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Epidemiologic Study of Vinyl Chloride Workers: Mortality through December 31, 1972

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A population of 10,173 men, employed in 37 plants, was identified as having worked for at least one year in jobs involving probable exposure to vinyl chloride monomer (VCM) prior to January 1, 1973. Of the 9677 men whose vital status was determined, 707 were known to have died. For 699, death certificates were obtained. The standardized mortality ratio (SMR) for all causes was 89, that for all malignancies was 104. The only type of malignancy found in significant excess was in the category of malignant neoplasms of the brain and other parts of the nervous system; 12 deaths occurred where 5.9 were expected, for an adjusted SMR of 203. There were slight but inconclusive upward trends in all malignancies, and for malignancies of the respiratory tract, digestive tract, and central nervous system associated with reported levels of maximum exposure to VCM. When groups in whom less than 20 years had elapsed from the first exposure were compared with those with 20 or more elapsed years, and 25 or more elapsed years, no significantly different SMR's were detected for major primary sites of malignancy. Plans for an updated study of mortality, to include deaths in the period 1973–1979 are briefly discussed.

The epidemiologic studies of vinyl chloride workers summarized in this report were carried out during the period June 15, 1973 through December, 1976 by Tabershaw-Cooper Associates, Inc., and Equitable Environmental Health, Inc., for the Manufacturing Chemists Association (MCA) (now the Chemical Manufacturers Association).

An initial report, dealing with 8,384 workers from 34 plants, was prepared May 3, 1974 (*1*). A summarized version (*2*) was published in 1974. The study population was subsequently increased and follow-up was improved. After an interim report in 1976 (*3*), a final report based on 10,173 workers was prepared in January, 1978 (*4*). In all of these studies the observation period ended December 31, 1972.

Participating Plants

In mid-1973, the MCA identified 43 plants in the United States, belonging to 19 companies, which either produced vinyl chloride monomer (VCM) or used it in the production of poly(vinyl chloride) (PVC). Of these, 34 were included in the initial study; four were excluded because they had been in operation less than 5 years, one had stopped production in 1966, and in others information on job histories or exposures was deficient. Three plants were subsequently added to the original 34, so the 1978 report included 37 plants. Of these, 11 produced only VCM, 18 produced only PVC, three produced both, and five plants produced homopolymers and copolymers, with or without VCM and PVC.

The geographical distribution of those in the study, as shown in Table 1, indicates a disproportionate number of workers from the South, particu-

Table 1. Geographical distribution of 10,173 vinyl chloride workers in 1978 report.

Region	U.S. males (1970), %	Workers in study, %
Northeast	23.8	25.9
North Central	27.9	18.4
South	30.9	64.8
West	17.4	0.9

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larly from the East South Central and West South Central States. The South, with 30.9% of the total U.S. male population in 1970, supplied 64.8% of the study population.

Of the plants participating, the one which had first begun operations with VCM had done so in 1935, the most recent was in 1968. Four plants had begun in 1942 or earlier, 13 in 1952 or earlier, and 27 in 1962 or earlier.

The Study Population

The objective was to include all male employees whose work had involved exposure to vinyl chloride for at least one year prior to December 31, 1972. The designation of jobs which involved exposure to VCM was made by staff members at individual plants or by a corporate industrial hygienist. In approximately two thirds of the study population, TCA staff copied personnel records on individuals who were identified as having been in exposed jobs. In the remaining portion of the population, detailed information on exposed individuals was provided by plant personnel. The methods used in doing this are described in the complete reports cited earlier.

Study Period

The period of time in which the work-force of a plant was included in the study depended upon the date it began making or using VCM and also upon the earliest date when personnel records were complete for all employees, if that was later than the foregoing. This was done to eliminate periods when there was differential record retention of workers terminated, deceased, or retired. The end of the study period was December 31, 1972.

Estimates of Exposure

In each plant, every job and location with VCM exposure was graded in terms of probable exposure. Originally, a job history form was designed in the expectation that the exposures could be quantified in parts per million. This proved impossible in practice. However, for each plant, jobs and locations involving the highest exposures could be classified as "high", and other jobs classified as "medium" or "low" relative to the "high". It is recognized that this subjective classification is of questionable validity in categorizing the past and present exposure of a given worker. From the number of months spent in jobs with classifications of 3 (high), 2 (medium) and 1 (low), a number of exposure categories were developed for use in later analyses. As shown in Table 2, individual exposures in various papers were classified in a number of ways, including the maximum level at which an individual had been exposed for at least 12 months, an integrated or cumulative exposure, and an exposure index based on the cumulative score divided by the number of months.

