An Industry-Wide Study of Respiratory Cancer in Chemical Workers Exposed to Chloromethyl Ethers [1,2]

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ABSTRACT—An industry-wide retrospective cohort mortality study was conducted on 6,152 chemical workers (2,460 exposed and 3,692 nonexposed) engaged in chloromethyl ether manufacture at 7 major U.S. companies between 1948 and 1980. A previous study at 6 companies from 1948 through 1972 reported excess respiratory cancer (RC) mortality and significant exposure-response relationships in exposed workers at 1 company (company 2). The present study, which extended follow-up of an additional 7 years for companies 1-6 and included company 7 for follow-up from 1953 through 1980, found excess RC mortality in exposed workers at company 2 [observed (Obs)=32, standardized mortality ratio (SMR)=430] and company 7 (Obs=9, SMR=603). External comparisons of RC mortality at both companies showed significant exposure-response relationships with respect to cumulative time-weighted exposure. At company 2, where the greatest number of RC deaths occurred, external comparisons showed that RC risk remained constant in relation to age at first exposure and decreased with increasing time since last exposure. With the use of Mantel-Haenszel and relative risk (RR) regression methods, internal comparisons at company 2 demonstrated significant findings of increasing RR with cumulative duration of exposure and cumulative time-weighted exposure and with decreasing time since last exposure. No association was found between RR and age at first exposure. An interesting finding was a significant negative interaction between cumulative time-weighted exposure and age at risk. The best-fitting logistic regression model for the exposed group predicted RR at 2.79 (95% confidence interval= 1.66-4.69) for workers with the mean cumulative exposure score of the 32 RC deaths (lagged by 6 yr) compared with those with negligible exposure (assuming mean age at risk of the RC deaths, 51 years old, and time since last exposure held constant). Qualitative assessment of the results suggests that chloromethyl ether exposure affects both an early as well as a late stage of a putative multistage respiratory malignant process.—JNCI 1987; 78:1127-1136.

Commercial-grade CMME and its 1-8% contaminant BCME are alkylating agents used in the chemical industry primarily in the manufacture of ion-exchange resins. Seven U.S. companies have been involved in the large-scale production of CMME, one since as early as 1948 and seven by 1958. Experimental studies in animals and bacterial test systems have established the carcinogenic and mutagenic properties of both compounds, with BCME by far the more potent of the two (*1-2*). Several epidemiologic studies investigating the human carcinogenicity have provided evidence in support of chloromethyl ethers as human respiratory tract carcinogens (*3-17*). After the carcinogenicity of CMME and BCME was well established in the early 1970's, their use became restricted; and hermetically closed and remotely controlled equipment was required to ensure safe handling. At this time only, two producers of CMME remained; however, two other companies continued using CMME. Travenius has written an extensive review on the formation, occurrence, and prevention of BCME in the chemical industry (*18*).

A previous retrospective cohort mortality study from 1948 through 1972 of 1,827 CMME-exposed workers and 8,870 control workers at six of the seven companies reported excess RC mortality in CMME-exposed workers at only one company (company 2) where higher exposures occurred (*12*). Using U.S. white male rates for comparison, Pasternack et al. (*12*) reported a significant excess mortality from RC (Obs=23, SMR=506). Internal comparisons of RC mortality showed significant exposure-response relationships between risk of RC death and cumulative duration of exposure and cumulative time-weighted exposure score. Analyses of RC latency (time from first CMME exposure to RC death) in relation to exposure level demonstrated an inverse relationship between cumulative exposure and median latency.

For better characterization of RC risk at low-dose levels (because of an apparent inverse relationship between latency and exposure level) and for further examination of the relationship between important time-related factors, including age at first exposure and time since last exposure, follow-up on this cohort was extended 7 years

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ABBREVIATIONS USED: BCME=bis(chloromethyl)ether; CI=confidence interval; CMME=chloromethyl methyl ether; df=degree of freedom; Exp=expected number; ICD=International Classification of Diseases; Obs=observed number; OCMAP=Occupational Cohort Mortality Analysis Program; PY=person-year-at-risk; RC=respiratory cancer (ICD-8 codes 160-163); RR=relative risk; SMR=standardized mortality ratio; SRR=standardized rate ratio; SSA=Social Security Administration.

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and the seventh major company was included for follow-up from 1953 through 1980.

SUBJECTS AND METHODS

Study subjects.—The study population was defined from company records and consisted of CMME-exposed and -nonexposed workers at six companies included in the previous study (1948-72) and consisted of additional workers employed at these companies since January 1, 1973 (*12*). The study population also included exposed and nonexposed workers at the seventh producer company for follow-up from January 1, 1953, through December 31, 1980. The exposed group consisted of all workers with known or presumed exposure to CMME during the time of CMME manufacture or use at the company. Due to varying record keeping practices by companies, different methods were used to select controls or nonexposed workers. A major goal in the control selection process at each company was to achieve a size two to three times the size of the exposed group while maintaining comparability with respect to employment history, birth cohort, and type of work. This approach was not feasible at companies 5, 6, and 7 where all nonexposed workers served as controls and at company 4 where all workers were presumed to have been exposed. For the present study, the oversized control group at company 1 in the previous study was reduced from 6,408 to 916 by frequency matching (i.e., stratified random sampling) on dates of birth and first employment.

