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

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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.

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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Large doses of the chemical in rats reportedly produced cancer of the skin, lung and other organs.[6] Unpublished but public information[7] indicates that inhalation experiments with rats in doses easily reached in manufacturing operations produces in addition to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

and the duration of exposure, that is workers with a higher EI do not differ substantially in duration of exposure from those with a lower EI. One implication is that in assessing the relationship between mortality and exposure, both duration and level of exposure can be examined separately, as well as in combination.

Calculation of Risk of Death

The risk of death is expressed as a Standardized Mortality Ratio (SMR), which is the ratio of the number of observed deaths in the study population to the number of deaths to be expected in a comparable population of U.S. males SMR's were calculated for overall mortality and for 33 major cause groups.

Table 4 shows observed and expected deaths, and the SMR, for each of these causes for the total study group. In calculating the SMR's for specific causes, the 24 deaths for which no certificates were found were assumed to have the same cause distribution as those for which certificates were available.

In the standard population, each SMR would be equal to 100. Therefore, the statistical significance of the deviation of each SMR in the study population from the expected value of 100 was tested.[8] A single dagger indicates those SMR's which differed significantly from 100 at the 5% level, that is, which had a probability of 05 or less of occurring by chance. A double dagger indicates those which were significant at the 1% level. SMR's based on fewer than five observed cases were not tested for significance.

Table 5 shows the same SMR's for workers with an Exposure Index below 1.5 versus those at 1.5 or above. The dividing point of 1 5 represents a level halfway between "low" and "medium."

Table 6 shows similar results for workers with less than five years exposure versus those with five years or more.

In order to examine the possible interaction between duration and level of exposure, the study population was divided into four groups on the basis of both EI (low vs high) and duration of exposure (short vs long) using the same dichotomization as Tables 5 and 6.

Table 7 shows the results for short versus long exposure in the low EI group, and Table 8 shows the same comparison in the high EI group.

In each of the above tables, deaths for which certificates had not been received were assumed to be distributed as a uniform percentage of all causes. The cause specific SMR's were therefore adjusted upward by a percentage which varied in each subgroup.

Table 2. — Distribution of Months in Exposed Employment by Year in Which Exposure Began, for 7128 Vinyl Chloride Workers with Completed Follow-up.

Year Exp. Started	Total	Months of Exposure							
		< 60	60-119	120-179	180-239	240-299	300-359	360-419	Unknown
1930-39	35	2	4	1	4	6	13	5	
1940-49	1048	135	93	119	151	277	237	34	2
1950-59	1962	389	257	383	531	282			20
1960-69	3368	1714	1442	195					17
1970-71	715	715							
Total	7128	2955	1796	698	786	565	250	39	39

Results of Analysis

The overall mortality of the study population is statistically significantly lower than that of the U.S. male population. There were 352 observed deaths compared with 467 expected, for an SMR of 75.

Table 4 shows that no specific cause of death was statistically significantly greater than expected. Several, particularly heart disease, accidents and "other diseases" not detailed in the tables, were significantly below their expected values.

When the study population is divided according to intensity and duration of exposure (Tables 5 and 6) and combinations of these measurements (Tables 7 and 8) three major patterns emerge

For malignant neoplasms as a whole, the SMR increases with increasing exposure, whether measured by level, duration, or both. In the high exposure group with 5 years or more exposure (Table 8) there are 36 observed cases and 26.11 expected.

For cardiovascular — renal diseases as a group; there are also increases in the SMR with increasing exposure, but the numbers of observed cases remain less than expected, the differences being statistically significant in all groups except the high exposure, long duration group in Table 8.

For all other causes, there are no consistent relationships with exposure.

Within the malignant neoplasms, the largest (although not statistically) significant SMR is in cancers of the buccal cavity and pharynx, with five observed, 2.84 expected, and an SMR of 189. However, Tables 5 to 8 show that all these cases have Exposure Indexes below 1.5 and four out of the five have less than five years exposure. Table 10 is a listing of these deaths with age at death, duration of exposure, and cause as stated on the death certificate.

Cancer of the digestive system shows

Table 3. — No. and % of 7128 Vinyl Chloride Workers by Months of Exposed Employment and Exposure Index.

