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Mortality Experience of Workers in a Vinyl Chloride Monomer Production Plant

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The evidence associating exposure to vinyl chloride with the risk of tumors of various sites, including lung cancer, is inconsistent. In 1976 a mortality follow-up study of 464 white males employed in a vinyl chloride monomer (VCM) production plant since 1948 was conducted. Vital status was ascertained for 100% of the cohort. Eight (28.5%) of the 28 deaths observed were due to malignant neoplasms. No angiosarcomas or other liver tumors were observed. A statistically significant excess was noted for malignant neoplasms of the respiratory system (p=.03). The effect of smoking, duration of exposure to VCM, level of exposure, and the combined effect of duration and level of exposure were analyzed separately. A five-year latency requirement was maintained for all analyses except for the smoking analysis. Levels of exposure to VCM prior to 1971 were estimated from monitoring data available for the period 1971-75 by extrapolating the relative levels for job classifications backwards in time. Smoking histories were not available for 27.6% of the cohort. When it was assumed that all "unknowns" smoked, a significant excess of respiratory cancer was still observed (p=.05). When the minimum latency period of five years restricted analysis to the mortality experience after five years from date of initial exposure to VCM for the 314 employees satisfying this criterion, the excess of respiratory cancer was moderate but not significant (p=.06). Both a longer duration and a higher level of exposure during the first five years following the date of initial exposure were associated with a statistically significant excess of respiratory cancer (p=.02 and p=.03, respectively). However, when duration and level of exposure were combined in an overall exposure index, the results were not significant (p=.07). The discrepancy in the results from the dose-response analyses may be due to the potential error in the estimated levels and the small number of events observed, but the results do suggest that a relationship exists between exposure to VCM and respiratory cancer.

The association of vinyl chloride and the development of angiosarcoma of the liver has been well documented. Vinyl chloride has also been described as a multi-system carcinogen causing tumors in the lung, central nervous system, and hematopoietic systems.[1-4] Most recently it has been suggested that vinyl chloride is a chemical mutagen and teratogen.[5]

Early in 1974, three cases of angiosarcoma of the liver, an extremely rare tumor, were reported among workers in a vinyl chloride polymerization plant.[6] All three workers had at one time been involved in the manual cleaning of polymerization reactors.[7] In a recent report from Canada, this pattern was confirmed in 10 cases of angiosarcoma of the liver.[8] Seven of the workers cleaned reactors, and the rest were either operators or maintenance personnel. Initial exposures for all cases occurred before 1962.

Following early reports, several epidemiologic studies of workers exposed to vinyl chloride were initiated. The first of these investigations was a proportionate mortality study by Monson and Peters.[1] The study involved 161 deaths from two vinyl chloride plants: a plant producing vinyl chloride monomer (VCM), and the polymerization plant where the initial cases of angiosarcoma were identified. The deaths, which occurred between 1947 and 1974 among active and retired employees, were analyzed for excesses in cancer mortality. Monson and Peters reported a 50% excess in the proportion of deaths due to all malignant neoplasms. Specific excesses were found for liver and biliary tract, lung and brain. These results suggested that vinyl chloride may be a multi-system carcinogen, although the excesses reported were based on propor-

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tionate mortality ratios, which are not specifically a measure of risk.

In 1974, Tabershaw and Gaffey[7] published results of an industry-wide historical prospective study of 8,384 workers involved in the manufacture of vinyl chloride and vinyl chloride polymers in 33 plants. The study was restricted to individuals who had at least one year of exposure to vinyl chloride before December 31, 1972. Excesses for the specific causes of death were not statistically significant, except for cancer of the digestive system, consisting primarily of previously identified angiosarcomas of the liver. The excesses for cancers of the respiratory system and lymphomas, while not statistically significant, were suggestive of possible risks which appeared to be related to the dose of vinyl chloride. Dose was measured by an average monthly exposure score determined for each worker and based on a subjective estimate of relative levels of exposure for jobs within each plant. The authors quite correctly point out that exposure levels between plants may not have been comparable. In addition, the inclusion of many workers with inadequate latency periods, some as short as one year, may have obscured the exposure effects. This study had been extended to more adequately evaluate latency and to include more complete information regarding the study cohort.[8] The final report is therefore based upon a total group of 10,173 employees from 37 plants, of whom 9,677 (95.1%) were successfully traced. While there were no statistically significant excesses of site specific malignancies except for liver (angiosarcoma) and brain, the risk of malignant neoplasms of the respiratory system does appear to be associated with intensity of exposure—a standardized mortality ratio of 92 for the low intensity category compared to that of 141 for the high intensity category.

In a study presented at the New York Academy of Science conference on vinyl chloride, Nicholson et al[9] described an excess in total mortality and in overall cancer mortality among 257 men with five or more years of exposure occurring before 1963 in a polymerization plant. In addition, they reported three deaths due to angiosarcoma of the liver, one due to cancer of the brain, two due to lymphoma and none due to lung cancer.

