

Mortality Study of Workers in the Manufacture of Vinyl Chloride and its Polymers*

Irving R. Tabershaw, M.D. and William R. Gaffey, Ph.D.

Animal studies have shown that inhalation of vinyl chloride produces in rats angiosarcoma of the liver as well as cancers of the lung, kidney, skin and other sites. Although workers in occupations involving exposure to vinyl chloride have been found to have an increased risk of hemangiosarcoma, no excess of other cancers has so far been reported.

This historical prospective mortality study of 8384 men who had at least one year of occupational exposure to vinyl chloride before December 31, 1972, demonstrated that cancers of the digestive system (primarily angiosarcoma), respiratory system, brain, and cancers of unknown site, as well as lymphomas, occurred more often than expected in those members of the study population with the greatest estimated exposure. The mortality from other cancers was lower than that of the general male population, with the exception of cancers of the buccal cavity and pharynx. There was an excess of these cancers, which however was inversely related to estimated exposure. The explanation for the latter finding is not apparent.

The other major findings of the study are: (1) The overall mortality of the study population was approximately 75% of what would be expected in a comparable population of U.S. males; (2) No cause of death showed a statistically significant excess over what would be expected in a comparable U.S. male population; and, (3) No deaths identified as angiosarcoma of the liver were found other than those previously identified.

This is the first epidemiological study which suggests that in humans vinyl chloride may also be associated with cancer of multiple sites.

Dr. Tabershaw and Gaffey are from Tabershaw-Cooper Associates, Inc., Suite 308, 6000 Executive Blvd., Rockville, MD 20852.

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Vinyl chloride in its manufacture and polymerization has been identified as a narcotizing agent,¹ as a liver toxin,^{2,3} and as a vasospastic agent producing a specific occupational disease, acroosteolysis.⁴ Recently, vinyl chloride has been incriminated as a carcinogen producing in a group of workers engaged in the manufacture of polyvinyl chloride a rare fatal liver tumor, hemangiosarcoma.⁵ Large doses of the chemical in rats reportedly produced cancer of the skin, lung and other organs.⁶ Unpublished but public information⁷ indicates that inhalation experiments with rats in doses easily reached in manufacturing operations produces in addition to angiosarcoma of the liver, skin, kidney and other malignant lesions.

The present study, however, was not restricted to the conditions and sites suggested by the above investigations, but concerned itself with the entire spectrum of causes of death, to the extent permitted by the size of the study group. The objectives of the study were: (1) To compare the mortality of individuals who have worked in vinyl chloride plants with that of the general population; (2) To compare mortality patterns within the population of vinyl chloride workers, based upon estimated occupational exposure; and (3) To compare mortality among vinyl chloride workers with the mortality of other occupational groups.

The study population consisted of individuals from 33 plants who had worked for at least one year in a job involving exposure to vinyl chloride before December 31, 1972, and included retired and terminated as well as active workers. For each such worker the date of birth and an employment history were obtained, and the vital status of the worker as of December 31, 1972, was ascertained. For those found to have died, those death certificates that were available were obtained and the cause of death determined. The observed mortality was compared with that of the United States male population.

Data Collection

In each plant, data were collected for each worker stated by the plant management to have been employed for at least one year in a job involving exposure to vinyl chloride. In some plants,

particularly those producing the monomer, this determination could be made on the basis of job titles. Usually, however, exposure was a function of both job title and the location of the job in the plant, so that the assessment of exposure had to be made on a case-by-case basis by plant officials.

Data were collected for as far back in time as complete records were kept. In most cases this covered the entire history of the plant. In others, records were kept for a fixed period such as a decade. In a few, records were kept for different periods, depending on whether the worker had died on the job or had left employment.

In most plants it was impossible to quantify exposure. However, industrial hygiene and safety personnel in each plant were able to identify certain jobs and locations as involving the highest exposures in the plant, and to classify other exposures as medium or low relative to the "high" represented by the jobs with the greatest exposure. Consequently, each exposed job in a worker's history was scored 1, 2, or 3 to indicate low, medium or high estimated exposure.