Demographic information and work histories.—Information requested from companies included Social Security number and name; sex; race; dates of birth and employment; job classification at first employment (hourly or salaried); company record status at the study's closing date (employed, retired, separated, dead); vital status at the study's closing date (alive, dead, unknown); and date of retirement, separation, or death when applicable. The closing date or end of follow-up for companies 1-6 was September 1, 1979. For company 7, the closing date was December 31, 1980. Information on workers' smoking histories was also requested, along with copies of death certificates if available. For exposed workers, additional information was requested on job titles, starting and stopping dates, and exposure intensities.

Exposure assessment.—The main route of exposure to CMME in the chemical industry is through inhalation. Another less likely route is skin absorption. Few measurements were made of workplace air concentrations before the early 1970's. Travenius estimated that workroom air concentrations may have ranged from 1 to 10 ppm for CMME and from 10 to 800 ppb for BCME (*18*). Varying amounts of information were available from the seven companies in this study on exposure intensities since CMME operations began. Only two companies had air-measurement data, mostly on air level concentrations of BCME and CMME in the early 1970's. Despite the paucity of air-level concentration data, a rank order estimate of exposure intensity (i.e., score) by job classification was developed at each company. The exposure classification scheme reflected changes in CMME manufacturing processes, these changes impacting exposure levels at each company. Factors considered in the assignment of exposure scores included the changing proximity of jobs in relation to CMME operations, degree of enclosure, production-schedule frequency and quantity, and prevailing wind patterns or air movement. A 7-point exposure scale at company 2 and an 11-point exposure scale at company 7 was adopted. It was not possible to assign actual concentrations to exposure scores or define relative differences between companies.

Mortality ascertainment.—Follow-up resources included the SSA, telephone directories, state motor vehicle bureaus, voter registration records, post offices, and employment records. Company 4 did not provide identifying information on workers, and follow-up was limited to an SSA search. Workers lost to follow-up were considered alive up to the date of last contact, which in many cases was the date of employment termination. Underlying causes of death were classified according to the Eighth Revision of the ICD (*19, 20*). For RC deaths, up to three letters were sent to hospitals, attending physicians, and coroners' offices, requesting copies of medical records for the determination of histologic cell type.

Statistical methods.—Analyses using external controls: The overall mortality and selected cause-specific mortality of CMME-exposed and -nonexposed workers at each company separately and at all companies combined was analyzed using a modified life-table computer program, OCMAP (*21*). In OCMAP, workers contribute one PY for each year they are alive between the cohort entry date and withdrawal. The cohort entry date for exposed workers was their date of first exposure to CMME. For nonexposed workers, the entry date was their date of first employment or date of first use or manufacture of CMME at the company, whichever occurred later. The withdrawal date corresponded either to the date of death, to the date last known alive for those lost to follow-up, or to the study's closing date for known survivors. PYs were specific for sex, race, age group, calendar period, and years since entry into the cohort. Expected deaths were derived from corresponding U.S. population death rates specific for cause, sex, race, and quinquennia of age and calendar period. SMRs were calculated as the ratio of Obs to Exp of deaths multiplied by 100. OCMAP permitted analysis of cause-specific mortality in relation to latency and cumulative time-weighted exposure score—summation of the product of exposure score and duration (mo) across all jobs with exposure divided by 12, a quasi-dose unit. For exposure-response analyses, exposure categories (low, medium, high) were chosen so that PYs were approximately equally distributed. This approach resulted in low (<0.6), medium (0.6-5.0), and high (>5.0) cumulative time-weighted exposure score categories at company 2.

The age-time specific cohort death rates were extracted manually and used in direct standardization in a manner described by Doll et al. (*22*). The method reported by Breslow et al. was used to test for linear trends in SMRs (*23*), and the method of Smith and Doll was used to test for linear trends in excess absolute risk, (Obs−Exp)/PY (*24*). SRRs were obtained when examining RC Obs and Exp of deaths by age at first exposure and time since last exposure for workers at risk from ages 30 through 69 years old (*25*). Mantel's extension of the Mantel-Haenszel χ^2 test was used to test for trends in SRRs (*26*). An extension of Smith and Doll's method for testing trends in excess absolute risk was used to test for trends in age-adjusted excess absolute risk when examining age at first exposure and time since last exposure (*27*). Two-sided *P*-values were used for all tests of significance involving external and internal controls.

Analyses using internal controls: For internal comparisons of RC mortality, an adaptation of the Mantel-Haenszel procedure was used to compute summary chi-squares and RRs in exposure subgroups (*26, 28, 29*). This procedure uses a life-table approach for internal comparisons, and workers may contribute PYs to more than one exposure category as they advance through follow-up. Exp of deaths are internally derived for each category of the exposure factor based on the combined experience of all categories. Adjustment for confounding variables is achieved by separately calculating Exp of deaths for each stratum of the confounder and summing over all strata in each exposure factor category for a total Exp of deaths (assuming no association of mortality with the exposure factor). The analyses accommodated the time-dependent nature of the exposure variables, included adjustment for confounding variables, yielded tests for linear trends among exposure subgroups, and provided mean and median life-table latency estimates of RC mortality (*30, 31*).