Exposure Index	Total No. %	Months of Exposure							
		< 60 No. %	60-119 No. %	120-179 No. %	180-123 No. %	240-299 No. %	300-359 No. %	360-419 No. %	Unknown
1.0-1.4	4032 (100)	1715 (43)	1125 (28)	402 (10)	406 (10)	247 (7)	92 (2)	18 (0)	
1 5+	3057 (100)	1240 (41)	671 (22)	295 (10)	380 (12)	291 (10)	159 (5)	21 (1)	
Unknown	39								39
Total	7128 (100)	2955 (41)	1796 (25)	697 (10)	786 (11)	565 (8)	251 (4)	39 (1)	39 (1)

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*
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	189
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 aleukemia (204)	3/3.77	85
Lymphomas (200 203, 205)	6/6.06	106
Diabetes mellitus (260)	7/6.31	120
Major cardiovascular and renal diseases (330-334, 400-468, 592 594)	155/207.46	80 ‡
Vascular lesions affecting CNS (330-334)	13/24.48	57 ‡
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	5/6.87	78
Arteriosclerotic heart disease (420)	121/137.33	95
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	82
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)	21/45.78	49 ‡
Motor vehicle accidents (810-835)	17/32.70	56 ‡
Other accidents (800-802, 840-962)	18/30.64	63 ‡
Suicide (963, 970-979)	16/16.83	102
Homicide (964, 980-985)	1/11.98	9
No. of workers	7128	
Person-years	77846	

*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 EI 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.[9,10] 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)	9/6.57	146	8/4.52	190
Leukemia and aleukemia (204)	1/2.18	49	2/1.57	136
Lymphomas (200-203, 205)	1/3.48	31	5/2.54	212
Diabetes mellitus (260)	5/3.65	146	2/2.65	81
Major cardiovascular and renal diseases (330-334, 400-468, 592-594)	84/120.11	75 ‡	69/86.99	85 †
Vascular lesions affecting CNS (330-334)	7/14.42	52 ‡	6/10.06	64
Rheumatic fever & chronic rheumatic heart dis. (400-402, 410-416)	3/3.98	80	2/2.85	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 (780-795)	0/4.22	0	1/3.09	34
All other diseases (residual)	14/21.90	68 †	6/15.89	41 ‡
Motor vehicle accidents (810-835)	8/19.08	45 ‡	9/13.46	72
Other accidents (800-802, 840-962)	11/17.83	66 †	6/12.67	50 ‡
Suicide (963, 970-979)	9/9.73	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, cancer 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

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)	13/19.96	78	65/57.61	116
Malignant neoplasms, buccal cavity and pharynx (140-148)	4/0.70	688	1/2.16	47
Malignant neoplasms, digestive organs and peritoneum (150-159)	2/5.26	46	17/16.56	106
Malignant neoplasms, respiratory system (160-164)	3/5.52	65	21/18.51	116
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 aleukemia (204)	1/1.25	96	2/2.53	81
Lymphomas (200-203, 205)	1/2.01	60	5/4.07	126
Diabetes mellitus (260)	2/1.80	134	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	1/2.78	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 (543, 571, 572)	1/0 40	301	0/0.92	0
Cirrhosis of liver (581)	1/4.49	26	2/11.18	18
Hyperplasia of prostate (610)	0/0.07	0	0/0.33	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	16/26 34	63 †
Motor vehicle accidents (810-835)	10/16.14	75	7/16.65	43 ‡
Other accidents (800-802, 840-962)	7/12.94	65 †	10/17.82	58 †
Suicide (963, 970-979)	6/6.34	114	10/10.28	100
Homicide (964, 980 985)	1/5.80	20	0/6.20	0
No. of Workers	2955		4134	
Person-years	34201		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)	0/1.41	0	0/1.97	0
Tuberculosis of respiratory system (001-008)	0/1.31	0	0/1.85	0
Malignant neoplasms (140-205)	8/12.86	73	29/31.46	95
Malignant neoplasms, buccal cavity and pharynx (140-148)	4/0.45	1036	1/1 17	88
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)	0/0.68	0	2/1.62	127
Malignant neoplasms, urinary organs (180-181)	0/0.55	0	1/1.53	67
Malignant neoplasms, other and unspecified sites (190-199)	1/0.97	120	8/4.43	187
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)	0/0.50	0	1/1.02	101
Chronic & unspecified nephritis & renal sclerosis (592-594)	0/0.97	0	0/1.53	0
Influenza and pneumonia (480-493)	3/1.86	188	2/3.95	53
Ulcer of stomach and duodenum (540, 541)	0/0.68	0	1/1.53	67
Appendicitis (550 553)	0/0.15	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)	1/2.80	42	1/6.09	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	63	10/12.92	79
Motor vehicle accidents (810-835)	3/9.87	35	5/9.22	56
Other accidents (800 802, 840-962)	3/7.98	44	8/9.85	83
Suicide (963, 970 979)	3/4 08	86	6/5.66	109
Homicide (964, 980-985)	0/3.55	0	0/3.43	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 aleukemia (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, senility and ill-defined conditions (780-795)	1/0.80	158	0/2.30	0
All other diseases (residual)	0/4.02	0	6/11.88	51 †
Motor vehicle accidents (810-835)	7/6.05	146	2/7.43	28
Other accidents (800-802, 840-962)	4/4.73	107	2/7.96	26
Suicide (963, 970-979)	3/2.40	158	4/4.62	88
Homicide (964, 980-985)	1/2.18	58	0/2.76	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.

