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Cancer Mortality of a Group of Canadian Workers Exposed to Vinyl Chloride Monomer

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The present study was undertaken to find out whether there was an excess of cancer mortality from causes other than angiosarcoma of the liver among a group of workers heavily exposed to vinyl chloride monomer (VCM). The mortality of 451 workers exposed to VCM for more than five years was compared with that of 870 workers from the same company who had not been exposed to VCM. The relative risk for digestive cancer was significantly higher than 1 (6.25, confidence interval 2.69 to 14.52) in the exposed group. The standardized mortality ratio (SMR) for digestive cancer was also higher (SMR 259.26 $p < 0.01$) than that of the general population. No other cancer was in excess. Since the exposed workers are known to have had a cigarette smoking experience similar to that of those who were not exposed, it is concluded that the association between lung cancer and VCM exposure, if present, is indeed rather small.

Several studies have demonstrated that vinyl chloride monomer (VCM) produces angiosarcoma of the liver among people exposed at work.[1-7] There is, however, much controversy about the capability of VCM to generate other types of cancer in man. One author,[8] using a proportional mortality ratio technique, described excesses of lung cancer (observed, 13; expected, 7.9; obs/exp 1.6) and brain cancer (observed, 5; expected, 1.2; obs/exp 4.2) in a group of 161 workers from two vinyl chloride plants.[8] Another author,[9] who studied the mortality of a group of 1,294 American workers exposed to VCM, reported excesses of lung cancer (observed, 11 expected, 7.5; SMR 194, $p < 0.05$) and brain cancer (observed, 3; expected, 0.6; SMR 498, $p < 0.05$) among men who had had their first exposure more than 15 years before their death. While most authors have not been able to document a significant excess of any other cancer in their studies, they have noted that such an excess may exist.

In order to better document the cancer mortality associated with exposure to VCM, the present study of the workers of the Shawinigan vinyl chloride polymerization plant was undertaken.

The main objectives of the study were (1) to compare mortality among vinyl chloride workers with the mortality of workers from a nearby industrial complex; and (2) to compare the mortality of the VCM workers with that of the general population. The Shawinigan vinyl chloride plant opened in 1943 as an independent company which produced both VCM and PVC (polyvinyl chloride). In 1958, it was merged into an industrial complex (to be used as the comparison group) of which it became the Canadian Resins Division. In the late 1960s, the VCM production ceased and only the polymerization process continued operation. In 1972, this division was sold and again became an independent plant. Over the years, the VCM and PVC productions fluctuated. The average annual work force at the plant was 225 men. In 1965, VCM production was estimated at 90 million pounds and PVC at 60 million pounds. In 1974, PVC production was 22.3 million pounds.[10] Since several episodes of unconsciousness among workers were reported, the level of VCM in the air at the workplace is believed to have been high during this period. Ten cases of angiosarcoma of the liver have been reported since then.[7]

The industrial complex from which the comparison group was drawn comprises several divisions: a carbide division which produces calcium carbide and acetylene black; a chemicals division which produces several chemicals derived from acetylene: acetone, chloral, butanol, acetic acid, acetaldehyde, several acetates, solvents and resins; a stainless steel division which consisted of a small foundry and a division formed in 1957, which produced