Two additional mortality studies[10,11] resulted in essentially negative results. One of these, a mortality follow-up study of 594 employees at the Dow Chemical Company polymer plant in Midland, Michigan, by Ott et al,[10] revealed excesses in overall cancer only in the high exposure category (> 220 ppm). In this study, evaluation of the effects of vinyl chloride was confounded by the fact that 72 of the 594 employees had also been exposed to arsenic, a known carcinogen affecting the respiratory system. Analysis of the mortality experience among the cohort without the aresnic exposed workers indicated a statistically significant increase in mortality due to malignant neoplasms, particularly lung cancer, among workers exposed to levels of vinyl chloride above 220 ppm.

Duck et al[11] found no significant excesses in overall or cause specific mortality in a British Petroleum chemical industry population of 2,120 male workers exposed to vinyl chloride. The analysis included a separate evaluation of mortality for autoclave workers (reactor cleaners), polymer plant workers, and monomer plant workers. The authors observed no relationship between length of exposure and risk of cancer. This particular analysis, however, has been challenged as methodologically inappropriate due to the misallocation of person-years.[12]

In 1975, the National Institute for Occupational Safety and Health reported results from a follow-up study of 1,294 workers at four polymerization plants, two of which also produced vinyl chloride monomer.[4] All workers included in the study had been exposed for five or more years with at least ten years' latency period (ten years since initial exposure). Significant risks for cancer of the liver, lung, brain and central nervous system were found for workers with 15 years of latency. An increased risk was also observed for lymphatic and hematopoietic cancers.

By contrast, the study reported by Fox and Collier[13] of 7,000 workers exposed to vinyl chloride in the British industry did not indicate that cancers other than those of the liver were associated with exposure to vinyl chloride monomer. In this study initial exposures for a fairly high proportion of the workers occurred after 1960, and follow-up by three of the eight factories was poor. In addition, the determination and analysis of exposure were questionable in that a measure of level of exposure ascertained retrospectively and subjectively by the participating industries was used rather than duration of exposure, some combination of level and duration, or specific job classifications.

Some background information on vinylidene chloride (VDC), a structurally similar chlorinated hydrocarbon, is also important in this review since exposures to VDC at lower concentrations often occur simultaneously in the VCM production area studied. VDC is a known hepatotoxin[14] and has been recently described as a genetically active compound in the bacterial test systems used.[15,16] The literature contains only one report on the health and mortality experience of workers exposed to VDC without simultaneous exposure to vinyl chloride.[17] In this study of 138 workers, Ott et al[17] reported no excess mortality due to malignant neoplasms or adverse health effects attributable to exposure to vinylidene chloride.

Based upon this review of the literature, the evidence associating vinyl chloride with the risk of tumors at various sites is strongly suggestive. However, some results, particularly those reported for lung cancer, are inconsistent, and several questions remain regarding the strength of the association and the effects of varying levels of exposure. The present study was undertaken to further delineate the carcinogenic risk associated with exposure to vinyl chloride by utilizing more definitive information regarding duration and level of exposure, to evaluate the effects at lower doses, and to address some of the methodological problems found in other studies.[18,19,20] Although it would be desirable to evaluate the specific effects of vinylidene chloride in the population studied, unfortunately, it is not possible to separate its effects from those of vinyl chloride.

Materials and Methods

Subjects of this investigation were persons employed in a vinyl chloride monomer production plant of the Dow

Chemical Company. The facility began operations in 1948 when a small area of the chemical plant was dedicated to this operation and to the simultaneous production of vinylidene chloride. The criterion for inclusion in the study was that an employee had worked at least two consecutive months in the vinyl chloride department between August 1, 1948, and September 25, 1975.

Company personnel rosters were used to enumerate the cohort of persons who had worked in the department since 1948. Company records were utilized to compile information on date of birth, race, sex, and inclusive dates for each job and departmental assignment during employment. The vital status of employees who had left the company was determined by standard follow-up techniques.

Death certificates were requested for all deceased employees. The certificates were coded according to the 8th Revision of the ICDA and reviewed by a nosologist provided by the Environmental Epidemiology Branch of the National Cancer Institute. Pathologic or clinical information was requested from the attending physician or hospital named on the death certificate for all cancer deaths. Clinical and pathology reports received were reviewed by the UTMB Pathology Department.

Personnel monitoring data at the plant since 1971 and information from the Department of Industrial Hygiene and plant supervisors allowed the grouping of all classifications with respect to potential exposure to vinyl chloride. Seven job classification groups with similar potential for exposure within each group were identified. An industrial hygienist and a panel of five persons who had long-term experience with the production process and job assignments ranked the seven categories in terms of potential for exposure to vinyl chloride during the periods 1948-70 and 1971-75. The categories were listed randomly and each member of the panel independently ranked the seven groups. The rankings were consistent from one time period to the other, suggesting that although actual levels of exposure may have changed over time, relative levels had not and the recent monitoring data could be extrapolated backwards in time.