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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	186	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	216	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	318	Generalized metastasis undifferentiated (7 mos.) Squamous cell carcinoma, primary site undetermined	yes
5789	69	166	Metastatic carcinoma of abdomen 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 should be investigated.

Table 10. — Malignant Neoplasms of Buccal Cavity and Pharynx (140-148, I.C.D.) in VCM Epidemiology Study Population.

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.) Adeno-carcinoma 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

Table 11. — Angiosarcoma Deaths in VCM Epidemiology Study Population.

Study No.	Age at Death	Mos. Exposed	Cause as Given	Autopsy
4250	54	203	Cirrhosis of liver (sev. weeks)	yes
4255	60	281	Bleeding from hepatoma (3 days) (Laennecs cirrhosis)	yes
5765	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

References

1. Lester D, Greenberg LA, Adams WR: Effects of single and repeated exposures of humans and rats to vinyl chloride. *Am Ind Hyg Assoc J* 24:265-75, 1963

2. Marsteller HJ, Leibach WK, Muller R, et al: [Chronic toxic liver lesions in the PVC (polyvinyl chloride) — producing workers.] *Dtsch Med Wochenschr* 98:2311-14, 1973.

3. Kramer CG, Mutchler JE: The correlation of clinical and environmental measurements for workers exposed to vinyl chloride. *Am Ind Hyg Assoc J* 33:19-30, 1972.

4. Dodson VN, Dinman BD, Whitehouse WM, et al: Occupational acroosteolysis III. A clinical study. *Arch Environ Hlth* 22:83-91, 1971

5. Creech JL, Johnson MN: Angiosarcoma of liver in the manufacture of polyvinyl chloride. *J Occup Med* 16:150-51, 1974

6. Viola PL, Bigotti A, Cuputo A: Oncogenic response of rat skin, lungs, and bones to vinyl chloride. *Cancer Res* 31:516-22, 1971.

7. Occupational Safety and Health Administration. Occupational Safety and Health Standards. Emergency Temporary Standard for Exposure to Vinyl Chloride. Federal Register 39 (67) 12342-44, April 5, 1974.

8. Chiang CL. Standard error of the age-adjusted death rate. *Vital Statistics Special Reports*, 47 (1961) pp 275-285

9. Lloyd JW, Ciocco A. Long-term mortality study of steelworkers; I. Methodology. *J Occup Med* 11:229-310, 1969

10. Tabershaw/Cooper Associates, Inc., unpublished

11. Redmond CK, Ciocco A, Lloyd JW, Rush HW. Long-term mortality study of steelworkers: IV. Mortality from malignant neoplasms among coke oven workers. *J Occup Med* 14:621-629, 1972

Additional information from two other sources is given in table 5. The small excess reported provides little further evidence of an occupational hazard, as one of the two deaths observed in the Swedish study occurred in a young man who had been employed for less than a year when the diagnosis was made, while the excess death rate for brain cancer observed in the German study was less than that observed among chemical workers not exposed to vinyl chloride (2.9 deaths after allowance for deaths from unknown causes against 1.6 expected) and among workers in the PVC fabrication industry (5.9 deaths after allowance for deaths from unknown causes against 1.1 expected).