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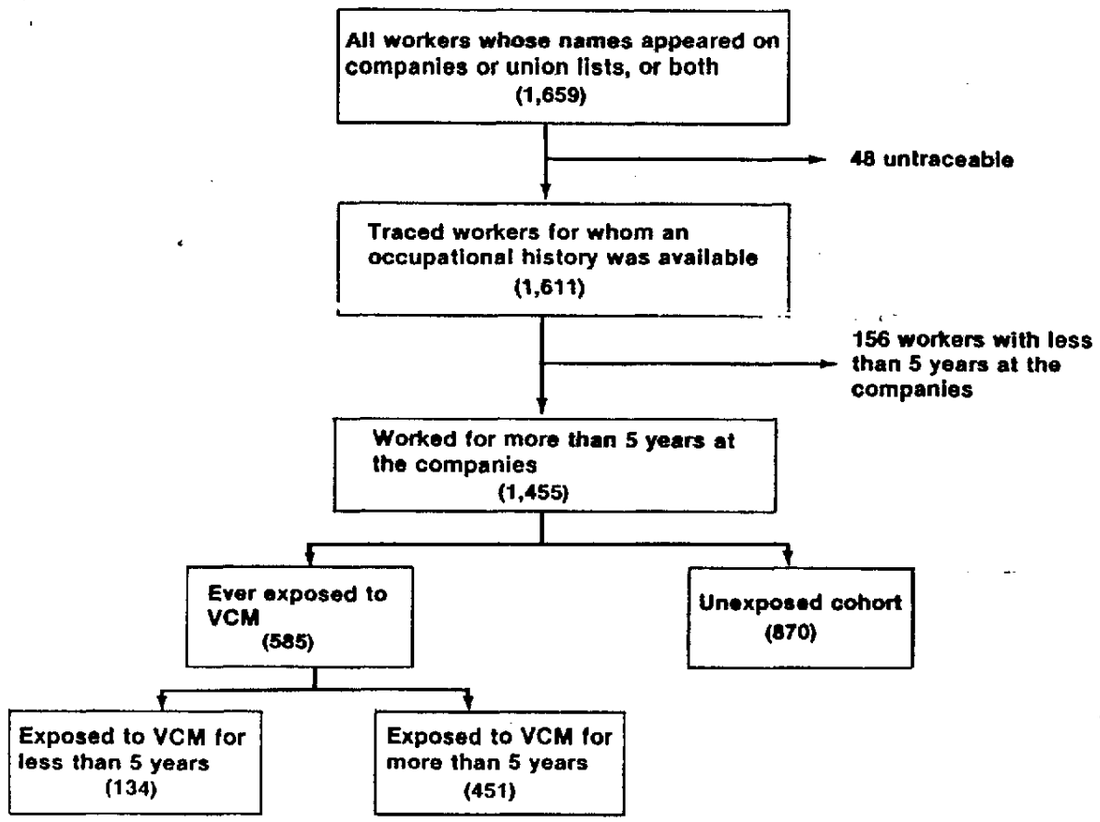

Fig 1. — Population under study.

sulfuric acid, chlorine and cyanide. This complex started operations in 1927; some of its divisions opened at a later date; others closed in the late 1960s or early 1970s. The annual number of male workers averaged 1,000.[12]

Methods

Population Under Study. — All production workers whose names appeared on the unions' lists or the companies payrolls of the VC plant and the industrial complex between January 1, 1948, and December 31, 1972, constituted the population under study. Several methods (old addresses, telephone books, Quebec motor vehicles bureau, inquiries with fellow workers and families, searches in homes for retired persons) were used to trace these men, 18% of whom were still working for the same companies. Once identified, the worker himself or his next of kin (spouse, child or close relative) was questioned at home or at work by a trained interviewer. The questions permitted the reconstruction of a detailed occupational history within and outside the companies under study. Questions were also asked regarding smoking habits. For each deceased person believed to have been exposed to VCM, the occupational history was confirmed with the help of a fellow worker.

The men whose number of years of work for these companies, as established through occupational histories, did not exceed five were removed from the study. The remaining population was then subdivided into three groups. The first group (known as the unexposed cohort) consisted of men who stated they had not been involved with the production of VCM or PVC, or both, for a period greater than five months. The second group (constituting the exposed cohort) comprised men who declared they had worked on the production of VCM-PVC for more than five years. Finally, the third group consisted of the men who had worked on the production of VCM-PVC for a period of six months to five years. This group was excluded from analysis because it neither fulfilled the definition of the exposed nor the unexposed cohort.

Data Sources. — The vital status of these men was established as of December 31, 1977. Causes of death were determined from death certificates. They were coded according to the 8th revision (ICDA) by one of the authors, who was unaware at the time of the coding as to which group the man belonged. For cancer cases, a histopathological confirmation was sought on autopsy, biopsy or cytology reports contained in the medical files at the hospital. Information on Quebec's population and mor-

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Table 1. — Age Distribution of the Men in the VCM-Exposed and Unexposed Cohorts as of December 31, 1977 (Deceased Excluded).

Age	Exposed		Unexposed	
	No.	%	No.	%
25-29	0	—	1	0.2
30-34	0	—	3	0.5
35-39	1	0.3	6	0.9
40-44	28	7.1	45	7.1
45-49	75	19.1	55	8.6
50-54	96	24.5	84	13.2
55-59	102	26.0	112	17.6
60-64	53	13.5	110	17.3
65-69	30	7.7	113	17.7
70-74	6	1.5	65	10.2
75 +	1	0.3	43	6.7
Total	392	100.0	637	100.0

tality by cause, age and sex was secured from Statistics Canada for the year 1971. In order to ensure the validity of the results, only the causes of death which appeared on the death certificates were used in the computations.