Job classifications considered to have a relatively high potential for exposure included control lab personnel, loaders, and production personnel (control operators). A control lab worker sampled the product at several stages during the production process and analyzed it for purity. Much of this sampling is now automated. In earlier years it was common for the control lab worker to deliberately, but briefly, expose himself to vapors by methods such as the "sniff" test for sample purity, thereby incurring very high short-term exposures. Loaders are exposed to vinyl chloride in the process of connecting or disconnecting pipelines to tank cars and tank trucks. The control operators are responsible for monitoring the production process, performing minor maintenance procedures in order to insure proper functioning of equipment, and preparing equipment for major repairs. Maintenance workers generally have lower eight-hour time weighted average exposures than do the control operators, but they often experience relatively high short-term exposures to vinyl chloride while repairing worn equipment. Employees with the lowest exposures are those in supervisory positions followed by persons in the development lab. The assignments of supervisory personnel are such that they are not required to spend extended periods of time in the production area or to be physically close to the source of vapor emissions. Development lab personnel usually work with small quantities of vinyl chloride in evaluating the product or production process. The time weighted average exposures to vinyl chloride by job classification, based upon available monitoring data, were averaged for the period 1971-75 and are summarized in Appendix A.

Table 1. — Follow-up Status of 464 Workers in a VCM Production Plant, August 1, 1948 - September 25, 1975.

Still employed at company		291
No longer employed, alive		145
Retired	27	
Released	118	
Deceased		28
Died while employed	17	
Died after leaving company	11	
Died while retired	0	
Unknown status		0
Total		464

Standardized mortality ratios (SMR's) were computed in the analysis of the mortality experience of the cohort. Expected numbers of deaths for the study population were calculated by applying 1950-59 and 1960-69 age-cause specific death rates for white males in Texas to the observed distribution of person-years of observation, categorized into five-year age groups. Significance testing is based on the assumption of a Poisson distribution for the observed number of deaths, utilizing a one-sided test of significance. In the analysis of the data, the effect of smoking, duration of exposure, level of exposure and the combined effect of duration and level of exposure were each considered separately, although a five-year latency requirement was maintained for all analyses except that of the effect of smoking.

Results

Four hundred eighty-one males were identified for inclusion in the study population. Evaluation of mortality risks was restricted to white males due to the small number of nonwhite males (17) in the cohort. The ascertainment of vital status for the 464 white males as of the cutoff date was 100% complete, and is described in Table 1. Follow-up investigation was required for 129 individuals who were no longer employed. Eleven of the total 28 deaths occurred among this group of 129 workers.

Table 2 shows the distribution of the 28 deaths by underlying cause. Eight deaths (28.5%) were due to malig-

Table 2. — Distribution of 28 Deaths Observed Among Workers in a VCM Production Plant by Cause of Death.

Causes of Death (ICDA 8th Revision)	No. of Death
Cancer (140-209)	8
Heart (390-458)	10
Accident (E800-E999)	7
Other (038.9, 330.4 and 513)	3
All causes	28

Table 3. — Case Summaries of Eight Cancer Deaths Observed Among Workers in a VCM Production Plant.

Underlying Cause of Death (8th Revision ICDA)	Date of Death	Age at Deaths (Years)	Date of Initial Exposure to VCM	Age at Initial Exposure (Years)	Years of VCM Exposure	Interval from Date of Initial Exposure to Date of Death (Years)	Smoking History	Pathologic Confirmation
1. Cancer of lung (162.1)	4-21-74	60	11-15-48	34	7.3	25.4	Yes	Yes — X-ray report presumptive
2. Primary carcinoma lungs (162.1)	12-01-58	53	10 18-48	43	10.1	10.2	Yes	No reports available
3. Carcinoma of lung (162.1)	5-21-73	58	8-31-51	36	21.7	21.8	Yes	No reports available
4. Alveolar cell carcinoma (162.1)	11-14-71	52	2-11-57	38	10.9	14.8	Yes	Yes — Biopsy
5. Malignant mediastinal tumor unclassified with generalized metastasis (163.1)	1-28-63	21	1-15-62	20	1.0	1.0	Unk	Yes — Autopsy
6. Carcinoma of colon (153.8)	4-12-71	48	11-17-52	29	.6	18.4	Yes	No — Biopsy report not received
7. Carcinoma of lip metas. to lung & neck (140.9)	9-03-66	31	8-01-62	27	4.1	4.1	Unk	No reports available
8. Metastatic squamous cell cancer, palate (145.1)	9-28-71	57	4-18-49	35	6.0	22.4	Unk	Yes — Autopsy

nant neoplasms, four of which were confirmed upon review of autopsy, biopsy or x-ray reports by the UTMB Pathology Department. Case summaries for the eight cancer deaths are shown in Table 3. No angiosarcomas or other liver tumors were observed. The eight persons who died of cancer were initially exposed to vinyl chloride prior to 1963, and the four with lung cancer, prior to 1958. Length of exposure to vinyl chloride ranged from seven years to 22 years in the cases of lung cancer, and the interval from date of initial exposure to date of death ranged from 10 years to 25 years. Six of the 28 deaths reported here, including two of the eight deaths due to malignant neoplasms (malignant teratoma and alveolar cell carcinoma), occurred among a special subgroup of 165 workers exposed to 1,4-dioxane. These data were reported in an earlier mortality study of workers exposed to 1,4-dioxane.[21]

Table 4a shows the observed and expected numbers of deaths by cause. For overall mortality, the standardized mortality ratio was 11% lower than expected. The total number of observed deaths due to malignant neoplasms was not significantly different from the expected (8 observed vs. 5.19 expected). There is, however, a statistically significant difference between observed and expected for malignant neoplasms of the respiratory system (5 vs. 1.73, $p = .03$).