Cancers of lymphatic and hematopoietic tissues. The idea that vinyl chloride might cause cancer of the lymphatic and hematopoietic tissues — more specifically the lymphatic tissue — was suggested by Tabershaw & Gaffey (45) and by Waxweiler et al (50) in two cohort studies, when they found, respectively, five deaths from lymphomas in the most heavily exposed workers against 2.54 expected and four deaths from cancers of the lymphatic and hematopoietic tissues against 2.5 expected. These small excesses might have been ignored if the laboratory findings had not been interpreted as suggesting that lymphomas were produced experimentally in animals exposed to vinyl chloride by inhalation (29). The idea that similar exposure might also cause lymphomas in humans, therefore, merits serious consideration. The data from the four principal studies that are summarized in table 4 provide little support for the hypothesis when all cancers of the lymphatic and hematopoietic tissues are considered together (57 deaths against 50.87 expected, SMR 112) and very little more is obtained from the separate data for cancers of the lymphatic system (Tabershaw & Gaffey's definition of ICD list numbers, eighth revision, 200—203 and 205 being used) that are shown in table 1 (35 deaths against 29.40 expected). The position is, moreover, hardly altered if the data in Tabershaw & Gaffey's initial report are subtracted (29 deaths against 23.36 expected, SMR 124).

Little additional information is provided by the results of the German study (49). (See table 5.) This study obtained an SMR of 214 for exposed workers (based on 15 observed deaths, increased to 16.5 when allowance is made for the number of deaths from unknown causes) against SMR values of 77 and 34 for an unexposed group of chemical workers and a group of PVC fabricators. It showed that the excess of the exposed workers was present only for men who had been exposed for more than one year and that this excess was most marked for men who had been exposed for five years or more (10.7 deaths after allowance for the number of deaths from unknown causes against 4.0 expected, SMR 268, P one-tailed <0.01).

Melanoma. An excess of melanoma was reported for Norwegian workers by Heldaas et al (22), who raised the possibility that vinyl chloride might have produced the disease. Four cases were observed when 0.79 were expected, and three of the four were in men whose occupations involved the highest exposures (against 0.51 expected). At the time of the writing of their report, one further case had been detected with onset three years after the closure of the study. Subsequent studies in other countries have, so far, reported only two deaths against 2.0 expected. (See tables 1 and 5.)

Thyroid cancer. An excess of thyroid cancer was also reported in the Norwegian study (22), in which two cases were observed against 0.16 expected. The investigators were not aware of any other studies indicating an excess of this type of cancer, and they drew no conclusion from their observation. Two of the three major studies that have been reported since the Norwegian observation was made gave no data for thyroid cancer; the third reported two deaths against 0.43 expected. (See table 1.) One death from thyroid cancer, it may be noted, was reported in the US by Monson et al (36).

Cancers of the digestive tract. Suggestions that vinyl chloride might cause cancers of the digestive tract in general have sometimes been made, but they have not taken adequate account of the contribution of cancers of the liver to the total number of cancers of the digestive system, particularly when it is borne in mind that some liver cancers are likely to be misdiagnosed as cancers of other organs. The combined data from the four principal studies shown in table 4 weigh heavily against the idea that any such effect has been produced.

Other cancers. One of the remaining types, or classes, of cancer listed in table 4 shows a statistically significant excess, namely, the heterogeneous group of "other cancers" (83 observed deaths against 65.24 expected, P two-sided <0.05). This excess is only marginally significant and may be a chance observation. The most likely explanation is, however, that a few angiosarcomas of the liver were not recognized and were diagnosed as secondary liver cancer or carcinomatosis, site unknown, the number of deaths in this category therefore being increased.