Table 2. Bases for development of VCM exposure categories.

Criterion	Unit
Duration of exposed employment	Months
Interval from beginning of exposure to end of observation	Months
Estimated maximum level to which an individual was exposed for at least 12 months, classified as high, medium, or low.	High Medium Low
Integrated or cumulative exposure, crediting 1 for each month at low, 2 for each month at medium and 3 for each month at high exposure to VCM	1 2 3
Exposure index (EI) = Cumulative score/average number of months	

Follow-Up

As is customary in historical prospective studies, all who had left employment were traced when possible. Methods included form letters sent by mail and use of retail credit follow-up. For the first report, there was insufficient time to utilize Social Security Administration records, but for subsequent reports such follow-up was used.

In the first, or 1974 report, 85% of the study population was located; for the final or 1978 report, the percentage had been increased to 95%.

The mortality calculations were based only on those who were successfully traced, which is equivalent to assuming that mortality among those not found was the same as among those who were found. This usually, but not always, results in some overestimation of mortality.

Calculation of Standardized Mortality Ratios

Each worker in the study, i.e., everyone whose vital status was ultimately known, was considered to have been under observation from the date on which he attained a year of exposed employment or from the date when his plant's records were complete, whichever came later. Observation periods ended December 31, 1972, or on the date of death, whichever occurred first.

Observed deaths were classified by cause according to the 7th (1955) revision of the International

Classification of Diseases. The expected number of deaths by cause were calculated by using age and cause-specific mortality rates for United States males with the same birth years and age distribution for the years 1950, 1955, 1959, 1965, 1967 and 1970.

Deaths for which death certificates could not be obtained were assumed to have the same cause distribution as the death certificates that were obtained. Appropriate increases were made in calculated SMR's.

The statistical significance of the deviation of each SMR in the study population from an expected value of 100 was tested by a method derived from Chin Leong Chiang (*5*). The formula for determining the standard error of the SMR was

$$SE = \sqrt{\frac{100 \times SMR}{\text{No. expected deaths}}}$$

If an observed SMR differed from 100 by more than 1.96 standard errors, it was regarded as significant at the 5% level; if it differed by more than 2.57 standard errors, it was regarded as significant at the 1% level. SMR's based on fewer than five observed deaths were usually not tested for significance.

Results

Table 3 summarizes the numbers of individuals, success of follow-up, person-years and deaths in successive phases of the study. The number of deaths per 1000 man-years of observation, which in general reflects the age distribution of the work force, suggests that the proportion of older individuals increased in the study population as it was expanded and follow-up improved. Even so, the 5.88 deaths per 1000 man-years indicates that a relatively young population was being observed; the U.S. male population 20 and above has about 11 deaths per 1000 man-years. Some published occupational epidemiologic studies will show 20 or more.

Table 3. Numbers of individuals, success of follow-up, person-years, and deaths analyzed in successive phases of the study.

	Report 1, 1974	Report 2, 1976	Report 3, 1978
No. of men	8,384	9,109	10,173
No. found	7,128	8,714	9,677
% found	85%	96%	95%
No. deaths	352	525	707
No. certificates	328	511	669
Total man-yr	77,846	94,221	120,203
Deaths/1000 man-yr	4.52	5.57	5.88

Duration of Exposure to VCM

In the first report, only 15.2% of those studied had begun exposure prior to 1950 (22 years before end of the observation period). In the third report, 33.4% had had 20 or more years for observation since exposure began. This resulted from finding more early employees by improved follow-up, and the inclusion of an older group from one plant in the augmented population.

Standardized Mortality Ratios

Standardized mortality ratios (SMR's) for selected causes of death are shown in Table 4, based on the 352 deaths analyzed in Report 1 and the 707 deaths analyzed in Report 3. Results in the first report led Tabershaw and Gaffey (*1*) to conclude that vinyl chloride may be associated with cancer of a number of sites, notably digestive cancer, respiratory cancer, cancer of other and unspecified sites (primarily those of the central nervous system) and lymphomas. This was based not on statistically significant excesses in each category, but upon apparent trends when different levels and durations of exposure were compared.

With the enlarged study group, the SMR for malignancies in the entire population dropped slightly, as did the SMR's for malignancies of the buccal cavity and pharynx, digestive tract and respiratory tract. However, tumors of the brain and central nervous system, when examined separately, still appeared to be in excess.