Two major variables were considered as confounders in analyses of exposure-response relationships. These were age at risk and time since first exposure. Age at risk is important because incidence rates for epithelial tissue cancers increase in proportion to the fifth or sixth power of age (*32*). Time since onset of exposure is also important since most chronic diseases require a latent period before the effect of exposure on risk becomes apparent. For RC with a latency of at least 10 years, inclusion of early PYs in analyses yields diluted risk estimates because no effects of exposure are expected at this time. Another consequence of including early PYs is the potential alteration of the exposure-response curve, since early PYs are concentrated in lower exposure categories. To allow for some minimal latency, analyses excluded the first 5 PYs. Properly accounting for latency involves not only excluding early PYs but also exposure lagging so that exposure increments in the preceding lag number of years have diminished or have no effect on risk (*30, 33*). Some lag period is justified since recent exposures may be less important to current risk. An exploratory series of exposure-response analyses with varying lag periods was performed to determine if lagging was appropriate and if so the proper choice of the lag period (*30*).

The final phase of the analyses involved a time-matched case-control methodology using conditional logistic regression (*34, 35*). As a preliminary step in case-control analyses, 32 CMME-exposed RC cases at company 2 were classified according to birth year and calendar year at death. Complete risk sets included all CMME-exposed workers who were at company 2 with the same birth year as that of the corresponding case and who were alive in the calendar year of that for the case's death. Matching was relaxed to within 5 years of the case's birth year when too few controls were available. A total of 622 matched controls were obtained for the 32 "complete" risk sets. For 32 "partial" risk sets, a random number of 5 controls per case was selected (without replacement) from the noncase members of the risk set, for a total of 160 matched controls. Time-dependent exposure variables for noncases were computed at the same age as that of the corresponding case, and exposure lags of 5, 6, and 8 years were used in regression analyses. Time-matched conditional logistic regression analysis using complete risk sets for each case, as used here, is equivalent to Cox's RR regression method (i.e., proportional hazards model with stratification on birth year and age as the time variable) for full cohort analysis (*36*). Parallel analyses using complete risk sets and partial risk sets (i.e., 5:1 matching) were done to compare results for methodologic purposes.

Cumulative time-weighted exposure was considered to be the primary exposure variable—incorporated as a time-dependent covariate in the manner indicated above. A number of other variables were also evaluated and considered for inclusion in the RR logistic regression model (*see* table 11). Two time-related factors, age at first exposure and age at risk, were viewed as potential modifiers of effect; thus their interaction with cumulative CMME exposure was examined. The square of the standardized regression coefficient (χ^2 with 1 df) was used to assess the statistical significance of covariates included in the regression analyses. With these constraints in mind, the choice of the most appropriate model was based on the overall goodness of fit as measured by the likelihood ratio statistic.

RESULTS

Cohort Characteristics and Follow-up

The numbers of CMME-exposed and -nonexposed (control) workers by company are given in table 1. Of the total cohort, 40% were exposed workers. Of the total study population, 97% were white and 96% were male workers. Of female workers, 96% were from company 7, where 26% of all workers were female. On the closing date, 32% of the workers were employed, 56% had separated or retired, and 12% were known dead. Follow-up completion was greater than 95% for all companies. Of 744 known deaths, death certificates were obtained for 98%. Table 2 shows the distribution of PYs for exposed and nonexposed workers by company. Roughly, half of the total PYs were from company 2, where the average duration of follow-up was 20 years. The average dura-

TABLE 1.—*Number of exposed and control workers by company*

Study group	Company 1	2	3	4	5	6	7	Total
Exposed	203	762	129	215	531	67	553	2,460
Control	713	2,023	287	0	131	276	262	3,692
Total	916	2,785	416	215	662	343	815	6,152

tion of follow-up ranged from 10 years at company 7 to 24 years at company 1.

Overall and Cause-Specific Mortality

At all companies combined, significant excess mortality occurred only in exposed workers for all malignant neoplasms (SMR=160, 95% CI=126-200) due to excess RC mortality (SMR=301, 95% CI=224-398). This excess was attributed to excess RC mortality in exposed workers at company 2 (SMR=430, 95% CI=296-616) and company 7 (SMR=603, 95% CI=276-1,144).

A significant excess total mortality occurred at company 4, where all workers were exposed and 16 deaths were observed compared to 6.9 expected. Follow-up for this company was independently handled, and 25% of total mortality was of unknown cause because death certificates could not be obtained. The only significant excess mortality in nonexposed workers occurred at company 7, where deaths from cancer of the digestive organs and peritoneum were 2 compared to 0.2 expected (SMR=1,000, 95% CI=121-3,612).

Significant deficits in mortality at all companies combined were confined to nonexposed workers for all causes of death (SMR=89, 95% CI=80-97) and for all accidents (SMR=49, 95% CI=31-72). Nonexposed workers at company 3 had significant deficits in mortality for all causes of death (SMR=60, 95% CI=46-76) and for all circulatory disease (SMR=58, 95% CI=40-80). The other significant deficit occurred in nonexposed workers at company 2 for all accidents (SMR=18, 95% CI=6-42). The only significant deficit in a company's exposed group was at company 3 for all causes of death (SMR=42, 95% CI=18-83).

Respiratory Cancer Mortality: Exposure-Response, Latency, and Time-Related Factors

External Analyses

A total of 90 RC deaths occurred, including 52 CMME-exposed workers and 38 CMME-nonexposed workers. Among 32 exposed cases with RC deaths with verifiable cell type, the highest proportion of cell types was oat cell (38%). In 20 nonexposed cases with RC deaths, the highest proportion was adenocarcinoma (31%).