Hazards of nonmalignant disease

No previous study has suggested that any nonmalignant cause of death other than cirrhosis of the liver would be likely to be increased as a result of exposure to vinyl chloride, and cirrhosis of the liver is presumed to be increased only because of the liver changes that were observed as part of the "vinyl chloride illness" (24, 31, 33). Two other possibilities have, however, been raised, namely, the production of nonmalignant respiratory disease, because of the changes in lung function and radiographic appearances that have been

Table 7. Mortality from selected nonmalignant causes and all causes in the four principal studies combined. (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Type of disease	O	E	SMR	Source of information[a]
Bronchitis, emphysema[b]	80	66.83	120	1, 2
Other respiratory disease	71	125.78	56	1, 2
All respiratory disease	160	200.82	80	1, 2, 3, 4
Ischemic heart disease	797	885.73	90	1,2
Other circulatory disease[c]	252	264.55	95	1,2
All circulatory disease[c]	1 103	1 209.35	91	1, 2, 3, 4
Cirrhosis of the liver	46	66.26	69	1, 2, 4
Other disease	238	368.07	65	1, 2, 3, 4
All nonmalignant disease	1 547	1 844.50	84	1, 2, 3, 4
All external causes	226	295.15	77	1, 2, 3, 4
All nonmalignant causes	1 773	2 139.65	85	1, 2, 3, 4
All causes	2 441	2 747.85	89	1, 2, 3, 4

[a] 1 = United States study (14), 2 = United Kingdom study (25), 3 = Canadian study (46), and 4 = Italian study (4).
[b] Bronchitis in the United Kingdom study, emphysema in the United States study.
[c] Includes cerebrovascular disease in the United Kingdom and Italian studies.

Table 8. Mortality from chronic obstructive lung disease[a] in the series from the United States (US) (14) and the United Kingdom (UK) (25) by characteristics relevant to an occupational hazard (O = observed number of deaths, E = expected number of deaths, SMR = standardized mortality ratio)

Data characteristic[b]	Category 1			Category 2		
	O	E	SMR	O	E	SMR
Observed 20 years or more after first employment in the US (1), others in the US (2)	30	15.8	190	11	7.0	157
Employed 10 years or more in the US (1), others in the US (2)	16	10.9	147	25	12.0	208
Employed before 1956 in the UK (1), others in the UK (2)	26	30.17	86	10	13 60	74
Ever employed as an autoclave worker in the UK (1), others in the UK (2)[c]	3	6.55	46	33	37.22	89

[a] Described as emphysema in the US study and as bronchitis in the United Kingdom study.
[b] The numbers in parentheses designate the category.
[c] Men ever employed as a bagger or drier, occupations which would have caused the greatest occupational exposure to polyvinyl chloride dust, experienced one death from bronchitis against 4.98 expected.

recorded for men exposed to PVC dust (2, 26, 27, 44), and acute cardiac death, from analogy with the effect of other halogenated hydrocarbons (25) and the observation of an increased mortality from myocardial infarction in the few years following the cessation of exposure in the Swedish PVC processing industry (35). Relevant figures for the numbers of deaths from these and other nonmalignant causes that are obtainable from the four principal studies were given in table 2, and they have been summarized in table 7.

Cirrhosis of the liver. Three of the four principal studies gave separate figures for cirrhosis of the liver, none of which showed an increased mortality (table 2); in combination they gave an SMR of 69 based on 46 deaths. The fourth study, which did not give separate data for cirrhosis of the liver, reported four deaths from all diseases of the digestive system combined against 3.85 expected and noted that the four included two that were certified as due to cirrhosis of the liver, but actually due to angiosarcoma (46). In the two supplementary studies in which data were given for this disease, the SMR was 82 in one, based on 15.1 deaths after allowance for the number with unknown causes (49), and 133 in the other, based on seven deaths (37).

Nonmalignant respiratory disease. The data for nonmalignant respiratory disease are confusing in that the total SMR from the combined data for the four principal studies is 80 and is the sort of figure that is commonly found in healthy industrial populations, yet the US study recorded a substantially increased mortality from emphysema (41 deaths and an SMR of 180 before any allowance was made for deaths from unknown causes). No such excess was found in the UK, where 36 deaths from bronchitis gave an SMR of 82. International comparisons of chronic nonmalignant respiratory disease are complicated by the usage of different terms to describe what it is now agreed is best called chronic obstructive lung (or pulmonary) disease, but which in the past tended to be called emphysema in the US and chronic bronchitis in the United Kingdom. It must, therefore, be presumed that the two categories of "emphysema" and "bronchitis" used respectively in the two large national studies were meant to describe the same thing. One must assume, therefore, that the experiences in the two countries were very different, despite the fact that both related to cohorts that had very similar experiences of angiosarcoma of the liver and so, presumably, fairly similar exposures to vinyl chloride.

