected deaths*	7.0	10.2	13.4	34.6	629.8	(p = .02)	(p = .05)
Relative risk	0.3	1.0	1.0	0.5	1.0		
All Other Disease							
Observed deaths	0	4	3	7	142	3.4	0.6
Expected deaths*	1.8	2.5	2.9	6.8	142.0	(p > .10)	(p > .10)
Relative risk	—	1.6	1.0	1.0	1.0		
External Causes of Death							
Observed deaths	1	1	4	14	104	9.5	0.0
Expected deaths*	1.0	1.5	2.4	8.2	110.9	(p = .05)	(p > .10)
Relative risk	1.1	0.7	1.7	1.8	1.0		
Man-years-at-risk	1405	2770	4388	15166	182173		

* Adjusted for company, age by decade, interval since onset of exposure by quinquennia. The Combination X^2 was calculated by the Mantel-Haenszel method[10] and the Linear Trend X^2 by the method of Tarone.[12]

tiates that CMME and BCME are human respiratory tract carcinogens.

Discussion

This study did not detect excess respiratory cancer at Firms 1, 3, 4, 5, and 6 (Table 6) where indications are that exposure levels were lower than at Firm 2, or among the groups with the lowest exposure levels at Firm 2 (Tables 8 and 9). This may indicate one of several possibilities: (a) a practical threshold of carcinogenic effect at some low dose level; (b) too small a sample to detect a small effect; or (c) too short a period of observation, since there is an apparent inverse relationship between exposure level and latency.[8 13] The available data do not permit one to exclude any of these possibilities. However, given the inverse relationship between exposure level and latency and the relatively small number of persons with low exposure who have been observed for 20 or more years (< 10% of man-years at risk at ≥ 20 years since onset of exposure for low exposure workers at Firm 2; < 5% of man-years at risk similarly defined at all other firms combined), it would be imprudent to view the data as supporting a threshold effect at this time.

The cases independently identified in our study included fourteen cases located by a separate approach by Figueroa et al,[14] and nineteen cases reported by Defonso and Kelton.[13] The 27 cases we had identified as occurring prior to January 1, 1973 in our overall study, with an additional one subsequently identified during 1973, but not included in the tables, and the six reported from a West Coast plant[16] give a total of 34 cases of lung cancer associated with exposure to these compounds in the United States. There have been two reports from other countries, one from Germany reporting eight cases of lung cancer (of which five involve worker exposure and three, laboratory exposure)[17] and a report from Japan that describes five cases of lung cancer in laboratory workers.[18] All in all, it appears that there have been at least some 47 cases of lung cancer in association with these compounds. Both of these compounds, BCME and CMME, have now been included in the NIOSH list of carcinogens.

One feature of the excess respiratory cancer risk at Firm 2 was the early age at death. The respiratory cancer SMR for ages 15-44 among CME-exposed workers was 1200 (seven observed, 0.58 expected), while for ages ≥ 45 the SMR was smaller (SMR = 357; 14 observed, 3.92 expected). The difference in SMR's is statistically significant, p < .05.[15]

It should be noted that the predominant histologic type of bronchogenic cancer reported in CME-exposed workers has been small cell-undifferentiated or oat cell carcinomas.[13 14 17 18 19] A similar predominance of this histologic type has been noted for bronchogenic cancers associated with radon daughters[20] and with nitrogen mustard.[21] By way of contrast, the predominant type associated with cigarette smoking is squamous cell carcinoma.

It is also noteworthy that most, but not all, of the men who developed lung cancer had smoked cigarettes. The fact that some nonsmokers are in the group and that the lung cancers occur at much younger ages and are of a different cell type than normally found with cigarette-induced lung cancers provide further evidence that BCME is the primary agent, rather than cigarette smoke.[22 23]

Until a short time ago, it appeared that BCME was an occupational health problem and not a general environmental health problem for the entire population. This was because most of the

Table 8. — Analyses of Respiratory Cancer Mortality at Firm 2 by Duration of CME Exposure for the Period Five or More Years Since Onset of Exposure.

	Duration of Exposure (Yr.)				
	10-19	5-9.9	2-4.9	0.1-1.9	Control
Observed deaths	3	7	10	3	18
Expected deaths*	0.2	1.9	2.8	6.7	29.4
Relative risk	26.6	6.0	5.7	0.7	1.0
Man-years-at-risk	97	1024	1981	5591	21909

Combination χ^2 = 81.8,* 4 d.f., p < .00001
Linear Trend χ^2 = 61.8,* 1 d.f., p < .00001

*Expected deaths and the Combination χ^2 calculated by the Mantel-Haenszel method[10] and the Linear Trend χ^2 by the method of Tarone,[12] with age (by decade) and interval since onset of exposure (by single year) as covariates.

Table 9. — Analyses of Respiratory Cancer Mortality at Firm 2 by Cumulative Weighted Exposure* for the Period Five or More Years Since Onset of Exposure.

	Cumulative Weighted Exposure				
	20-50	10-19.9	5-9.9	0.1-4.9	Control
Observed deaths	8	8	4	3	18
Expected deaths†	0.9	2.4	1.6	6.7	29.4
Relative risk	14.5	5.4	4.2	0.7	1.0
Man-years-at-risk	482	1398	1176	5637	21909

Combination χ^2 = 80.0,† 4 d.f., p < .00001
Linear Trend χ^2 = 75.6,† 1 d.f., p < .00001

*Cumulative weighted exposure = $\sum$ (duration x intensity of exposure) across all exposure periods up to the given man-year-at-risk.

†Expected deaths and the Combination χ^2 calculated by the Mantel-Haenszel method[10] and the Linear Trend χ^2 by the method of Tarone,[12] with age (by decade) and interval since onset of exposure (by single year) as covariates.

production of the compound was utilized by the corporation manufacturing it; little was sold outside the plant. However, gaseous mixtures of hydrochloric acid and formaldehyde may be present in a large number of biological and chemical laboratories, and these may combine to form BCME under certain conditions. The extent of hazard from the combination of formaldehyde and HCl to form BCME is unknown at present. Measurable concentrations of BCME have been found in atmospheric reaction mixtures containing the two reactants.[24,25]

The present data provide evidence that the duration and intensity of exposures sharply increase the carcinogenic risk (Tables 8 and 9). However, owing to the apparent inverse relationship between dose and latency period, the exposed population has not yet been followed long enough to adequately establish the risk associated with low level exposures. It is this which is of greatest concern today. The high-level exposures have been eliminated by the firms producing CMME, and the biological and chemical laboratories would have only low-level, chronic exposures. Thus the most important questions concerning BCME-CMME require further study of the exposed population.

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