Effect of Smoking

The excess in mortality due to respiratory cancer necessitates a consideration of the effect of smoking as an explanatory variable. Differential patterns of smoking among the vinyl chloride workers as compared to the Texas white male reference population might account for this excess. The case summaries indicate that four of the five workers who died of respiratory cancer had a history of smoking; the smoking status of the fifth worker is unknown (Table 3). In addition, smoking histories are not available for a large proportion (27.6%) of the 464 white males in the total cohort. Because of the missing data on smoking status, it is difficult to identify the effect that smoking patterns may have on the results obtained.

The potential effect of smoking on the expected mortality was examined, however, by noting the consequence of an assumed pattern of smoking for the "smoking unknown" category. Assuming the availability of standard age specific rates for the two smoking categories, the expected mortality, under the conservative assumption that all those in the "smoking unknown" category were actually smokers, was computed. Unfortunately, an appropriate standard set of age specific rates according to smoking status was not readily available, but a reasonable set of rates was constructed from available information. The construction of these standard rates is described in Ap-

Table 4a. — Observed and Expected Numbers of Deaths Among 464 White Males in a VCM Production Plant, August 1, 1948 to September 25, 1975.

Cause of Death	Observed	Expected	SMR
All causes	28	31.63	89
All malignant neoplasms	8	5.19	154
Malignant neoplasms of the respiratory system	5	1.73	289*

*p = .032, one-tailed test

Table 4b. — Observed and Expected Numbers of Deaths Occurring Five or More Years Past Initial Exposure Among 314 White Males in a VCM Production Plant Prior to September 25, 1970.

Cause of Death	Observed	Expected	SMR
All causes	22	25.18	87
All malignant neoplasms	6	4 34	138
Malignant neoplasms of the respiratory system	4	1.49	268*

*p = .06, one-tailed test

pendix B. Under the extreme assumption that all "unknowns" actually smoked, the expected number of respiratory cancer deaths for the 464 white males is 1.98. With five deaths observed, this excess is of borderline significance ($p = .05$) Since it is extremely unlikely that all persons in the "unknown" category smoked, smoking appears to be an unlikely explanation for the excess respiratory cancer mortality.

Effect of Five-Year Latency

The latency period for occupationally induced cancers may range from five to 20 years from the date of first exposure. In the above mortality comparisons, the experiences of all workers, regardless of the length of time elapsed since initial exposure, are included. This technique may mask the effects of exposure in that a sufficient latency period may not have accrued prior to death or observation. When the SMR's in Table 4a were recalculated utilizing a minimum latency period of five years from the date of initial exposure to vinyl chloride, the resulting SMR for malignant neoplasms for the 314 employees satisfying this criterion was slightly lower, 268 versus 289 (Table 4b).

Effect of Duration of Exposure

Fifty-four percent of the cohort had less than two years of exposure to vinyl chloride. The average length of time spent in a vinyl chloride area for all 464 workers was 4.6 years. The values ranged from a minimum of two months to a maximum of 26.9 years.

It is important to determine whether increased duration of exposure is associated with higher mortality. When looking for such a relationship, bias may occur if the exposure and observation periods overlap.[20] Death may terminate exposure prior to the satisfaction of some minimum exposure requirement, so that some deaths fall in the category of short duration of exposure, regardless of whether the death was causally related to the exposure. In addition, a long duration of exposure implies a long latency period in which malignancies possibly due to other chemicals in the environment may be observed. These problems can be avoided by the following technique, which separates the exposure and observation periods.

Duration of exposure during the first five years following date of initial exposure was noted for each individual exposed prior to September 25, 1970, counting only exposures incurred prior to that date. Individuals surviving the first five years after the date of initial exposure were then classified into two groups according to duration of exposure in the first five years. The groups were divided at the median value for duration of exposure, 2.29 years. Person-years of observation and the expected numbers of deaths for the period following the first five years since date of initial exposure were then calculated for the two groups. This procedure removes observed and expected deaths occurring among workers before completion of the minimum five-year latency period. Fig 1 illustrates the determination of these intervals for three individuals. The results of this analysis are shown in Table 5. There is a statistically significant excess of deaths due to respiratory cancer in the longer exposure group (4 observed vs. 1.05 expected, $p = .023$).

Effect of Level of Exposure

In order to further explore the relationship between exposure to vinyl chloride and cancer mortality, one can consider a second dimension of exposure: the estimated level of exposure, or concentration. As previously mentioned, levels of exposure to vinyl chloride in the population studied have decreased substantially in recent years, but based upon subjective evidence, the relative potential for exposure has not changed extensively. Therefore, the time weighted averages of exposures to vinyl chloride for the period 1971-75 were extrapolated backward in time to obtain an estimate of minimum exposure levels for the various job categories. Average exposure indices were obtained for each individual for the five-year period following initial exposure by multiplying the extrapolated exposure level for each job classification by the time spent in that job during the initial five-year period. These products were summed over all jobs in the initial period, then divided by the total time exposed to vinyl chloride in this initial five-year period. Only exposures before September 25, 1970 were counted, thereby allowing for a five-year latency period as defined above. Categories of high and low level exposure were defined by the median extrapolated level of exposure for the 314 individuals alive and under observation at the end of the initial five-year period. The mortality experience observed subsequent to the initial five years for the categories of high and low average levels of exposure is illustrated in Table