A number of analyses were done in the third report in an attempt to sharpen the focus on work exposures.

There appeared to be a slight but definite trend in the SMR's for all malignancies, malignancies of the digestive tract, the respiratory tract, and for other and unspecified sites with increasing levels of estimated maximum exposure (Table 5). However, the numbers of expected deaths were relatively few in some categories and the groups differed widely in age distribution as manifested by deaths per 1000 person-years.

To reduce dilution of the study population by men whose exposures had begun only recently, a separate analysis was carried out on those whose exposures to VCM had begun 20 years or more prior to 1972, and on those whose exposures had begun 25 years or more prior to 1972 (Table 6).

Another analysis was made of a population of men who had worked in plants producing only PVC

(where VCM exposures were presumably high), whose exposures had begun 20 years or more before the end of the study period and who had been reported as having medium or high VCM exposures for a year or more (Table 7). This group experienced 210 deaths where 249.7 had been expected. The pattern of mortality from malignancies was not appreciably different from that of the total study group.

In summary, increasing the study population and

Table 4. Observed and expected deaths (O/E) and standardized mortality ratios for selected causes (SMR's adjusted for missing death certificates).

Cause (ICD Mo, 7th Rev)	1974 Report		1978 Report	
	O/E	SMR	O/E	SMR
All causes	352/467	75[a]	707/795	89[a]
All malignancies (140–205)	79/77	110	139/141	104
Buccal and pharynx (140–148)	5/2.84	189	5/5.19	102
Digestive (150–159(	19/21.7	94	29/40.8	75
Respiratory (160–164)	45/44.3	112	25/23.9	107
Other and unspecified (190–199)	17/11.75	155	28/20.2	147
Brain and CNS (193)	—	—	12/5.9	203[b]
Leukemia and aleukemia (204)	3/3.77	85	9/6.65	143
Lymphomas (200–203, 205)	6/6.06	106	11/10.36	112
Major cardiovasc. renal (330–334, 400–468, 592–594)	155/207	80[a]	347/385	95
Cirrhosis liver (581)	3/15.6	21	14/26.5	56[b]
No. of workers	7,128		9,677	
Person-yr	77,846		120,203	

[a]Significant at 1% level.
[b]Significant at 5% level.

Table 5. Observed and expected deaths (O/E) and standardized mortality ratios for selected causes as related to maximum level of reported exposure to vinyl chloride monomer (SMR's adjusted for missing death certificates).

Cause (ICD Mo, 7th Rev)	Reported maximum exposure VCM					
	Low		Medium		High	
	O/E	SMR	O/E	SMR	O/E	SMR
All malignancies (140–205)	65/71	98	56/53.5	109	18/16.5	112
Digestive (150–159)	14/20.9	72	10/15.6	67	5/4.4	117
Respiratory (160–164)	19/22.2	92	19/17.1	116	7/5.1	141
Other and unspecified (190–199)	11/9.9	119	13/7.5	180	4/2.7	150
No. of workers	4,925		3,021		1,731	
Person-yr	58,741		39,927		21,535	
Deaths/1000 person-yr	6.16		6.6		3.9	

Table 6. Analysis of deaths based on time from beginning of exposure to end of study period (SMR's adjusted for missing death certificates).

Cause of death (ICD No. 7th revision)	< 20 yr		> 20 yr		> 25 yr	
	No.	SMR	No.	SMR	No.	SMR
All causes	158	77[a]	549	93	393	96
All malignancies (140–205)	31	95	108	107	73	104
Digestive (150–159)	8	96	21	70	16	74
Respiratory (160–164)	8	80	37	116	22	100
Other and unspecified (190–199)	6	108	22	162	13	146
Leukemia (204)	3	155	6	137	4	137
Cardiovascular-renal	68	84	279	97	211	105

[a]Significant at 1% level.

improving follow-up did not strengthen the suggested associations between VCM exposure and malignancies other than those caused by hepatic angiosarcoma, as will be pointed out later, and a suggested association with tumors of the brain and central nervous system.

Table 7. Deaths in plants producing only PVC, based on workers whose first exposures began before 1952, and who had medium or high VCM exposures (SMR's corrected for missing death certificates).

Cause of death (ICD No, 7th revision)	O/E	SMR
All causes	210/249.7	84[a]
All malignancies (140–205)	46/46.04	106
Digestive (150–159)	9/13.63	70
Respiratory (160–164)	17/14.75	122
Other and unspecified (190–199)	10/ 6.33	167
Cirrhosis of liver (581)	6/7.95	80

[a]Significant at 1% level.