This gross classification has two major failings, as a result of the subjective nature of the estimates. The first is that the scores represent estimated relative exposure within a given plant. It is therefore possible that, in objective terms, a "high" score in one plant corresponds to a "medium" or even "low" score in another. The second is that the scores usually do not take into account changes in exposure over time. A worker with long service may therefore have had jobs in the remote past which involved "low" exposure relative to other jobs at that time, but which might be "high" in comparison with current exposures in the same job. This subjective classification is therefore of questionable validity in characterizing the exposure of a given worker. For epidemiological purposes, however, those who have high scores can reasonably be expected, on the average,

to have had the greatest exposure, while those with low scores will have had the least, even though the true exposure in each group may vary considerably from person to person.

The estimated exposure history of each worker was summarized by calculating an Exposure Index (EI). This was done by multiplying the number of months on each job by the exposure score, totalling these overall exposed jobs, and dividing by the total number of months of exposure.

Follow-up of Study Population

A follow-up procedure was instituted for those who had left employment and whose vital status could not be determined at the local plant, using direct mail follow-up and retail credit bureau investigations. Table 1 shows the vital status of the population as of December 31, 1972. Follow-up is 85% complete. Those who were not found were born (and began their exposure) about ten years before the group on which follow-up was complete, and had about half the duration of employment in exposed jobs with a slightly higher EI. Although there appears to be nothing very unusual about this group in terms of work history and exposure, it is nevertheless true that their exposures took place further back in time than that of the group successfully traced. It is therefore possible that their mortality, after a substantial latent period, might show a somewhat different pattern from that of the traced group.

All of the subsequent analysis is concerned with the 7128 workers on whom follow-up was complete. Table 2 shows their distribution by duration of exposed employment and the year in which that employment began. Although almost half the study group first entered exposed employment in 1960 or later, there are nevertheless 854 workers with 20 years or more exposure, and 1640 with 15 years or more. Table 3 shows the relationship between duration of exposure and EI. There does not appear to be a close relationship between the EI

Table 1. — Follow-up Status of 8384 Vinyl Chloride Workers.

	Total	Alive	Dead	Unknown	Death Certificates	
					Rec'd.	Not Rec'd.
Number	8384	6776	352	1256	328	24
Percent	100.0	80.8	4.2	15.0	92.7	7.3

Table 4. — Observed Deaths, Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers.

Cause of Death with I.C.D. Number	Obs-Exp	SMR ^a
All causes	352/467.28	75 ⁺
Tuberculosis (001-019)	1/5.71	19
Tuberculosis of respiratory system (001-008)	1/5.34	20
Malignant neoplasms (140-205)	79/77.16	110
Malignant neoplasms, buccal cavity and pharynx (140-148)	5/2.84	139
Malignant neoplasms, digestive organs and peritoneum (150-159)	19/21.67	94
Malignant neoplasms, respiratory system (160-164)	25/23.93	112
Malignant neoplasms, genital organs (170-179)	3/3.55	91
Malignant neoplasms, urinary organs (180-181)	1/3.60	30
Malignant neoplasms, other and unspecified sites (190-199)	17/11.75	155
Leukemia and leukemia (204)	2/3.77	35
Lymphomas (200-203, 205)	5/6.06	106
Diabetes mellitus (250)	1/6.31	120
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	155/207.46	30 ⁺
Vascular lesions affecting CNS (330-334)	13/24.48	57 ⁺
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	5/6.87	78
Atherosclerotic heart disease (420)	121/137.33	35
Nonrheumatic endocarditis (421, 422)	1/6.58	16
Hypertensive heart disease (440-443)	3/9.33	35
Other hypertensive disease (444-447)	3/2.60	124
Chronic & unspecified nephritis & renal sclerosis (592-594)	0/4.27	0
Influenza and pneumonia (480-493)	5/9.96	54
Ulcer of stomach and duodenum (540, 541)	2/3.83	56
Appendicitis (550-553)	0/0.66	0
Hernia and intestinal obstruction (560, 561, 570)	1/1.51	71
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	1/1.31	32
Cirrhosis of liver (581)	3/15.60	21
Hyperplasia of prostate (610)	0/0.39	0
Symptoms, senility and ill defined conditions (780-795)	1/7.34	15
All other diseases (residual)	21/45.73	43 ⁺
Motor vehicle accidents (810-835)	17/32.70	56 ⁺
Other accidents (800-802, 340-962)	18/30.54	53 ⁺
Suicide (863, 970-979)	16/16.83	122
Homicide (964, 980-985)	1/11.98	9
No. of workers	7128	
Person-years	77846	

^a SMR's adjusted for deaths with cause unknown.⁺ Significant at 5% level⁺ Significant at 1% level

no excess in the study population as a whole. However, in those workers with an SI of 1.5 or higher, there are 12 observed cases where 9.14 are expected (Table 5). In the subgroup of the above workers with five years or more exposure, there are 11 observed cases and 7.47 expected.