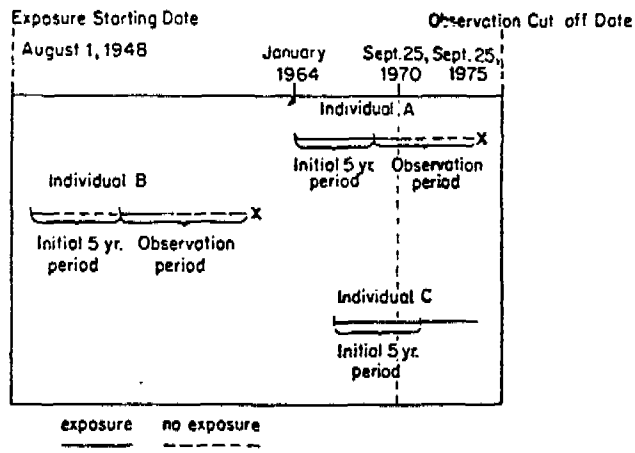

Fig 1. — Example of determination of duration of exposure during five years following date of initial exposure to vinyl chloride for three employees exposed prior to date allowing for 5-year latency (September 25, 1970). The initial date of exposure for Individual A was January 1, 1964, prior to September 25, 1970 (the cutoff date minus 5 years). He died on January 1, 1975. Since Individual A was continuously exposed for the entire five-year interval from the date of his initial exposure, the person-years of observation after January 1, 1969, and his death would be assigned to the long exposure category, > 2.29 years. By contrast, Individual B was exposed for only two years during the five-year interval from the date of his initial exposure, contributing approximately eight person-years to the short exposure category. Individual C represents an additional category of observations: those individuals for whom an initial five-year interval was not completed prior to September 25, 1970 (the study cutoff date minus 5 years) and were therefore excluded from these analyses.

Table 5. — Observed and Expected Deaths Among 314 White Males in a VCM Production Plant by Initial Five-Year Duration of Exposure.*

Initial 5-Year Duration (Years)	No. of Persons	Person-Years	All Causes			All Malignant Neoplasms			Malignant Neoplasms of the Respiratory System		
			Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
Short (≤ 2.29)	157	1123	7	7.75	90	1	1.32	76	0	.45	0
Long (>2.29)	157	2227	15	17.43	86	5	3.02	166	4	1.05	381†

* For 314 individuals exposed before September 25, 1970 and exposures incurred before that date, counting deaths occurring five or more years after initial exposure

† p = .023, one tailed test

6. Again, there is a statistically significant excess of respiratory cancer in the group with a high average level of exposure (3 deaths observed vs. .68 expected, p = .032).

Effect of Duration and Level of Exposure

Finally, a dose-response analysis was carried out for a cumulative exposure index of information regarding both duration and level of exposure. This index, for a given individual and period of exposure, is the product of the duration of the period of exposure and the time weighted average level as previously defined. The mortality experience occurring five years after initial exposure for index groups of high and low level exposures, as defined on the basis of the first five years from initial exposure, is given in Table 7. The excess in the high level exposure group is not statistically significant (p = .07).

Results With Limited Follow-up

It is of methodologic importance to the evaluation of results from studies with incomplete follow-up, as well as to the conduct of future studies, to compare the results obtained with complete follow-up to those obtained with limited follow-up, that is, by "standard" techniques utilizing individuals who are easy to locate (current employees and retirees, and deaths occurring in these two groups only). Table 8 shows that the results with limited and with complete follow-up are similar when comparing overall mortality between the two groups, but that results differ somewhat when comparing mortality due to malignant neoplasms, specifically malignant neoplasms of the respiratory system. There are several sources of error inherent in the SMR's reported with limited follow-up. First of all, individuals removed from the analysis were certain to have survived up to their termination date. If they had died before termination, they would have been included in the study. Removing from the analysis those persons who terminated employment creates a tendency to overestimate the SMR, as noted in Table 8. A second potential source of bias in the analysis with limited follow-up stems from the possibility that persons terminating employment before retirement may differ in certain demographic or environmental characteristics related to mortality. Lastly, the elimination of a significant number of individuals from the study reduces the precision of the estimate of the SMR. This is particularly undesirable when small numbers of deaths are involved. Despite these problems, it is not uncommon to find this type of limited follow-up analysis in the literature. To avoid the various sources of error in this type of analysis, it is preferable to strive for a complete cohort, as was done in this study.