At companies 2 and 7 where RC mortality was significantly elevated, RC SMRs were analyzed in relation to latency and cumulative time-weighted exposure. Tables 3 and 4 show RC SMRs for companies 2 and 7, respectively. In each table, over all the latency categories, significantly elevated SMRs appear only in the highest exposure category. In other analyses varying the boundaries of cumulative exposure, significant excesses were not confined to the highest exposure category. No RC deaths occurred in nonexposed workers at company 7. The trend for increasing RC mortality with increasing cumulative exposure at company 7 was not significant for the Obs/Exp ratio, but was significant for the excess absolute risk, (Obs−Exp)/PY, (P=.002). At company 2, the trend was highly significant for increasing RC mortality with increasing cumulative exposure for the Obs/Exp ratio ($P<.0001$) and the excess absolute risk ($P<.0001$). All RC deaths at company 2 (table 3) occurred after 5 years' latency with the largest SMR in the 15- to 19-year (not shown) latency category. At company 7 (table 4), one RC death occurred before 5 years' latency, with the largest SMR occurring in the 5- to 9-year (not shown) latency category.

Since the number of RC deaths at company 7 was only 9, the following results pertain to analyses of RC mortality at company 2. Table 5 shows Obs and Exp of deaths, at this company, among nonexposed and exposed workers by era and age at risk. During both eras of risk, 1948-64 and 1965-79, exposed workers younger than 45 years of age had SMRs of 1,300, whereas exposed workers in the age-at-risk category of 45-64 years old had SMRs of 300 to 400.

Table 6 presents data on RC mortality by age at first exposure. The trend test for SRR with increasing age at first exposure was not significant. Similarly, the trend test for the age-adjusted excess absolute risk was not significant. Table 7 shows RC deaths by time since last exposure. Both SRR and the age-adjusted excess absolute risk show a statistically significant decrease with increasing time since last exposure.

Internal Stratification Analyses

Internal comparisons of RC mortality at company 2 are shown in tables 8-10. Analyses of Obs and Exp of deaths by cumulative duration of exposure and cumulative time-weighted exposure were performed controlling for age at risk by decade and for 5-year interval since

TABLE 2.—*PYs by company*

Study group	Company 1	2	3	4	5	6	7	Total
Exposed	3,068	15,564	2,705	2,340	8,173	1,066	5,795	38,711
Control	18,773	39,961	6,899	0	2,076	3,987	2,655	74,351
Total	21,841	55,525	9,604	2,340	10,249	5,053	8,450	113,062

TABLE 3.—*Respiratory cancer SMR at company 2 by cumulative time-weighted exposure score and time since entry*[a]

Time since entry, yr		Cumulative time-weighted exposure score				
		Control	Low	Medium	High	Total
<5	Obs	0	0	0	0	0
	Exp	0.32	0.10	0.14	0.07	0.64
	SMR	0	0	0	0	0
5-14	Obs	5	0	0	10	15
	Exp	2.13	0.40	0.56	0.69	3.78
	SMR	235	0	0	1,449[b]	397[b]
15-24	Obs	8	2	4	13	27
	Exp	5.39	0.77	1.25	1.59	9.00
	SMR	148	260	320[c]	818[b]	300[b]
≥25	Obs	8	1	0	2	11
	Exp	9.60	0.16	0.48	1.22	11.46
	SMR	83	631	0	163	96
Total	Obs	21	3	4	25	53
	Exp	17.44	1.42	2.44	3.58	24.88
	SMR	120	211	164	699[b]	213[b]

[a] Test for trend in SMR: $\chi^2=46$, $P<<.0001$. Test for trend in (Obs−Exp)/PY: $\chi^2=65$, $P<<.0001$.
[b] $P<.01$.
[c] $P<.05$.

TABLE 4.—*Respiratory cancer SMR at company 7 by cumulative time-weighted exposure score and time since entry*[a]

Time since entry, yr		Cumulative time-weighted exposure score				
		Control	Low	Medium	High	Total
<5	Obs	0	0	1	0	1
	Exp	0.02	0.04	0.08	0.05	0.18
	SMR	0	0	1,284	0	563
5-19	Obs	0	1	0	5	6
	Exp	0.14	0.05	0.19	0.74	1.13
	SMR	0	2,000[b]	0	676[c]	531[c]
≥20	Obs	0	0	0	2	2
	Exp	0.09	0.00	0.00	0.34	0.43
	SMR	0	0	0	588	464
Total	Obs	0	1	1	7	9
	Exp	0.25	0.09	0.28	1.13	1.74
	SMR	0	1,104	361	622[c]	517[c]

[a] Test for trend in SMR: $\chi^2=.67$. Test for trend in (Obs−Exp)/PY: $\chi^2=9.35$, $P=.002$.
[b] $P<.05$.
[c] $P<.01$.

TABLE 5.—*Respiratory cancer SMR at company 2 by era and age at risk*[a]

Era of risk	Age at risk, yr	Control			Exposed		
		Obs	Exp	SMR	Obs	Exp	SMR
1948-64	30-44	1	0.5	204	3	0.2	1,304[b]
	45-64	6	2.5	245[c]	3	0.9	330[c]
	65-84	2	0.7	303	0	0.1	0
1965-79	35-44	0	0.8	0	5	0.4	1,316[b]
	45-64	10	9.1	110	19	4.8	395[b]
	65-84	2	3.8	52	2	1.1	190
Total		21	17.4	120	32	7.5	430[b]

[a] Exp of deaths based on U.S. rates.
[b] $P<.01$.
[c] $P<.05$.

entry (≥5 yr since entry). Cumulative exposures were lagged 6 years, the lagging period where the χ^2 test for trend in exposure-response was largest in prior analyses using a series of time-lagged (yr) cumulative time-weighted exposures. Lagging exposures by other intervals (2-10 yr) and no lagging resulted in similar findings. Table 8 shows a highly significant trend of increasing Obs/Exp ratios with increasing cumulative duration of exposure ($P<.0001$). Similarly, a highly significant trend of increasing Obs/Exp ratios with increasing cumulative time-weighted exposure is evident as shown in table 9 ($P<.0001$).