Statistical Analysis. — The results were analyzed using the "man-years at risk" method as described by Hill.[13] The number of person-years of observation was established for each five-year age group and for each five-year period between 1948 and 1977.

The mortality in the exposed cohort was compared with that in the unexposed cohort according to the method of relative risk. The tests of significance used were those of Mantel, Haenszel[14,15] and Miettinen.[16,17] The observed mortality was also compared with the mortality expected from the population of the Province of Quebec according to the method of the standardized mortality ratio (SMR).[14] The test of significance used was the one described by Bailar and Ederer.[17]

Quality Control Procedures. — A thorough occupational history was developed for workers who were exposed within the VC plant. The questionnaires presented a detailed profile of the plant while specifying possible jobs within its major units. Before the beginning of the study, it was pre-tested with former employees.

Interviewers who contacted the workers had received training by the same person and were supervised during the entire study. The completed questionnaires were reviewed weekly by one of the authors and missing information was sought by telephone. Data entered in the computer were systematically checked against the original questionnaires.

Results

As shown in Fig 1, the population under study originally comprised 1,659 workers. Of these, 48 men were untraceable, leaving the number in the study population at 1,611 (or 97.1% of the original number). After the removal of the 156 men who had worked at the companies for a period not exceeding five years and the 134 men who had been exposed to VCM for a perod extending from six months to five years, the exposed cohort comprised 451 men and the unexposed one, 870 men. In the exposed cohort, the proportion of men who responded to the questionnaire for themselves was 84.3%. In the unexposed cohort, this proportion was somewhat lower at 68.2%.

The age distributions of the workers in the exposed and unexposed cohorts as of December 31, 1977, reveals that workers in the unexposed cohort (Table 1) were somewhat older. Since the industrial complex had been in operation for several years when the VC plant opened, the finding of older people in the latter cohort was predictable.

Table 2 shows the distribution of the exposed workers according to their length of exposure and their observation period (time between first employment and end of follow-up). Among these, 81% (365 out of 451) had an observation period of 15 years or more. For 23% of them, the time elapsed between first exposure and the end of the follow-up period exceeded 29 years. The mean observation period for the exposed cohort was 22.6 years.

Table 3 gives the diagnosis at death and the diagnosis after histopathological review of all the cancer cases found in the exposed group. On the death certificates, eight cancers of the liver were reported. The histopathological review rejected one of them as being a cancer of the sigmoidal flexure of the colon, but added another as an incorrectly diagnosed cancer of the peritoneal cavity. All eight cancers of the liver turned out to be angiosarcoma of the liver. It is noted that two more angiosarcomas of the liver were certified as cirrhosis on the death certificates and were considered as such throughout this study.

Table 4 compares the mortality of the exposed workers with the mortality of the unexposed workers. The confidence interval (95%) of the relative risk indicates that there is a significant excess of mortality due to cancers of the digestive system in the exposed group (RR 6.25, confidence interval 2.69 to 14.52). There is no excess in the other causes of death.

Table 5 shows the standardized mortality ratios (SMRs) for the exposed workers in comparison with the entire population of the Province of Quebec. The SMR for all causes is 83.02, thereby showing no excess of death in the exposed cohort. Although the SMRs for all cancers, respiratory system diseases and digestive system diseases ex-

Table 2. — Distribution of Exposed Workers by Length of Exposure and Observation Period.

Exposure (Years)	Observation Period (Years)						
	5-9	10-14	15-19	20-24	25-29	30 +	Total
5- 9	30	28	7	40	2	4	111
10-14	—	28	26	19	17	5	95
15-19	—	—	17	35	19	8	79
20-24	—	—	—	22	24	15	61
25-29	—	—	—	—	34	33	67
30+	—	—	—	—	—	38	38
Total	30	56	50	116	96	103	451

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Table 3. — Age at Death, Diagnosis on Death Certificate and Diagnosis on Histological Review of the 20 VCM-Exposed Workers Who Died of Cancer.