Discussion

One of the most challenging problems in a cohort study of the type presented here is the delineation of exposure. Although no historical documentation of exposure to vinyl chloride exists prior to 1970, it was reported that during the early period of production (1948-1960), exposures in the range of several hundred ppm (200-500 ppm) were not uncommon. During the 1950's and early 1960's the standard for exposure to vinyl chloride (threshold limit value, TLV) was 500 ppm.[24] In 1961, based on chronic toxicity testing, the Dow Chemical Company voluntarily reduced their exposure standard to a TWA of 50 ppm (100 ppm ceiling).[25] In 1974 the permanent OSHA standard for exposure to vinyl chloride was reduced from 50 ppm to 1 ppm for an eight-hour period.[26]

As previously noted, workers in the cohort under study were simultaneously exposed to VCM vapors and varying

Table 6. — Observed and Expected Deaths Among 314 White Males in a VCM Production Plant by Estimated Relative Level of Exposure for Initial Five-Year Exposure Interval.*

Avg. Level of Exposure During Initial 5 Years†	No. of Persons	Person-Years	All Causes			All Malignant Neoplasms			Malignant Neoplasms of the Respiratory System		
			Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
Low	160	1374	10	13.56	74	2	2.38	84	1	.82	122
High	154	1977	12	11.62	103	4	1.95	205	3	.68	441‡

* For 314 individuals exposed before September 25, 1970, exposures incurred during the five-year interval from date of initial exposure, and counting deaths occurring five or more years after initial exposure

† Based on 1971-75 monitoring data

‡ p = .032, one-tailed test

Table 7. — Observed and Expected Deaths Among 314 White Males in a VCM Production Plant by Exposure Index for Initial Five-Year Exposure Interval.*

Initial 5-Year Exposure Index†	No. of Persons	Person-Years	All Causes			All Malignant Neoplasms			Malignant Neoplasms of the Respiratory System		
			Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
Low	157	1143	9	9.40	95	3	1.62	185	1	.56	180
High	157	2207	13	15.79	82	3	2.72	110	3	.94	319‡

* For 314 individuals exposed before September 25, 1970, exposures incurred during the five-year interval from date of initial exposure, and counting deaths occurring five or more years after initial exposure

† Based on 1971-75 monitoring data

‡ $p = .07$, one-tailed test

concentrations of vapors from the production of VDC, ethylene dichloride, methyl chloroform and ethyl chloride. A weakness of most mortality studies of chemical indistry employees is that workers may have been exposed to many other chemicals while working in other areas of the production facility or in other chemical companies before or after the period of specific observation.We were able to determine that no members of the cohort had been exposed to arsenic or asbestos while they were employed at the Dow Chemical Company.

In view of the lack of data regarding levels of exposure prior to 1971, an assumption was made that while levels of exposure were higher before 1971, the ratios of levels for any two job classifications remained approximately constant. It is believed that reasonable estimates of the relative levels of exposure prior to 1971 were made by backwards extrapolation of post-1971 exposure data.

It is also important to note that initial exposure to vinyl chloride occurred in mid-career (34-43 years of age) for all four persons who died of lung cancer (Table 3). In this regard, the lack of information on previous employment or occupational exposures for these individuals adds to the difficulty of interpreting the significance of these statistical findings.

To pursue the question of whether this excess may be causally related to VC exposure, a dose-response relationship was examined. Dose was considered to have two dimensions, duration and level of exposure. In testing for a dose-response relationship, a comparison of mortality may be biased if the periods of exposure and observation overlap. We avoided this source of bias by looking at an initial five-year exposure period and a subsequent observation period, thereby also allowing for a five-year latency period past initial exposure. With regard to duration of exposure in the first five years following initial exposure, there was a statistically significant excess of respiratory cancer occurring after the initial five-year period (4 versus 1.05 expected, $p = .02$) among workers in the longer exposure group. No such excess was observed for workers in the shorter exposure group.

In the three analyses of dose-response performed in this study, the most accurate and objective measure of dose available is duration of exposure, which ignores the concentration component of dose. On the other hand, the cumulative index takes into account both duration and level, is based on data extrapolated into the past, and assumes that the relative levels of exposure did not change over time. If this assumption were false, any existing dose-response relationship would be obscured, had the true cumulative indices been known. The use of the time weighted average levels as a measure of dose is not so heavily dependent on this assumption. Possible explanations for the fact that statistical significance was observed in two of these analyses, but not the level-duration index, may be due to the potential error in the estimated levels, and in the small numbers of events observed. It should be mentioned that our inability to detect an increase in mortality in the low level exposure groups does not necessarily indicate that no increase exists, but may be due to the low power associated with small expected numbers, and a longer latency period at lower doses.

A more appropriate statistical technique for these types of dose-response analyses might be a comparison of the increase in the high level (or long) exposure group to that in the low level (or short) exposure group. Statistical inference on the ratio of the true underlying SMR's for the two exposure groups can be carried out conditional on the number of deaths in the two groups combined.[17] However, when the numbers of deaths are small, the power of such a comparison is very low, and may even be zero. Because of this inefficiency, it was deemed appropriate not to report significance levels, but rather to note that although statistical significance was not observed, the probability of observing such was very low.

Throughout this study, as is common in occupational studies, the measure of mortality used is the SMR. There are, however, several problems with the use of SMR's that should be kept in mind when interpreting such results, especially when comparisons of SMR's are made.

Table 8. — Observed and Expected Deaths Among White Males in a VCM Production Plant by Type of Follow-Up.