Respiratory cancer shows a slight excess in the total group, and a similar pattern for different exposure categories, with 13 observed versus 10.28 expected when the Exposure Index is 1.5 or higher, and 12 observed versus 8.50 expected when, in addition, the duration of exposure is five years or more.

Malignant neoplasms of other and unspecified sites show an excess in the total group, and an increase with both level and duration of exposure (Tables 5 and 6). The relationship with exposure is more pronounced, since those with exposures of less than five years have fewer cases than expected.

The lymphomas, although occurring at about the expected rate when the whole group is considered, are concentrated almost entirely in the high exposure, long duration group. In that category there are four cases observed and 1.84 expected.

Cancers of the genital and urinary

organs, and leukemia, have fewer cases than expected. The number of cases is too small to examine any trends.

Discussion

The favorable overall mortality of the study population is a phenomenon commonly observed in working populations. Standardized Mortality Ratios in the low 80's and below have been found^{11,12} Even in occupations with well defined hazards which cause an increased risk from a specific cause, the overall mortality may still be favorable because of the low risk from other major causes of death, frequently in the cardiovascular — renal category.¹¹

Table 5. — Observed Deaths, Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers, by Estimated Level of Exposure.

Cause of Death with I.C.D. No.	EI < 1.5		EI ≥ 1.5	
	Obs. Exp.	SMR*	Obs. Exp.	SMR*
All Causes	188/270.33	70 *	157/195.68	80 *
Tuberculosis (001.019)	0/3.38	0	0/2.33	0
Tuberculosis of respiratory system (001.008)	0/3.16	0	0/2.18	0
Malignant neoplasms (140-205)	37/44.28	90	41/32.67	134
Malignant neoplasms, buccal cavity and pharynx (140-148)	5/1.62	330	0/1.21	0
Malignant neoplasms, digestive organs and peritoneum (150-159)	7/12.50	60 *	12/9.14	141
Malignant neoplasms, respiratory system (160-164)	11/13.56	86	13/10.28	135
Malignant neoplasms, genital organs (170-179)	2/2.30	93	1/1.43	75
Malignant neoplasms, urinary organs (180-181)	1/2.07	51	0/1.52	0
Malignant neoplasms, other and unspecified sites (190-199)	3/6.57	46	3/4.52	190
Leukemia and leukemias (204)	1/2.18	49	2/1.57	136
Lymphomas (200-203, 205)	1/3.48	31	5/2.54	212
Diabetes mellitus (250)	5/3.65	146	2/2.65	81
Major cardiovascular and renal diseases (330-334, 400-402, 410-416, 592-594)	34/120.11	75 *	59/86.39	95 *
Vascular lesions affecting CNS (330-334)	7/14.42	52 *	5/10.06	64
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	3/3.98	80	2/2.35	75
Arteriosclerotic heart disease (420)	68/78.94	92	51/58.05	95
Nonrheumatic endocarditis (421, 422)	0/4.20	0	1/2.89	38
Hypertensive heart disease (440-443)	1/5.48	19	2/3.86	56
Other hypertensive disease (444-447)	1/1.52	70	2/1.07	201
Chronic & unspecified nephritis & renal sclerosis (592-594)	0/2.50	0	0/1.77	0
Influenza and pneumonia (480-493)	5/5.80	92	0/4.13	0
Ulcer of stomach and duodenum (540, 541)	1/2.21	48	1/1.60	68
Appendicitis (550-553)	0/0.39	0	0/0.27	0
Hernia and intestinal obstruction (560, 561, 570)	0/0.88	0	1/0.63	171
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	0/0.76	0	1/0.55	196
Cirrhosis of liver (581)	2/8.90	23	1/6.64	16
Hyperplasia of prostate (610)	0/0.25	0	0/0.14	0
Symptoms, senility and ill-defined conditions (730-795)	0/4.22	0	1/3.09	34
All other diseases (residual)	14/21.30	68 *	5/15.39	41 *
Motor vehicle accidents (810-835)	3/19.08	45 *	9/13.46	72
Other accidents (300-802, 840-962)	11/17.33	66 *	6/12.67	50 *
Suicide (963, 970-979)	3/9.73	98	7/7.02	107
Homicide (964, 980-985)	0/6.98	0	1/4.94	21
No. of workers	4032		3057	
Person-years	45354		32108	