Case Number	Death Certificate	Histological Review	Age at Death (Years)	Total Exposure (Years)	Latency Period (Years)
1	Cancer of the liver	Cancer of the sigmoid flexure of the colon	73	15	28
2	Cancer of the intestine	Metastatic cancer of the colon	56	16	17
3	Carcinoma of the trachea	Carcinoma of the trachea	50	15	15
4	Angiosarcoma of the peritoneal cavity	Angiosarcoma of the liver	41	11	11
5	Cancer of the lung	(no review)	54	16	16
6	Cancer of the liver	Angiosarcoma of the liver	42	19	19
7	Cancer of the liver	Angiosarcoma of the liver	57	17	23
8	Cancer of the prostate	Cancer of the prostate	64	26	29
9	Angiosarcoma of the liver	Angiosarcoma of the liver	62	18	23
10	Cancer of the pancreas	Epithelioma of the head of the pancreas	40	8	13
11	Adenosarcoma of the intestine	Adenosarcoma of the intestine	53	25	28
12	Hepatoma	Angiosarcoma of the liver	53	24	24
13	Cancer of the liver	Angiosarcoma of the liver	53	22	23
14	Cancer of the pancreas	Anaplastic epithelioma of the pancreas	59	29	30
15	Chondrosarcoma	Chondrosarcoma	43	7	10
16	Hepatoma	Angiosarcoma of the liver	48	22	22
17	Primary cancer of the liver	Angiosarcoma of the liver	53	5	12
18	Cancer of the digestive track	Cancer of the cecum	52	26	26
19	Cancer of the biliary ducts	Cancer of the head of the pancreas	54	12	12
20	Lymphoid leukemia	Lymphoid leukemia	48	21	21

ceed 100, they are not statistically significant. On the other hand deaths by accident and violence are significantly lower ($p < 0.01$). As for specific cancer deaths, a significant excess is noted for cancer of the digestive system only. This excess is accounted for exclusively by cancer of the liver (8 cases observed versus 0.14 expected SMR 5,714.3%), no other cancers are in excess.

The cancer mortality among the workers who were still alive 15 years after their first exposure shows the same results as the mortality in the entire group, namely that only cancers of the digestive system are in excess in the exposed cohort (Table 6).

Discussion

Difficulties encountered in comparing the mortality of a group of workers with the mortality of a whole population are well documented. They are termed: "healthy population selection effect," "survivor population effect,"[20] "ethnic/cultural/social characteristics." They are believed to underestimate the actual mortality of a group of workers and therefore to underscore the effects of the risks to which these individuals are being exposed at work. There are no easy ways to avoid such difficulties. One method would be to compare a group of workers with another group of workers with the same characteristics except for the exposure to the risk under study. The problems encountered in so doing are no easier. Although the group most similar to industrial workers is probably another group of industrial workers from the same town, it is almost impossible to think of a group of industrial

Table 4. — Deaths Observed in the VCM-Exposed and Unexposed Cohorts, Age-Adjusted Relative Risks and Confidence Intervals of the Relative Risk.

Cause of Death		No. of Cases Exposed	No. of Cases Unexposed	Relative Risk	95% Confidence Interval of the Relative Risk
All cancers	(140-209)	20	52	1.48	0.84- 2.61
Mouth and pharynx	(140-149)	0	2	—	—
Digestive	(150-159)	14	9	6.25	2.69-14.52*
Respiratory	(160-163)	2	20	0.36	0.08- 1.58
Bone, skin, connective	(170-173)	2	2	1.67	0.21-12.99
Urogenital	(185-189)	1	7	0.83	0.10- 7.10
Eye, CNS	(190-192)	0	2	—	—
Leukemia	(200-209)	1	4	1.15	0.07-17.80
Other cancers		0	6	—	—
Cardiovascular	(390-458)	25	124	0.80	0.47- 1.36
Respiratory	(460-519)	6	15	0.81	0.44- 9.35
Digestive	(520-577)	4	12	1.44	0.49- 4.25
Accidents and violence	(800-899)	2	15	0.51	0.21- 1.24
Others		2†	15	0.57	0.14- 2.39
Total		59	233	1.07	0.79- 1.45

*Significant according to Miettinen's test[17]
†One cause unknown

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Table 5. — Observed and Expected* Numbers of Deaths in the VCM-Exposed Cohort and Standardized Mortality Ratios (SMRs).

Cause of Death		Observed	Expected	SMR
All cancers	(140-209)	20	16.37	122.17
Mouth and pharynx	(140-149)	0	0.64	—
Digestive	(150-159)	14	5.40	259.26†
Respiratory	(160-163)	2	5.78	34.60
Bone, skin, connective	(170-173)	2	0.38	526.32
Urogenital	(185-189)	1	1.33	75.19
Eye, CNS	(190-192)	0	0.50	—
Leukemia	(200-209)	1	1.67	59.88
Other cancers		0	0.54	—
Cardiovascular	(390-458)	25	31.67	78.94
Respiratory	(460-519)	4	3.33	166.91
Digestive	(520-577)	4	3.85	103.90
Accidents and violence	(800-999)	2	10.58	18.90†
Others		2‡	5.40	37.03
Total		59	71.07	83.02

*Expected numbers obtained from 1971 males Quebec death rates applied to person-years in each age group
†$p < 0.01$[19]
‡One cause unknown

workers not exposed to some kind of carcinogenic risks. In the present study, the authors decided to compare the exposed workers with both the general population and a group of unexposed workers. It must be noted that among the unexposed workers, no causes of death were found to be in excess when their mortality was compared with that of the general population.