	No. of Persons	Person-Years	Overall Mortality			Malignant Neoplasms			Malignant Neoplasms of the Respiratory System		
			Obs.	Exp.	SMR	Obs.	Exp.	SMR	Obs.	Exp.	SMR
Limited follow-up	335	3067	18	20.55	88	6	3.43	175	5	1.16	431*
Complete follow-up	464	5313	28	31.63	89	8	5.19	154	5	1.73	289†

* $p = .007$, one-tailed test

† $p = .032$

Although the SMR is an adequate measure of excess mortality as compared to the mortality of a standard population, the comparison of two SMR's depends not only on the differences in the age specific mortality rates of each group from the standard, but also on the age specific population weightings of the two groups. Thus, it is entirely possible, if the age distributions are vastly different, that the two study groups might have equal age specific mortality rates but somewhat different SMR's. Despite the problems in the use of SMR's, no alternative was considered because of the small numbers involved.

Conclusions

In view of our inability to detect a significant dose-response relationship, we cannot state that the observed excess in respiratory cancer deaths is due to exposure to vinyl chloride. However, the fact that excesses were seen in the group with the longer duration of exposure in the initial five years, and in the group with the higher average estimated exposure levels in the initial five years, suggests that a relationship may exist.

It is unfortunate that data were not available regarding the levels of exposure experienced 20 to 30 years ago, when the four workers with respiratory cancer were first exposed to vinyl chloride. It is also unfortunate that data were not available regarding exposures to other chemicals during these earlier decades.

The results of this study can only be considered in conjunction with other studies, both past and future. In view of inconsistent reports to date, more studies of the specific dose relationships and confounding exposures are needed.

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Appendix A

Estimated Time Weighted Average (8-Hour) Exposure to Vinyl Chloride by Job Classification, 1971-1975

Job Classification	Average 8-Hr. TWA	Percent of Total Person-Years Exposed
1. Control lab personnel	22.3	4.7
2. Development lab personnel	4.1	5.7
3. Production personnel		
Control A	7.7	16.6
Control B	2.8	7.5
Control C	4.4	8.9
Class 3 operators	—	.8
Total	5.7	33.8
4. Loaders and plant men		
Class 1, 2 operators	7.1	15.2
Head packaging operator	12.3	1.2
Material handling operator	.2	.1

Packaging operator, service technician	—	.1
Total	7.4	16.4
5. Certain supervisory positions		
Production superintendent, assistant production superintendent, production engineer, R&D engineer, engineer, safety engineer, Sr. production engineer.	1.9	9.3
Parts technician, Sr.	.2	.1
Manager	.3	.2
Assistant engineering technician	.0	.0
General superintendent, section superintendent, superintendent, supervisor, assistant superintendent, planning engineer, material control clerk, plant assistant, head clerk, chief material handling technician, shipping coordinator, maintenance coordinator, maintenance engineer	—	1.9
Total	1.8	11.6
6. Maintenance personnel		
Boilermaker, apprentice	1.4	1.2
Welder, apprentice	.2	1.1
Machinist, apprentice, helper, crew leader	1.1	1.7
Pipefitter, apprentice, helper	1.7	4.2
Utility man	.2	1.2
Instrument technician	3.2	3.7
Production foreman, shift foreman	4.3	5.5
Maintenance foreman	.4	.2
Utility crew leader, rotating shift foreman, foreman	—	5.2
Total	2.5	24.0
7. Other personnel		
Electrician, apprentice	3.8	2.0
Loading supervisor, technical foreman, coverer, -janitor, electrical foreman	—	1.8
Total	3.8	3.8
All groups combined	5.4	100.0

For some job classifications there were no monitoring data available for the interval 1971-75. The value assigned was determined by averaging all monitoring data available for job classifications within the group to which the specific job classification was assigned. The averages computed were weighted according to total person-years in the cohort spent in each job classification.

Appendix B

Despite the lack of suitable standard age specific rates for smokers (present or past) and nonsmokers (never smoked), it is possible to construct a reasonable set of rates from available information. The following two simplifying assumptions are made:

1. Age specific relative risks for smokers compared to non smokers from the study by Dorn[22] for U.S. white male veterans for the years 1954 to 1962, are applicable to the Texas white male populations of 1950-59 and of 1960-69.

2. The age specific percentages of smokers for U.S. males for the years 1955 and 1966[23] reflect the corresponding percentages for the Texas white male population in the time periods 1950-59 and 1960-69, respectively.

Using these two assumptions, a set of age specific rates for the Texas white male population according to smoking status was constructed for use as a standard, in the following manner. Let

M_i = cause specific mortality rate for age group i

M_{is} = cause specific mortality rate for smokers in age group i

M_{in} = cause specific mortality rate for nonsmokers in age group i

s_i = proportion of population in age group i who smoke

r_i = age specific relative risk for smokers compared to nonsmokers

Then

$$M_i = s_i M_{is} + (1-s_i) M_{in} = M_{in}[s_i r_i + (1 - s_i)]$$

$$M_{in} = M_i / [s_i r_i + (1-s_i)]; \quad M_{is} = r_i M_{in}.$$

Thus, the values for r_i and s_i are found for assumptions 1 and 2 above, and the desired mortality rates by smoking status are obtained.

Truth

Truth rests on several conditions. Among other things, truth rests on a regard for relevant facts, an intelligent assembling of them and on knowing how the facts matter. Truth also rests on knowing what is important and what is not, on judgmental capacity and on courage.