When RC mortality was analyzed in relation to age at first exposure—after adjusting for age at risk, for cumulative time-weighted exposure lagged by 6 years, and for interval since entry (≥5 yr since entry)—Obs/Exp ratios increased with increasing age at first exposure (χ^2 trend=4.99, $P=.03$). However, the trend disappeared when the time-dependent variables, average exposure intensity (cumulative time-weighted exposure/cumulative duration) and cumulative duration of exposure, replaced cumulative time-weighted exposure as adjustment variables in the same analysis (χ^2 trend=1.05). Results from the analysis of RC deaths by time since last exposure are given in table 10. Obs/Exp ratios decreased with increasing time since last exposure after controlling for age at first exposure, for cumulative time-weighted exposure, and for interval since entry (≥5 yr since entry) (χ^2 trend=3.45, $P=.06$).

With a follow-up potential of 31 years, the cumulative percent mortality from RC in exposed workers was about 7%. Text-figure 1 gives life-table median latency estimates (and their associated 95% CIs) in exposed workers in four cumulative time-weighted exposure categories. Median latency estimates decrease with increasing cumulative exposure score. While not shown, mean latency estimates similarly decrease with increasing cumulative exposure; exposed workers with cumula-

TABLE 6.—*Respiratory cancer mortality in exposed workers at company 2 by age at first exposure*[a,b]

Specification	Age at first exposure, yr					
	<25	25-29	30-34	35-39	≥40	Total
Obs	3	4	11	5	9	32
Exp	0.5	0.8	1.5	1.7	2.9	7.4
Obs/Exp	6.5	4.8	7.4	2.9	3.1	4.3
(Obs−Exp)/10^4 PY[a]	6.0	8.5	30.6	14.0	27.8	15.8
SRR[c]	1.7	3.4	6.7	3.2	3.4	4.6
(Obs−Exp)/10^4 PY*	9.0	15.0	35.7	16.9	18.1	24.3

[a] Exp of deaths based on U.S. rates specific for age and calendar period.
[b] Test for trend in SRR: $\chi^2=.41$. Test for trend in (Obs−Exp)/10^4 PY*: $\chi^2=.24$. *Directly standardized to exposed group, ages 30-49 and 50-69 yr.
[c] Directly standardized to U.S. population, ages 30-49 and ages 50-69 yr.

TABLE 7.—*Respiratory cancer mortality in exposed workers at company 2 by time since last exposure*[a,b]

Specification	Time since last exposure, yr						
	0-1	2-4	5-9	10-14	15-19	≥20	Total
Obs	7	5	4	4	9	3	32
Exp	0.6	0.3	0.7	1.1	1.6	3.2	7.5
Obs/Exp	12.7	16.1	5.7	3.7	5.6	0.9	4.3
(Obs−Exp)/10^4 PY[a]	17.5	22.9	10.8	11.4	35.6	—	15.7
SRR[c]	7.4	8.7	4.8	3.0	6.0	2.0	4.5
(Obs−Exp)/10^4 PY*	39.0	45.7	25.0	15.5	31.5	10.5	23.7

[a] Expected deaths based on U.S. rates specific for age and calendar period.

[b] Test for trend in SRR: $\chi^2=5.07$, $P=.02$. Test for trend in (Obs−Exp)/10^4 PY*: $\chi^2=6.17$, $P=.01$. *Directly standardized to exposed group, ages 30-39, 40-49, 50-59, and 60-69 yr.

[c] Directly standardized to U.S. population, ages 30-39, 40-49, 50-59, and 60-69.

tive exposure scores in excess of 15 had significantly shorter mean latencies (18 yr) than workers with scores of 15 or less (22 yr) ($P<.05$).

Internal RR Regression Analyses

RR logistic regression analyses using matched risk sets included time-dependent exposure variables and variables for the interaction between cumulative time-weighted exposure and both age at first exposure and age at risk. *See* table 11 glossary for meanings of the following variables. The best-fitting model included four variables with exposure lagged 6 years: EXPCUM, EXTORISK, AGERISK, and AGEDOSE. Table 12 gives regression coefficients and standard errors along with the 1 df χ^2 (square of the standardized regression coefficient) for variables in this model, using complete and partial risk sets. All variables were significant except AGERISK, a matching variable. Since the distribution of cumulative exposures was skewed, a logarithmic transformation of cumulative exposure was also examined. The fit of the models was less satisfactory than those using untransformed measures.