The comparison of the mortality of the exposed and the unexposed workers gave results similar to the one reached by the comparison with the general population. The number of cancer of the digestive system was significantly higher in the exposed cohort. No other cancer was in excess and there even seemed to be a deficit (not statistically significant) in respiratory cancers.

Considering the fact that animals experimentally exposed to VCM have developed not only angiosarcomas of the liver but also malignant tumors of several organs (skin, lung, bone, Zimbal glands, kidneys, mammary glands)[21,22,23] and since several epidemiological studies on VCM-exposed workers have found an excess of lung cancer,[24] the results of this study of heavily exposed men are surprising. Three questions can be raised. One concerns the ascertainment of the population. In retrospective studies conducted from old company or union records it sometimes happens that records of people who die or leave get lost. These losses could account for the low cancer rates observed. But this is a remote possibility, since the approach followed was a historical-prospective retrospective one, which began with old lists of workers composed in 1948 and 1952 and followed almost everyone through time, adding new workers as they first appeared on more recent lists. This was done without knowledge of exposure to VCM.

A second reason for low lung cancer rates could be a bias in the classification of persons as exposed or not exposed. The classification was made essentially on the basis of personal recollection for living persons and by family members with confirmation by co-workers for deceased persons. To minimize such bias, much attention had been given to the occupational history (with indication of the buildings the subject had worked in) and workers with VCM exposure shorter than five years were rejected. There remains the possibility that some of the men who died of liver cancer, had they lived longer, might have developed lung cancer.

The small size of the population under study increased the probability of not detecting an excess that was actually present. This was a case where "the number of person/years at risk may be too small to detect an increased risk of cancer."[25] It was particularly true for rare cancers such as cancer of the brain and cancer of the lymphatic system. Inasmuch as cancer of the lung was concerned,

Table 6. — Relative Risks and SMRs for Cancer Deaths Among Men Having an Observation Period of 15 Years and More.

Cancers		No.	Relative Risk	95% Confidence Interval of the Relative Risk	SMR
All cancers	(140-209)	15	1.30	0.97- 1.74	129
Mouth and pharynx	(140-149)	0	—	—	—
Digestive	(150-159)	11	5.68	2.72-11.58	281*
Respiratory	(160-163)	2	0.35	0.25- 4.73	47
Bone, skin, connective	(170-173)	0	—	—	—
Urogenital	(185-189)	1	0.82	—	—
Eye, CNS	(190-192)	0	—	—	—
Leukemia	(200-209)	1	0.59	—	—
Other cancers		0	—	—	—

*$p < 0.01$[19]

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the situation was somewhat different. When one applies the Quebec lung cancer death rate after adjustment for age to the exposed cohort, the probability of finding an excess twice as high as in Quebec was 73%. This probability would have been 99% had the excess been three times as great in the exposed group.[25]

In view of the fact that the smoking experience of the exposed workers was similar to that of the unexposed and considering that the subjects in this study are believed to have been heavily exposed to VCM, it seems reasonable to conclude that the excess of lung cancer associated with VCM exposure, if present, is indeed rather small.

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Reducing Financial Risks

There is too little evidence that the nuclear industry, which was never very good at calculating its own interest, is seriously contemplating the effect of another Three Mile Island on its future — or its fortunes. The industry has already returned to complaints that the safety bureaucracy is nitpicking it to death, running up construction costs and delaying licenses. The latest complaint is that, in the aftermath of the TMI accident, NRC diverted safety reviewers to deal with operating reactors and fell behind in approving new licenses.

There is a kind of tunnel vision in the failure to see the connection between safety and the special financial risk involved in nuclear investment. To use the current energy crisis to avoid safety requirements is to ignore the fact that safety is essential to protecting the heavy investment in nuclear power. Some hope lies in the fact that, although the industry thinks safety requirements are a pain in the neck, they may be forced to look at them as an investment in financial public relations to alleviate the bankers' skepticism.

— Victor Gilinsky, Commissioner, the Nuclear Regulatory Commission, as quoted in "Notable and Quotable," in *The Wall Street Journal*, May 21, 1981.