* SMR's adjusted for deaths with cause unknown

* Significant at 5% level

* Significant at 1% level

In view of these facts, SMR's which are higher than expected may be worthy of attention even if they are not statistically significant. This is especially true in the present study since the number of deaths from many causes is quite small, and even a relatively high SMR may not reach statistical significance.

If, in addition, a particular cause shows a consistent pattern of increase with exposure or estimated exposure, the findings are particularly interesting.

By these criteria, mortality from digestive cancer, respiratory cancer, can-

cer of other and unspecified sites, and lymphomas, appear to be related to exposure as defined in this study.

In view of the association between vinyl chloride exposure and angiosarcoma of the liver, the digestive cancers were examined further to see what contribution angiosarcoma made to the observed mortality pattern.

Of the 19 digestive cancers, seven were liver cancers, of which two were angiosarcomas according to the death certificate. However, among angiosarcoma deaths in vinyl chloride workers

identified by other investigators, there were six which occurred in the present study population during the study period. They were all found in the course of the study. Table 11 shows these cases with the cause of death as given on the death certificate. Note that one case was certified as cirrhosis, and was so considered throughout this study, since the validity of comparisons with population data required that cause of death be determined only from information on the death certificate. The other five were correctly classified as

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Table 6. — Observed Deaths, Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers by Duration of Exposed Employment.

Cause of Death with I.C.D. No.	< 60 months		≥ 60 months	
	Obs. Exp	SMR*	Obs. Exp	SMR*
All causes	94 140.53	67 -	251 329.30	76 -
Tuberculosis (001-019)	0 2 23	0	0 3 55	0
Tuberculosis of respiratory system (001-008)	0 2 07	0	0 3 33	0
Malignant neoplasms (140-205)	13 19 36	78	55 57 61	116
Malignant neoplasms, buccal cavity and pharynx (140-148)	4 0 70	588	1 2 16	47
Malignant neoplasms, digestive organs and peritoneum (150-159)	2 5 26	16	17 16 56	106
Malignant neoplasms, respiratory system (160-164)	3 5 52	65	21 13 51	115
Malignant neoplasms, genital organs (170-179)	0 0 99	0	3 2 76	112
Malignant neoplasms, urinary organs (180-181)	0 0 83	0	1 2 79	37
Malignant neoplasms, other and unspecified sites (190-199)	2 3 40	71	15 8 23	187
Leukemia and leukemia (204)	1 1 25	36	1 2 53	31
Lymphomas (200-203, 205)	1 2 01	50	5 4 07	126
Diabetes mellitus (260)	2 1 30	124	5 4 54	113
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	28 51 45	65 *	125 157 39	81 *
Vascular lesions affecting CNS (330-334)	4 5 97	81	9 18 71	49 *
Rheumatic fever & chronic rheumatic heart dis (400-402, 410-416)	2 2 39	101	3 4 53	68
Arteriosclerotic heart disease (420)	21 32 54	78 *	98 105 39	96
Nonrheumatic endocarditis (421, 422)	0 1 79	0	1 5 35	20
Hypertensive heart disease (440-443)	1 2 42	49	2 7 01	30
Other hypertensive disease (444-447)	0 0 79	0	3 1 82	170
Chronic & unspecified nephritis & renal sclerosis (592-594)	0 1 55	0	0 2 76	0
Influenza and pneumonia (480-493)	3 2 93	123	2 7 09	29
Ulcer of stomach and duodenum (540, 541)	1 1 07	112	1 2 73	37
Appendicitis (550-553)	0 0 24	0	0 0 43	0
Hernia and intestinal obstruction (560-561, 570)	0 0 42	0	1 1 10	93
Gastritis, duodenitis, enteritis and colitis (540-570, 572)	1 0 40	301	0 0 92	0
Cirrhosis of liver (581)	1 4 49	26	2 11 18	18
Hyperplasia of prostate (510)	0 0 07	0	1 0 33	0
Symptoms, senility and ill-defined conditions (780-795)	1 2 28	53	0 5 09	0
All other diseases (residual)	4 11 97	40	15 26 34	63 *
Motor vehicle accidents (810-835)	10 16 14	75	7 16 65	43 *
Other accidents (800-802, 840-862)	7 12 34	65 *	10 17 32	58 *
Suicide (863-870-879)	6 6 14	114	10 10 18	100
Homicide (854-840-885)	1 5 30	20	1 6 20	1
No. of Workers	2955		4134	
Person-years	14201		43240	