Text-figures 2 and 3 graphically illustrate implications of this model based on complete risk sets. Text-figure 2 shows the relationship between the increasing RR of RC death and cumulative time-weighted exposure ranging from 0 to 50. RRs were calculated for workers with mean age at risk of 51 years old and with time since last exposure fixed. From the equation defining this curve, $\mathrm{RR}=\mathrm{Exp}\ (.083\times \mathrm{EXPCUM}-.070\times \mathrm{EXTORISK}+.133\times \mathrm{AGERISK}-.009\times \mathrm{AGEDOSE})$, workers with the mean EXPCUM of 12.37 (i.e., the mean of the 32 RC deaths lagged by 6 yr) have an RR of 2.79 (95% CI= 1.66−4.69) compared to exposed workers with negligible (i.e., with zero) EXPCUM. Exposed workers could have an effective exposure of zero because of exposure lagging; zero exposure can also be obtained as an artifact of the model resulting from extrapolation. Text-figure 3 displays the negative interaction between cumulative exposure and age at risk. The curves illustrate that the increase in RR with cumulative exposure varies according to age at risk and that the rate of increase in RR is higher among younger workers. For not constraining the effect of age to be linear in either its main effect or its interaction with cumulative exposure, the analysis was redone using indicator variables for age and its interaction with cumulative exposure. The finding of a significant negative association remained. The negative interaction also remained when the model was augmented by inclusion of the variable INTENSITY (*see* table 11 for definition). This inclusion was done to ensure that the interaction was not reflecting differences in exposure patterns.

Alternatives to the exponential (i.e., log linear) form of RR were examined, and neither an additive linear model nor a linear model with exponential transformation of parameters resulted in improved goodness of fit (*35*).

TABLE 8.—*Respiratory cancer mortality at company 2 by cumulative duration of exposure for 5 or more years since onset of exposure*[a]

Specification	Cumulative duration of exposure, yr					
	Control	<1	1-4	4-9	>9	Total
Obs	21	4	13	11	4	53
Exp	35.6	7.2	5.7	3.7	0.8	53
Obs/Exp	0.6	0.6	2.3	3.0	4.9	1.0

[a] Adjusted for attained age and interval since entry. Exposures lagged 6 yr. Test for trend in Obs/Exp: $\chi^2=40$, $P<.0001$.

TABLE 9.—*Respiratory cancer mortality at company 2 by cumulative time-weighted exposure score for 5 or more years since onset of exposure*[a]

Specification	Cumulative time-weighted exposure score				
	Control	Low	Medium	High	Total
Obs	21	3	4	25	53
Exp	35.7	3.5	6.0	7.9	53
Obs/Exp	0.6	0.9	0.7	5.5	1.0

[a] Adjusted for attained age and interval since entry. Exposures lagged 6 yr. Test for trend in Obs/Exp: $\chi^2=62$, $P<.0001$.

TABLE 10.—*Respiratory cancer mortality in exposed workers at company 2 by time since last exposure for 5 or more years since onset of exposure*[a]

Specification	Time since last exposure, yr						
	0-1	2-4	5-9	10-14	15-19	≥20	Total
Obs	7	5	4	4	9	3	32
Exp	5.6	1.7	5.4	8.4	5.9	5.1	32
Obs/Exp	1.3	3.0	0.7	0.5	1.5	0.6	1.0

[a] Adjusted for age at first exposure, cumulative time-weighted exposure, and interval since entry. Test for trend in Obs/Exp: $\chi^2=3.45$, $P=.06$.

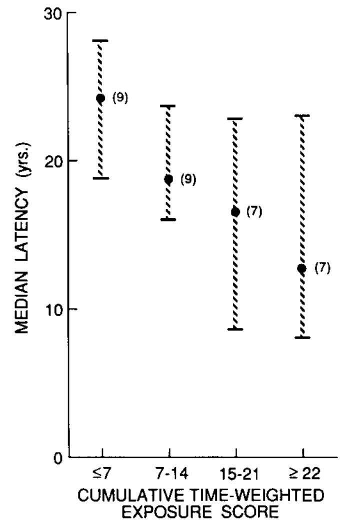
TABLE 11.—*Glossary of exposure variables used in conditional logistic regression analyses of partial and complete risk sets in exposed workers at company 2*

Variable	Description
EXPCUM	Cumulative time-weighted exposure score.
DURCUM	Cumulative duration of exposure (yr).
EXTORISK	Time from last exposure to yr at risk (yr).
AGEXP	Age at first exposure.
INTENSITY	Average exposure intensity=EXPCUM/ DURCUM.
EXPGAP	Exposure gap (%)=(time from first exposure to last exposure−DURCUM)/time from first exposure to last exposure.
AGERISK	Age at risk.
AGEDOSE	Interaction term for EXPCUM and AGERISK=EXPCUM×(AGERISK−51).
AGEXPDOSE	Interaction term for EXPCUM AND AGEXP=EXPCUM×(AGEXP−34).

DISCUSSION

This study found excess RC mortality at companies 2 and 7. Company 2 was the only company in the previous study where excess RC deaths occurred; company 7 was the newly included company. In the previous study (*12*) of six companies, high exposures were reported at company 2. Occupational exposure to CMME at this company has been described elsewhere (*9, 16*). On the basis of information from interviews and plant inspections on the scale and nature of CMME operations, the largest production facilities in the present study were at companies 1, 2, and 7. Company 1 was distinct from the other two in its early adoption and maintenance of a superior industrial hygiene program. While no quantitative data were available on actual exposure conditions at companies 2 and 7, the two other largest producer companies, excess RC mortality at these companies presumably was a consequence of higher exposures.

