NEOPLASTIC RISK AMONG WORKERS EXPOSED TO VINYL CHLORIDE

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Introduction

As early as 1930 the first adverse health effects of vinyl chloride (VC) were reported.[1] Since then, numerous observations and studies have indicated a wide range of toxicity attributable to the effects of VC on the central nervous system, the liver, the bones of the fingers, and the lungs.[2-10]

Lately, the spectrum of known toxic effects of VC broadened to include malignant neoplasms. Viola *et al.*,[11] in 1971, reported the induction of tumors of the skin, lungs, and bones in rats exposed by inhalation to 30,000 ppm of VC for twelve months. However, widespread acceptance of the carcinogenic activity of VC did not occur until early in 1974 after the announcement of three cases of liver angiosarcoma among workers at a single VC polymerization facility in the U.S.A.[12] About the same time, Maltoni reported the same cancerous hepatic effect in animals following exposure by inhalation to VC.[13] Shortly thereafter, Maltoni and Lefemine [14] and Keplinger *et al.*[15] reported the induction of tumors of the brain, kidney, liver, lung, and lymphatic system in mice, rats, and hamsters exposed to VC by inhalation.

Consequently, an epidemiological evaluation was undertaken by the National Institute for Occupational Safety and Health (NIOSH) to assess the magnitude and spectrum of neoplastic effects in workers exposed to VC. This study included industrial hygiene surveys, retrospective cohort analyses of mortality patterns, and histopathologic evaluation of tumors.

Retrospective Cohort Study

Methods

Initially, two criteria were established for selection of facilities to be investigated. Only those facilities that 1) had been engaged in the polymerization of VC for at least fifteen years and 2) had a sizable work force were considered. Following a telephone survey of all facilities in the U.S.A. known to be polymerizing vinyl chloride, four facilities were selected from among the many which met the study criteria. These four plants in 1974 were employing 250, 75, 250, and 250 VC polymerization workers and had been polymerizing VC

for 28, 20, 24, and 32 years, respectively. Vinyl chloride monomer had been made at two of the four plants, as had the compounding of polyvinyl chloride (PVC). All four plants produced various copolymers of VC at different times, vinyl acetate copolymer being common to all four and vinylidene chloride copolymer common to three.

Since environmentally induced cancer often takes many years to become clinically manifest following exposure to a carcinogen, cohort study was restricted to those individuals having achieved five or more years of employment (exposure) and ten years since onset of initial employment (latency) in departments and jobs directly related to vinyl chloride. In each plant the departments and jobs with VC exposure were determined following a walk-through survey by NIOSH personnel and review of company process, engineering control, and air-sampling data. Those specific departments and jobs classified as having VC exposure included VC monomer production, VC polymerization, PVC compounding,* and maintenance.

Employment records were initially obtained of every individual who had ever worked at any of the four VC polymerization plants. All personnel records were subsequently checked to identify each individual who had ever worked in

TABLE 1

STATUS AS OF DECEMBER 31, 1973 OF WORKERS WITH AT LEAST 5 YEARS' EXPOSURE AND 10 YEARS SINCE INITIAL EXPOSURE TO VINYL CHLORIDE

Alive	1,151	(89.0%)
Deceased	136	(10.5%)
Lost to follow up	7	(0.5%)
Total	1,294	(100%)
Total person-years	12,720	

departments or jobs classified as VC-exposed since the beginning of VC monomer production and/or VC polymerization.

Follow-up of all study cohort members † was attempted from the time of termination of employment to December 31, 1973. Information from numerous state and federal governmental agencies and other sources permitted the vital status determination of more than 99% of the 1294 cohort members (TABLE 1). Persons for whom vital status could not be determined were assumed to be alive so as not to overestimate the true risk associated with vinyl chloride.

The death certificates obtained were coded by a nosologist according to the revision of the "International Lists of Diseases and Causes of Death" in effect at the time of death, and then converted into the 7th Revision numbers, using accepted rules of comparability for 135 of the 136 cohort persons who

* The PVC compounding department of Plant 1 was not included because it was located in the same building as a tire-manufacturing operation; thus, mixed exposures were anticipated.