* SMR's adjusted for deaths with cause unknown

* Significant at 5% level

* Significant at 1% level

Table 7. — Observed Deaths/Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers with Exposure Indices Below 1.5, by Duration of Exposed Employment.

Cause of Death with I.C.D. No.	< 60 Months Exposure		≥ 60 Months Exposure	
	Obs Exp	SMR*	Obs Exp	SMR*
All Causes	56 89.23	63*	132 181.28	73*
Tuberculosis (001-019)	3 1.41	0	0 1.97	0
Tuberculosis of respiratory system (001-098)	3 1.31	0	0 1.85	0
Malignant neoplasms (140-205)	3 12.36	73	23 31.46	35
Malignant neoplasms, buccal cavity and pharynx (140-148)	4 0.45	1036	1 1.17	38
Malignant neoplasms, digestive organs and peritoneum (150-159)	1 3.43	34	6 9.08	68
Malignant neoplasms, respiratory system (160-164)	2 3.58	65	9 10.00	93
Malignant neoplasms, genital organs (170-179)	2 0.58	0	2 1.62	127
Malignant neoplasms, urinary organs (180-181)	2 0.55	0	1 1.53	57
Malignant neoplasms, other and unspecified sites (190-199)	1 0.97	120	3 4.43	147
Leukemia and aleukemia (204)	0 0.79	0	1 1.40	73
Lymphomas (200-203, 205)	0 1.26	0	1 2.23	46
Diabetes mellitus (260)	2 1.15	203	3 2.50	124
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	21 33.38	73 *	63 86.82	75 *
Vascular lesions affecting CNS (330-334)	2 3.93	59	5 10.51	49 *
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	2 1.50	155	1 2.49	41
Arteriosclerotic heart disease (420)	16 21.14	88	52 57.87	93
Nonrheumatic endocarditis (421-422)	0 1.18	0	0 3.02	0
Hypertensive heart disease (440-443)	1 1.58	74	0 3.90	0
Other hypertensive disease (444-447)	2 0.50	0	1 1.02	101
Chronic & unspecified nephritis & renal sclerosis (582-584)	2 0.97	0	0 1.53	0
Influenza and pneumonia (480-493)	1 1.36	188	2 3.95	53
Ulcer of stomach and duodenum (540, 541)	2 0.58	0	1 1.53	57
Appendicitis (550-553)	2 0.15	0	0 0.24	0
Hernia and intestinal obstruction (560, 561, 570)	0 0.27	0	0 0.61	0
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	0 0.26	0	0 0.51	0
Cirrhosis of liver (581)	1 2.30	42	1 5.09	16
Hyperplasia of prostate (610)	0 0.05	0	0 0.20	0
Symptoms, senility and ill-defined conditions (780-795)	0 1.43	0	0 2.79	0
All other diseases (residual)	4 7.45	53	12 12.32	79
Motor vehicle accidents (810-835)	2 7.47	15	5 9.22	56
Other accidents (300-302, 340-362)	1 7.98	14	4 9.35	43
Suicide (863, 970-979)	1 4.28	46	5 5.66	109
Homicide (864, 980-985)	1 3.55	3	1 1.43	0
No. of Workers	1715		2317	
Person-years	21418		23920	

* SMR's adjusted for deaths with cause unknown

Significant at 5% level.