Angiosarcomas

Nine angiosarcomas are known to have occurred in the U.S. during the study period, i.e., prior to 12/31/72. As shown in Table 8, eight of these were found in the study, but only three were coded as angiosarcoma on the death certificate. However, four others were coded as tumors of the digestive tract. Unfortunately, two were coded 230x so as to fall out of the category for malignant tumors of the GI tract, and one was coded as cirrhosis of the liver.

As shown in Table 8, the angiosarcoma which was not found was in a man who had died in 1961. We have not determined how he failed to be in the study population. The years of exposure for the eight cases ranged from 4 to 23 years, while elapsed time from beginning of exposure to death ranged from 16 to 24 years.

Tumors of the Central Nervous System

The 12 tumors of the brain had been diagnosed on death certificates as follows: glioblastoma multiforme, 4 (1 confirmed by autopsy); astrocytoma, 2 (2 au-

Table 8. Angiosarcoma deaths and data on VCM exposures.

ICI No.[a]	First exposed	Year of death	Time from first exposure to death, yr	Total yr exposure	Est. max. exposure	Age at death
USA-02	1955	1971	16	14	High	38
-04	1949	1968	19	18	High	43
-05	1944	1964	20	20	High	52
-07	1944	1968	24	14	Med	45
-10	1946	1970	24	23	Low	70
-11	1951	1968	17	17	Med	60
-12	1949	1969	20	20	High	50
-16	1950	1969	19	4	High	41
-08	—	1961		Not in study group		

[a]*Number used in registry periodically prepared by J. Stafford, Imperial Chemical Industries Ltd., Plastics Division.*

Table 9. Summary of brain tumor deaths (ICD No. 205) and data on VCM exposures.

Case no.	First exposed	Yr of death	Time from 1st exposure to death, yr	Total yr exposure	Max. exposure	Age at death
1	1958	1972	14	5	Low	67
2	1967	1972	5	5	Low	43
3	1957	1968	11	7	Med	54
4	1941	1958	17	6	Med	61
5	1950	1970	20	8	High	43
6	1956	1971	15	3	Med	54
7	1947	1971	24	23	Low	57
8	1945	1963	18	18	High	44
9	1949	1971	22	21	Low	58
10	1947	1971	24	23	High	49
11	1935	1956	21	18	Low	59
12	1935	1967	32	22	Low	57

topsies); ependymoma of the 4th ventricle (autopsy); "malignant brain tumor" or "carcinoma of the brain," 5 (with no autospies). This group is currently being made the subject of more rigorous review. The information obtainable from our records, summarized in Table 9, is insufficient to prove or disprove a cause-and-effect relationship between occupational exposure and these tumors.

Conclusions

A study of 707 deaths in a population of 9677 men who had worked for one year or more in jobs involving exposure to vinyl chloride and whose vital status had been determined as of December 31, 1972, did not show a significant excess of deaths due to malignancies. There did appear, however, to be a significant excess of tumors of the brain and central nervous system, based on 12 such deaths. There also continued to be slight but inconclusive trends toward higher SMR's for deaths from digestive tract and respiratory tract tumors associated with maximum levels of past exposure. No striking changes in malignancy patterns were apparent when analyses were directed toward individuals in whom 20 to 25 years had elapsed since first exposure. The results suggest that, except for a proven association with hepatic angiosarcoma and a strongly suggestive association with central nervous system tumors, vinyl chloride probably is not associated with significant excess cancers of other sites.

It should be emphasized that the epidemiologic study summarized in this report was planned, the populations defined, and analysis under way before cases of hepatic angiosarcoma had been diagnosed in workers exposed to vinyl chloride (*6*). An update is scheduled with inclusion of additional deaths in the cohort during the years 1973 through 1979. The study can be improved by a separate analysis of data from the plants which began operations before 1960, and by separating, insofar as possible, exposures to vinyl chloride monomer, polyvinyl chloride, and various copolymers. It is also hoped that criteria for defining exposure and for rating levels of exposure can be improved to permit better indices of integrated exposure.

This study was begun June 15, 1973 under a contract between the Manufacturing Chemists Association, 1825 Connecticut Avenue, N.W., Washington, D.C. (now the Chemical Manufacturers Association) and Tabershaw/Cooper Associates, Inc. It was continued under later contracts with TCA and with Equitable Environmental Health, Inc.

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