The nature of the exposure data in this study demonstrates the limitations of epidemiologic observations, especially in risk assessment at low-exposure levels. Actual measurements of exposure concentrations, which are more relevant in characterizing a worker's dose, were not available. In the relative exposure scoring system used in this study, errors in the determination of workers' exposures derived from two sources. By far the most important source involved the accuracy of exposure score assignment, which was, in effect, a rank order measure of intensity subject to historical exposure uncertainties. The second, probably negligible compared to the first, involved the accuracy of data from the work history records on dates and job locations.



TEXT-FIGURE 1.—Life-table estimates of median latency for respiratory cancer deaths at company 2 by cumulative exposure. Number of deaths *in parentheses*. 95% CIs are given.

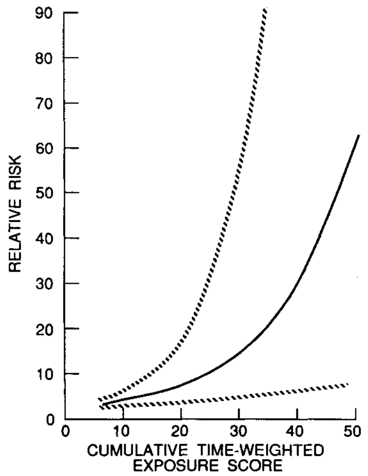
The finding of a high proportion of oat cell carcinomas in exposed workers is consistent with previous reports of CMME exposure associated with a predominance of this cell type and with reports of occupational populations exposed to asbestos, arsenic, chromium, and uranium (i.e., radon daughters) where proportions of oat cell type are higher than general population estimates of 20-25% where the occurrence of oat cell carcinoma is extremely rare in nonsmokers (*37-38*).

Unfortunately, smoking as a confounding factor or its role in effect modification could not be evaluated, since only limited information on smoking histories was obtained. However, a small follow-up study of 125 exposed workers at company 2 has suggested such an

TABLE 12.—*Conditional logistic regression analyses of 32 exposed respiratory cancer cases (deaths) matched to exposed controls (*m*) at company 2 in complete risk sets (*m*=622) and 5:1 matching in partial risk sets (*m*=160)*[a]

	Complete risk sets		Partial risk sets	
Variables[b]	B (SE)	χ^2 (df=1)[c]	B (SE)	χ^2 (df=1)[c]
EXPCUM	.083 (.021)	15.1	.102 (.033)	9.5
EXTORISK	−.070 (.029)	5.7	−.094 (.034)	7.7
AGERISK	.133 (.202)	0.4	.139 (.192)	0.5
AGEDOSE	−.009 (.003)	10.0	−.011 (.004)	6.7

[a] Exposures lagged 6 yr. B=regression coefficient.
[b] *See* table 11 for definitions.
[c] Square of the standardized regression coefficient.



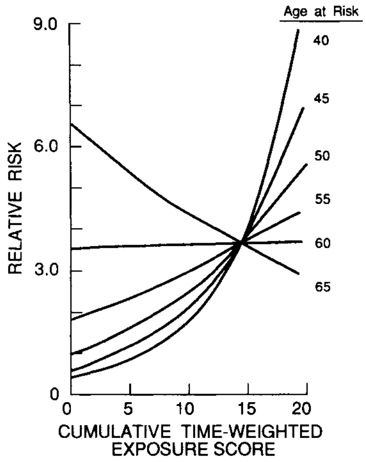
TEXT-FIGURE 2.—Relationship between RR of respiratory cancer death and cumulative exposure at company 2, by use of best-fitting RR regression model. RRs calculated for workers with mean age at follow-up of 51 yr and time since last exposure held constant. Exposures lagged 6 yr. *Dashed curves,* 95% confidence bands.

effect (*15*). When considering smoking as a potential confounder in lung cancer studies, Doll has stated that differences in group smoking habits are unlikely to be responsible for lung cancer RRs of more than twice that of the general population's (*39*). In theoretical calculations of the impact of uncontrolled confounding from smoking on lung cancer risk, Axelson concluded that uncontrolled smoking is unlikely to have a major effect on elevated risk measures on the order of fivefold to tenfold (*40*). In view of the present study's risk estimates (RC SMR in exposed workers of 430 at company 2 and 603 at company 7) and with no gross distortion assumed for among the exposure subgroups, confounding by smoking is expected to have little practical significance when interpreting results.

The time-matched RR regression analysis used in the present study permitted control for factors such as age at risk and birth cohort, which are associated with RC risk and cumulative exposure. This approach resulted in an estimated RR=2.79 for exposed workers (mean cumulative exposure=12.4; *see* text-fig. 2) compared to those with negligible exposure. This estimate is lower than the SMR that equals 430 for exposed workers at company 2, on the basis of U.S. rates. Note, however, that local (i.e., Philadelphia) RC mortality rates are about one-third higher than U.S. rates.

No published studies are available on the efficiency of time-matched "case-control-within-a-cohort" designs comparing m-controls (*see* table 12 for meaning) per case (partial risk sets) to all available controls (complete risk sets) when exposure variables are continuous. For binary exposure variables, the efficiency of designs with variable case-control ratios depends on the magnitude of the estimated RR and the exposure probability of controls in risk sets (*23*). For RR estimation between 1 and 10 and a control exposure probability of 0.30, the efficiency of a matched design with 5 controls per case is expected to be about 80% compared to a full cohort analysis. Ten controls per case should yield efficiencies of greater than 90%. These theoretical estimates are consistent with this study's selection of 5 controls per case yielding regression parameter estimates with efficiency (ratio of variances of the estimated regression coefficients) ranging from 40 to 110% (*see* table 12).