† Workers who were not considered part of the cohort study were also followed up for inclusion in the histopathology study.

died before the study-ending date. A modified life-table technique was used to obtain the 12,720 person-years at risk of dying, according to five-year age group, five-year calendar period, years of work experience (exposure), and time since onset of exposure (latency) to VC. Comparison was made between the observed number of deaths among the study cohort members and that expected on the basis of the U.S. white male death rates specific for age, and calendar year and cause.

Results

TABLE 2 shows that a total of 136 deaths occurred among workers exposed to vinyl chloride as contrasted with 126.3 deaths expected. Only two causes of death were in excess among workers exposed to vinyl chloride: "Nonmalignant Respiratory Disease" (6 observed deaths vs. 3.4 expected) and "All

TABLE 2

MORTALITY EXPERIENCE AMONG COHORT WORKERS EXPOSED TO VINYL CHLORIDE

Cause of Death	ICD Code *	OBS.	EXP.	SMR
All malignant neoplasms	(140–205)	35	23.5	149 †
Heart	(400–443)	57	54.7	104
Nonmalignant respiratory diseases	(470–527)	6	3.4	176
Cirrhosis	(581)	2	4.0	50
Violent deaths	(800–985)	13	14.2	92
Residual		22	26.5	83
Unknown		1	0	—
Total		136	126.3	108

* ICD = International Classification of Diseases, 7th Revision; OBS. = observed; EXP. = expected; SMR = (Standardized Mortality Ratio) $= \frac{\text{Observed}}{\text{Expected}} \times 100$.

† Significant at $p < 0.05$.

Malignant Neoplasms" (35 deaths observed vs. 23.5 expected), the latter excess being statistically significant at $p < 0.05$.

When malignant neoplasms were analyzed by site (TABLE 3), excesses were found for four organ systems: brain and central nervous system (CNS) (3 observed vs. 0.9 expected), respiratory system (12 vs. 7.7 expected), hepatic system (7 observed vs. 0.6 expected), and lymphatic and hematopoietic systems (4 observed vs. 2.5 expected).

The importance of latency when looking for occupationally induced malignant neoplasia is demonstrated by TABLE 4. When the excess risk of death due to all malignant neoplasms and malignant neoplasms of each of the four organ systems is compared in the cohort of persons who achieved ten or more years since onset of exposure versus the subset of persons who achieved 15 or more years, the excess risk increases in every cause of death. The Standardized Mortality Ratio (SMR) for all malignant neoplasms increases from 149 to 184; for the brain and CNS, from 329 to 498; for the respiratory system, from

TABLE 3

CANCER MORTALITY EXPERIENCE AMONG COHORT WORKERS EXPOSED TO VINYL CHLORIDE

Cancer Mortality	ICD Code	OBS.	EXP.	SMR
All malignant neoplasms	(140–205)	35	23.5	149 *
Brain & CNS cancer	(193)	3	0.9	329
Respiratory system cancer	(160–164)	12	7.7	156
Biliary & liver cancer	(155–156A)	7	0.6	1155 †
Lymphatic and hematopoietic system cancer	(200–205)	4	2.5	159

* Significant at $p < 0.05$.
† Significant at $p < 0.01$.

156 to 194; for the hepatic system, from 1,155 to 1,606; and for the lymphatic and hematopoietic system, from 159 to 176. Thus, for both the respiratory system and brain and CNS system these excesses of cancer become statistically significant at $p < 0.05$; and for "All Malignant Neoplasms," at $p < 0.01$.

Since Plant 4 contributed over two-thirds of the person-years to the cohort and since the plant included the three angiosarcomas of the liver announced prior to the initiation of this study, an additional analysis of malignant neoplasms was undertaken separating Plant 4 from the other three plants combined

TABLE 4

CANCER MORTALITY BY LATENCY AMONG WORKERS EXPOSED TO VINYL CHLORIDE

Cancer Mortality		≧10-Year Latency	≧15-Year Latency
All malignant neoplasms	OBS.	35	31
	EXP.	23.5	16.9
	SMR	149 *	184 †
Brain and CNS cancer	OBS.	3	3
	EXP.	0.9	0.6
	SMR	329	498 *
Respiratory system cancer	OBS.	12	11
	EXP.	7.7	5.7
	SMR	156	194 *
Biliary and liver cancer	OBS.	7	7
	EXP.	0.6	0.4
	SMR	1155 †	1606 †
Lymphatic and hematopoietic system cancer	OBS.	4	3
	EXP.	2.5	1.7
	SMR	159	176

* Significant at $p < 0.05$.
† Significant at $p < 0.01$.