+ Significant at 1% level

Table 8. — Observed Deaths/Expected Deaths and Standardized Mortality Ratios in Vinyl Chloride Workers with Exposure Indices of 1.5 or Greater, by Duration of Exposed Employment.

Cause of Death with I.C.D. No.	< 60 Months Exposure		≥ 60 Months Exposure	
	Obs./Exp.	SMR*	Obs./Exp.	SMR*
All Causes	38/47.93	79	119/147.81	81
Tuberculosis (001-019)	0/0.76	0	0/1.57	0
Tuberculosis of respiratory system (001-008)	0/0.71	0	0/1.48	0
Malignant neoplasms (140-205)	5/6.57	96	36/26.11	141
Malignant neoplasms, buccal cavity and pharynx (140-148)	0/0.23	0	0/0.99	0
Malignant neoplasms, digestive organs and peritoneum (150-159)	1/1.67	76	11/7.47	151
Malignant neoplasms, respiratory system (160-164)	1/1.79	71	12/8.50	144
Malignant neoplasms, genital organs (170-179)	0/0.29	0	1/1.41	73
Malignant neoplasms, urinary organs (180-181)	0/0.26	0	0/1.26	0
Malignant neoplasms, other and unspecified sites (190-199)	1/1.18	107	7/3.51	204
Leukemia and leukemia (204)	1/0.44	288	1/1.13	90
Lymphomas (200-203, 205)	1/0.71	178	4/1.84	222
Diabetes mellitus (260)	0/0.61	0	2/2.04	100
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	7/16.54	54*	62/70.46	90
Vascular lesions affecting CNS (330-334)	2/1.87	135	4/8.19	50
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	0/0.82	0	2/2.04	100
Arteriosclerotic heart disease (420)	5/10.41	61*	46/47.65	98
Nonrheumatic endocarditis (421, 422)	0/0.57	0	1/2.32	44
Hypertensive heart disease (440-443)	0/0.76	0	2/3.10	66
Other hypertensive disease (444-447)	0/0.27	0	2/0.81	253
Chronic & unspecified nephritis & renal sclerosis (592-594)	0/0.54	0	0/1.23	0
Influenza and pneumonia (480-493)	0/0.99	0	0/3.13	0
Ulcer of stomach and duodenum (540, 541)	1/0.35	362	0/1.25	0
Appendicitis (550-553)	0/0.08	0	0/0.19	0
Hernia and intestinal obstruction (560, 561, 570)	0/0.14	0	1/0.49	209
Gastritis, duodenitis, enteritis and colitis (543, 571, 572)	1/0.14	904	0/0.41	0
Cirrhosis of liver (581)	0/1.56	0	1/5.08	20
Hyperplasia of prostate (610)	0/0.01	0	0/0.13	0
Symptoms, sensory and ill-defined conditions (780-795)	1/0.80	158	0/2.30	0
All other diseases (residual)	0/4.02	0	5/11.98	51*
Motor vehicle accidents (810-835)	2/6.05	146	2/7.43	28
Other accidents (800-802, 840-962)	1/4.73	107	1/7.36	15
Suicide (953, 970-979)	1/2.40	158	1/4.62	18
Homicide (964, 980-985)	1/2.18	54	1/2.15	0
No. of Workers	1240		1817	
Person-Years	12828		19305	

* SMR's adjusted for deaths with cause unknown

Significant at 5% level

Significant at 1% level

Table 9. — Other Malignancies (190-199, I.C.D.) in VDM Epidemiology Study Population.