Several important findings emerged from the analysis of excess RC death at company 2. One striking feature was the early age at RC death of exposed workers (mean age=51) during both eras at risk, 1948-64 and 1965-79. RC SMRs for workers younger than 45 years of age were significantly elevated—1,300 as compared to 300 in workers at older ages during both eras. This finding along with the inverse relationship noted between life-table median latency estimates of RC mortality and cumulative time-weighted exposure argues in favor of CMME exposure acting to accelerate the carcinogenic process. A particularly interesting finding from RR regression analyses was the presence of a significant negative interaction between cumulative time-weighted exposure and age at risk. The apparent decline in the effect of exposure with age suggests that CMME-induced RRs vary with age and that enhanced exposure-response relationships may be evident in younger workers. To examine this possibility, Mantel-Haenszel analyses of RC deaths in exposed workers by cumulative duration of exposure and cumulative time-weighted exposure were redone, restricting workers' PYs to ages at risk of less than 60 years old. The exposure-response gradients as indexed by the Mantel trend test were magnified by a factor of 2 to 3 in three restricted analyses compared to analyses using all workers' PYs. No trends were evident with respect to cumulative duration and cumulative time-weighted exposure in workers with age at risk of 60 years old and above.



TEXT-FIGURE 3.—Relationship between RR of respiratory cancer death and age at risk for increasing cumulative exposure at company 2, by use of best-fitting RR regression model. RRs are relative to the risk of a 51-yr-old worker with cumulative exposure equal to zero and with time since last exposure held constant. Exposures lagged 6 yr.

This interaction has been used as an indirect means of assessing whether the carcinogenic exposure accelerates the clinical appearance of respiratory tract tumors (*36*). The significant negative estimate for this interaction in the present study is consistent with the finding of significantly elevated SMRs in younger workers (<45 yr old) and with the inverse relationship between median latency and cumulative time-weighted exposure. Together they substantiate the hypothesis that CMME exposure hastens the carcinogenic process.

An alternative explanation relates to host susceptibility. Older workers may be at lesser risk to exposures due to unmeasured environmental factors, social habits, or depletion of the pool of those most susceptible to CMME-induced respiratory cancer. A similar finding of a significant negative interaction between age at risk and exposure duration, although not intensity, was recently reported in a study of smoking and lung cancer in New Mexico (*41*). Older smokers were also reported at reduced risk in a study of lung cancer in British physicians (*42*). Older uranium mine workers also have been reported to have an apparent decrease in RR of lung cancer death from exposure to radon daughters (*43, 44*). Thomas (*45*), in his analysis of data on lung cancer mortality in relation to chrysotile asbestos exposure and smoking habits, showed an apparent decrease in RR from asbestos (and smoking) in workers in the older age-at-risk groups.

Smoking-related cancers may provide another explanation for the observed inverse relationship between exposure-response and age at risk. Since CMME-related lung cancers have much shorter latent periods than smoking-related cancers, it seems likely that CMME-related cancers would largely appear at earlier ages than smoking-related ones. The latter are most common in the 7th decade of life. If the cancers that occur after 60 years of age are primarily due to smoking, then the apparent lack of exposure-response in older workers would be explained. This explanation is consistent with the observation made by Weiss and Boucot (*6*) that the more highly exposed workers were more likely to be nonsmokers and light cigarette smokers—perhaps because of self-selection on the basis that both high CMME exposure and heavy smoking were apt to be an intolerable combination for some of the workers.

Two other important findings relate to the behavior of excess RC risk in relation to age at first exposure and time since last exposure. Examination of time-response relationships with respect to these two variables is especially relevant when predicting, within a multistage model framework, whether the carcinogenic exposure acts at an early or late stage of a multistage process. Use of the multistage model for the analysis of epidemiologic data has only recently been suggested and applied to occupational cohort studies (*45-48*). Both external and internal comparisons of this study found no association between excess RC risk and age at first exposure. While higher RR estimates in older ages at first exposure were shown in Mantel-Haenszel analyses controlling for cumulative time-weighted exposure, this association reflected the tendency of workers in older age at first exposure categories to be employed in the years of CMME production when exposure intensities were highest. (When intensity and cumulative duration of exposure were controlled for, no association was demonstrated.) The absence of any age-at-first-exposure effect is consistent with multistage predictions that CMME exposure acts at an early stage of the carcinogenic process to initiate changes in stem cells on the pathway to cancer.

The finding of an inverse association between excess RC risk and time since last exposure persisted in all phases of the analysis. This temporal pattern has been viewed as a means of assessing the possibility of repair in the latent damage caused by exposure (*49*). The negative relationship observed in this study is also consistent with the hypothesis that CMME exposure acts at a late stage by further transforming previously accumulated damaged cells. Interpretation of excess RC risk in relation to time since last exposure is complicated by factors such as health status, which may influence a worker's decision to terminate exposure or employment. High RR estimates associated with shorter times since last exposure may reflect the tendency of exposed workers with RC to terminate exposure or employment due to illness. However, this "terminating" effect was not demonstrated in analyses of RC deaths in nonexposed workers by time since last employment. Rather, a constant RR was found across time since last-employment categories.

The preceding RR methods of analysis have assumed that CMME exposure acts multiplicatively on underlying age- and time-specific RC death rates. Use of an additive RR model did not suggest any improvement of linear modeling over a multiplicative approach.

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