TABLE 5

CANCER MORTALITY AMONG WORKERS EXPOSED TO VINYL CHLORIDE WITH ≥15-YEAR LATENCY FOR PLANT 4 VS. OTHER PLANTS

Cancer Mortality	Plant 4		Other Plants	
	OBS.	EXP.	OBS.	EXP.
All malignant neoplasms	26	13.7	5	3.2
Brain & CNS cancer	2	0.5	1	0.1
Respiratory system cancer	9	4.6	2	1.1
Biliary & liver cancer	6	0.4	1	0.0
Lymphatic and hematopoietic system cancer	3	1.4	0	0.3

(TABLE 5). Although the number of deaths in the three other plants is small, there is no evidence to indicate that the observed cancer risk in these plants is any different from Plant 4 for those workers observed 15 or more years following initial exposure to VC.

HISTOPATHOLOGY STUDY

Methods

Irrespective of an individual's meeting the five-year exposure and ten-year latency criteria, in all cases where a tumor or malignancy of any site or liver disorder of any kind was indicated on the death certificate, attempts were made to obtain hospital records, pathology reports, and tissue specimens for evaluation by a panel of pathologists.‡

Some cases had previously never worked in a department or job directly related to VC as defined for the retrospective cohort study. These cases were occasionally exposed to low levels of vinyl chloride. Therefore, for these cases latency was defined as the interval between initial employment at the plant and death.

Results

As shown in TABLE 6, of the 14 histologically confirmed cases of biliary and liver cancer among workers from the four plants, eleven cases of angiosarcoma of the liver were diagnosed. All of the eleven had worked at one time or another as reactor cleaners.

Case 4 is noteworthy. This individual's only known exposure to vinyl chloride occurred sometime during 1950–1954 at the VC polymerization operation. Seventeen years following his initial exposure to VC, this individual died at the age of 41 of hepatic angiosarcoma—an observation consistent with

‡ Dr. Luis Thomas of the National Cancer Institute, Dr. Hans Popper of The Mount Sinai School of Medicine, City University of New York, and Dr. Marvin Kuschner of the State University of New York.

TABLE 6

HISTOLOGICALLY CONFIRMED LIVER AND BILIARY CANCER CASES AMONG WORKERS EXPOSED TO VINYL CHLORIDE

Case Number	Histologic Diagnosis	Age at Death (years)	Total Exposure (years)	Latency Period (years)
1	Angiosarcoma	38	15	15
2	Angiosarcoma	58	27	28
3	Angiosarcoma	49	22	24
4	Angiosarcoma	41	3	17
5	Angiosarcoma	43	14	15
6	Angiosarcoma	52	15	19
7	Angiosarcoma	51	19	19
8	Adenocarcinoma of gall bladder or common bile duct	61	24	24
9	Gall bladder cancer	71		19
10	Adenocarcinoma of common bile duct	70		21
11 *	Angiosarcoma	45	12	12
12 *	Angiosarcoma	43	18	20
13 *	Angiosarcoma	43	19	19
14 *	Angiosarcoma	46	13	21

* Alive as of March 1, 1975; thus latency, exposure, and age are calculated at date of diagnosis.

a basic tenet of carcinogenesis, that the cancer process once initiated is irreversible, even in the absence of further or prolonged carcinogenic stimulus/exposure.

As seen in TABLE 7, ten cancers of the brain (three among study cohort members) were diagnosed on death certificate, pathology report, and/or by tissue reevaluation, to have occurred among workers exposed to vinyl chloride. Of the ten brain cancer cases, nine were classified histologically as glioblastoma multiforme; no histologic diagnosis was available for the tenth. This cell type distribution appears unusual, vis-à-vis the Yale autopsy series in which 33% of the primary intracranial neoplasms were glioblastoma multiforme.[16] Of the nine cases of glioblastoma multiforme, six had worked for at least some time in the VC polymerization areas, whereas the remaining three had worked in lower VC exposure areas.