Study No.	Age at Death	Mos. Exposed	Cause as Given	Autopsy
2744	38	136	Widespread metastatic melanoma (1 yr.) Malignant melanoma of back	yes
3700	48	50	Malignant melanoma with widespread metastases	no
2096	67	69	Brain tumor (carcinoma) (8 mos.)	
3946	43	64	Meningitis and pneumonitis (5 wks.) Ependymoma, fourth ventricle brain (2 mos. post-op craniotomy)	no
4433	54	81	Astrocytoma, malignant-left cerebral hemisphere (1 yr.)	yes
4800	61	51	Carcinoma of the brain Arteriosclerosis Pneumonia due to static congestion	no
7279	57	271	Brain tumor, glioblastoma multiforme (18 mos.)	
7300	44	211	Brain tumor, malignant (2 mos.)	
7371	58	249	Brain tumor, malignant	no
7306	53	215	Thyroid carcinoma with metastases	no
5769	52	239	Carcinomatosis Carcinoma vertebral body	yes
5246	67	201	Liposarcoma with metastasis (3 mos.)	yes
2850	64	193	Carcinomatosis, primary region not known (Past history, rheumatoid arthritis, myocardial infarction)	no
4778	54	300	Cardiac arrest (1 hr.) Respiratory arrest and cerebral hypoxia (2 days) Widespread metastatic carcinoma (2 mos.)	
4786	61	313	Generalized metastasis undifferentiated (7 mos.) Squamous cell carcinoma, primary site undetermined	yes
5783	69	166	Metastatic carcinoma of unknown origin Critical site undetermined (Pulmonary emphysema)	
7301	55	133	Carcinomatosis (4 mos.) Primary site undetermined	no

liver cancer, but only two were specified as angiosarcoma.

If there had been no angiosarcomas, the number of deaths classified as cirrhosis in this study would have decreased by one, and the number classified as digestive cancer would have decreased by five. The pattern of duration and intensity of exposure in these five cases was such that if they had not been present there would have been no relationship between exposure and digestive cancer. The mortality pattern in this cause group is therefore attributable to angiosarcomas of the liver.

The other cause group worth further investigation is cancer of other and unspecified sites, both because it is a heterogeneous category and because it seems, unlike the other cancers, to be more related to duration than to level of exposures.

Table 9 shows a list of the specific causes included in this category, which is essentially brain cancer and generalized cancer with primary site unknown. About 40% of the observed deaths were due to brain cancer. In the general male population, about 22% of this category is due to brain cancer, so that not only is the mortality from cancer of other and unspecified sites excessive, but brain cancer is overrepresented within the category.

The possibility exists based on the lack of specificity of some of the listed causes that some of the brain cancers were not primary, but metastases from another unidentified site such as the lung.

The cancers of the buccal cavity and pharynx are difficult to explain because of their occurrence in the low exposure, short exposure group. It is possible that this is a chance occurrence, that exposures to other substances were involved, or that the mouth and pharynx may be peculiarly susceptible because of the gaseous nature of the chemical.

Possible Biases in the Calculation of Risk

There are two major potential sources of bias in the study. The first is that the follow-up rate is lower than is desirable. The second is that observations of workers with long exposures followed by a long latent period are not adequately represented, so that the power of the study to detect causes of death associated with long exposure and long latency is impaired. Populations with such characteristics exist and

Study No.	Age at Death	Mos. Exposed	Cause as Given	Autopsy
3003	31	49	Carcinoma of lip with metastasis to lung and neck (5 yrs.)	no
3431	56	30	Pulmonary edema (50 min.) Pulmonary metastases (Carcinoma, epidermoid, tongue and mandible)	no
3001	57	71	Metastatic squamous cell ca. primary lesion palate	yes
7365	54	40	Atelectasis due to metastasis to mediastinum (4 mos.) Multiple malignant metastases to brain, liver & mediastinum (1 yr.) Adenocarcinoma of nasal pharynx (2 yrs.)	yes
3354	63	26	Massive hemorrhage into tracheo-tree Status post laryngo-pharyngectomy, left radial neck dissection Well-differentiated keratinizing squamous cell carcinoma of left pyriform sinus (mos.)	yes

Study No.	Age at Death	Mos. Exposed	Cause as Given	Autopsy
4250	54	203	Cirrhosis of liver (sev. weeks)	yes
4255	50	281	Bleeding from hepatoma (3 days) (Laennec's cirrhosis)	yes
5755	45	167	Angiosarcoma rt. lobe of liver (10 mos.)	yes
7303	38	174	Liver failure (1 mo.) Cancer of liver, primary (15 mos.)	
7376	52	238	Cardiac tamponade and massive left hemothorax (mins.) Widely metastatic angiosarcoma of liver (4 mos.)	
7385	43	214	Hepatic failure Primary carcinoma liver	yes

should be investigated.

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