— From "When Values are Substituted for Truth" by J. Bennett, in *The Wall Street Journal*, July 25, 1978

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Angiosarcoma of the Spleen

A Report of Two Cases and Review of the Literature

Karl T. K. Chen, MD; J. Craig Bolles, MD; Enid F. Gilbert, MD

• **Results of the ultrastructural study of one of two cases of splenic angiosarcoma established the blood vessel origin of this tumor. Fifty-three previously reported cases were reviewed. None of the 55 patients had a history of exposure to thorium dioxide, vinyl chloride, or arsenic, which are known to be associated with hepatic angiosarcoma and other tumors. A comparison of the splenic and hepatic angiosarcomas showed that tumors not associated with exogenous material frequently involve the spleen and liver simultaneously, and that tumors associated with thorium dioxide, vinyl chloride, or arsenic commonly involve the liver with sparing of the spleen.**

(*Arch Pathol Lab Med* 103:122-124, 1979)

Angiosarcoma of the spleen is rare. The first case was reported by Langhans in 1879.[1] In 1974, Autry and Weitzner reviewed 49 cases and added one new case.[2] Subsequently, one case each was reported by Pollard and Millward-Sadler and Aranha et al.[3] To this list, one of the four cases reported as hemangioendothelioma of the liver by Alpert and Benisch[4] also should be added. To our knowledge no ultrastructural study of this splenic tumor has previously been reported.

This article describes two cases of splenic angiosarcoma and presents the ultrastructural features of one of these two cases.

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REPORT OF CASES

CASE 1.—A 31-year-old man was admitted to the hospital because of excessive bleeding following a tooth extraction. Physical examination showed hepatomegaly with the liver edge extending 5 cm below the right costal margin. The spleen was not felt. The hemoglobin value was 10 g/dL. The platelet count was 14×10^4/cu mm, and the WBC count was 10×10^3/cu mm. The serum chemistry showed a SGOT value of 80 units/L, an alkaline phosphatase concentration of 15 King-Armstrong units, and a lactic dehydrogenase level of 750 IU/L. A liver scan showed multiple filling defects. A laparotomy was performed and disclosed an enlarged spleen (three times normal size) and multiple tumor nodules up to 4 cm in diameter in the liver. A biopsy of the liver showed angiosarcoma. Postoperatively, he was treated with supportive measures and methotrexate. He died two months after the diagnosis. An autopsy was performed.

CASE 2.—A 65-year-old man was admitted to the hospital with a two-month history of left upper abdominal pain. Physical examination showed hepatosplenomegaly; the liver extended 10 cm and the spleen 12 cm below the costal margins. His hemoglobin level was 9.5 g/dL. The platelet count was 30×10^4/cu mm, and the WBC count was 8×10^3/cu mm. The serum chemistry and a bone marrow examination yielded normal results. A laparotomy disclosed a massively enlarged spleen and multiple nodules up to 2 cm in diameter in the enlarged liver. A splenectomy and biopsy of a hepatic tumor nodule were performed. The patient was treated with methotrexate postoperatively. He was alive three months after the diagnosis.

PATHOLOGY

The autopsy in case 1 showed multiple hemorrhagic tumor nodules up to 4 cm in diameter in the massively enlarged liver, which weighed 7,200 g (Fig 1). A single tumor nodule measuring 10 × 8 × 8 cm and weighing 1,000 g was found in the enlarged spleen. The spleen weighed 1,000 g (Fig 2). Other organs were not involved. The splenectomy specimen in case 2 weighed 1,730 g and measured 22 × 16 × 8 cm. Over 80% of the splenic parenchyma was replaced by multiple hemorrhagic tumor nodules measuring 6 cm in the largest diameter.

Microscopically, the tumor nodules in the spleens of both patients and the liver in patient 1 were composed of polygonal or oval hyperchromatic tumor cells lining small vascular spaces that were well outlined in reticulin stains (Fig 3). Considerable amounts of hemosiderin pigments were found adjacent to the tumor tissue in the spleens of both cases. The liver biopsy in case 2 showed scattered irregular sinusoidal spaces lined by similar tumor cells (Fig 4). Extramedullary hematopoiesis was present in the neoplastic vascular spaces in the liver and spleen from case 1. There was no evidence of liver cirrhosis or tissue deposition of foreign material in either case.

A portion of the tumor tissue in the

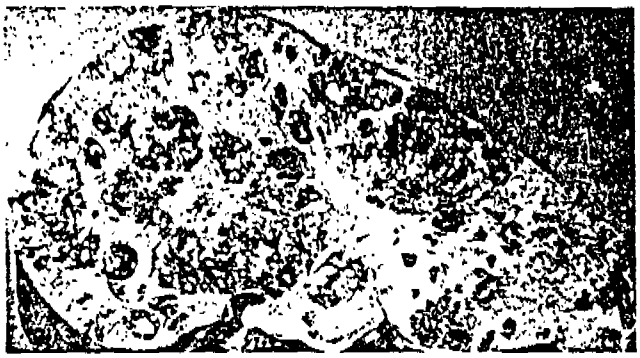

Fig 1.—Multiple dark reddish tumor nodules of liver (case 1).

Fig 2.—Spleen containing 10-cm tumor mass (case 1).