From the fourteen cases § of primary lung cancer which occurred among workers having at least five years of exposure and ten years since initial exposure to vinyl chloride, tumor specimens were available on eight. Among these eight bronchogenic carcinomas, no cases of squamous-cell or small-cell carcinoma were seen (TABLE 8), whereas five were classified as large-cell undifferentiated and three as adenocarcinoma. This distribution of cell type is

§ Twelve subjects with lung cancer were identified by death certificates. Two additional primary lung cancer deaths among cohort members, which had been misclassified on the death certificates, were confirmed by pathologic evaluation.

TABLE 7

BRAIN CANCER CASES HISTOLOGICALLY DIAGNOSED AMONG WORKERS EXPOSED TO VINYL CHLORIDE

Case Number	Histologic Diagnosis	Age at Death (years)	Latency (years)
1	Glioblastoma multiforme	49	25 *
2	Glioblastoma multiforme	44	17 *
3	Glioblastoma multiforme	53	30 *
4	Glioblastoma multiforme	54	15 † ‡
5	Glioblastoma multiforme	56	24 † §
6	Glioblastoma multiforme	43	20 † ‡
7	Glioblastoma multiforme	42	20 † §
8	Glioblastoma multiforme	58	21 † §
9	Glioblastoma multiforme	65	19 † ‡
10	—	33	3 † ‡

* Study cohort members: interval between initial *exposure* to vinyl chloride (VC) and death.

† Non-cohort members: interval between initial *employment* and death.

‡ Non-cohort cases who had worked in VC polymerization areas.

§ Non-cohort cases who *never* worked in VC polymerization areas.

not consistent with the hypothesis postulated by Kreyberg [17] and corroborated by Archer *et al.*[18] and Saccomanno *et al.*[19] that small-cell undifferentiated and epidermoid carcinomas of the lung are the principal types whose frequency is affected by inhaled carcinogens. Moreover, it differs from the findings of Whitwell *et al.*[20] that adenocarcinoma was the predominant cell type of lung cancer among male workers with asbestosis who had been cigarette smokers.

TABLE 8

LUNG CANCER CASES HISTOLOGICALLY CONFIRMED AMONG COHORT WORKERS EXPOSED TO VINYL CHLORIDE

Case Number	Histologic Diagnosis	Age at Death (years)	Exposure (years)	Latency (years)
1	Large cell undifferentiated	39	14	15
2	Large cell undifferentiated	40	13	18
3	Large cell undifferentiated	52	22	22
4	Large cell undifferentiated	61	16	17
5	Large cell undifferentiated	61	8	17
6	Adenocarcinoma	45	19	19
7	Adenocarcinoma	57	12	12
8	Adenocarcinoma	72	15	22

Discussion

Often in retrospective cohort studies of mortality among occupational groups there are overall deficits of observed deaths when contrasted with the deaths that would be expected to occur on the basis of U.S. general population rates. This observed deficit of mortality has recently been referred to as "healthy worker effect" [23] and has been attributed to several factors, including a disproportionate number of newly hired employees still showing the results of self-selection due to good health, or preselection by industry through pre-employment medical examinations and other health-screening mechanisms.[22] To minimize this "healthy worker effect," the present study was restricted to that period following ten years since initial exposure to vinyl chloride. Thus, whereas previous investigators reported an overall deficit of deaths among workers exposed to VC,[21] no such deficit was found either by this study or by a similar study conducted by Nicholson *et al.*[24]

Conclusion

Inhalation studies by Viola *et al.*,[11] Maltoni,[14] and Keplinger *et al.*[15] have demonstrated that vinyl chloride induces hepatic angiosarcoma, adenomas and adenocarcinomas of the lung, neuroblastoma of the brain, lymphoma, and various other tumors in a variety of animal species.

In the present study of workers exposed to vinyl chloride, an excessive number of deaths due to cancer of the same four sites was found, *viz* the liver, lung, and the lymphatic and central nervous system. The evidence, both epidemiologically and histopathologically, points to vinyl chloride as the causal agent in the etiology of such excessive cancer risk. The observation of the carcinogenicity of vinyl chloride, first in animals and subsequently in man, strongly supports the need for conducting animal bioassay prior to introduction of chemical and other agents into the industrial or community environs.

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