Separate figures are shown in table 8, where available, for the mortality observed among men with different durations and intensities of exposure. Unlike the data for cancer of the lung that were shown in table 6, they provide no consistent evidence of a greater risk in the groups in which an occupational hazard would

be expected to be concentrated. The authors of the Environmental Health Associates report (14) were unable to give any explanation for the increased mortality from emphysema, and they point out that it could hardly be due to excess cigarette smoking, as there was no overall excess for cancer of the lung. It is striking, however, that the excess is more than compensated for by deficiencies in the other categories of nonmalignant respiratory disease (pneumonia 15 deaths,[5] SMR 47.0; other respiratory disease 14 deaths, SMR 42.6), and the question arises whether the emphysema excess could be a classificatory artifact. Environmental Health Associates (14) list all the 41 deaths which show that they were coded under ICD number 527 which, in the out-of-date seventh revision that was used for the coding of all deaths in the study, was the code for "other respiratory disease not otherwise classified" and included emphysema. Under that revision, however, emphysema that was associated with bronchitis should be classified with bronchitis under ICD numbers 500 to 502, and the possibility may be considered that some of the emphysema deaths should have been classified in some category of respiratory disease other than ICD number 527. If this were the situation, it could account for both the excess mortality from emphysema and the grossly deficient mortality from other nonmalignant respiratory diseases.

No excess mortality from "bronchitis, emphysema, and asthma" was observed in the German study (SMR 44 with 6.3 deaths observed after allowance for the number of deaths from an unknown cause) (49).

Cardiovascular disease. Data for ischemic (or arteriosclerotic) heart disease (which may be presumed to include the vast majority of all deaths certified as due to acute cardiac disease) were given only by the two big national studies, and they provide no evidence of an increased mortality. The SMR values of 90 for this group of diseases and of 91 for all cardiovascular disease recorded in the four principal studies are typical of the SMR values of healthy industrial populations, and there is no suggestion of any occupational hazard in the subsidiary analyses provided by the two national studies. In particular, there is no evidence of an increased mortality within one month of leaving employment in the UK study either for all workers (52 deaths, SMR 61) or for the most heavily exposed autoclave workers (9 deaths, SMR 42).

A slight increase in ischemic heart disease mortality was recorded for the exposed workers in the German study (49), but it was less than that recorded for the unexposed chemical workers and the PVC fabricators (SMR values of 127, 131, and 158 based on 97.2, 126.7, and 109.7 deaths, respectively, after allowance for the number of deaths from unknown causes).

Discussion

The information that has now been obtained about the long-term health of men occupationally exposed to vinyl chloride is massive and compares favorably with that available for any other occupational group. Two facts are outstanding. First, the men have experienced a specific hazard of a type of cancer that is normally extremely rare, namely, angiosarcoma of the liver. The rarity of this disease under other conditions made the detection of the hazard easy; but the long latency period before the disease appears after first exposure (almost always more than 10 years and usually more than 15 years) meant that a large number of men had been exposed before the hazard was detected and that it will still be many years before the extent of the protection provided by the reduction in exposure in the 1960s and that of the further reduction that followed the recognition of the hazard in 1974 are known. There is, unfortunately, no effective treatment for the disease, and the number of cases is reflected in the number of deaths. Some 50 deaths have occurred among the 16 740 men who were followed in the four principal studies that have been reviewed in this report, so that approximately 1 in 335 men have been affected, 2 % of the deaths having been due to this one cause. Eventually many more men must be expected to develop the disease. One estimate (38) suggests that the total may be increased 10 times, but a more realistic estimate is two to three times (19).

The second outstanding observation is that the mortality of the exposed men, other than that due to angiosarcoma of the liver, is typical of the normally healthy industrial worker — that is not to say that no other hazard exists, but that the effect of any other hazard is small.

The massive data that are now available provide no reason for thinking that any hazard other than one of cancer has been overlooked. It is, however, still difficult to decide whether vinyl chloride produces a risk of developing cancer other than angiosarcoma of the liver which might be small compared to the risks produced by nonoccupational causes, but yet absolutely almost as large as the risk of developing the normally very rare angiosarcoma.

One of the many hazards suggested can be dismissed, as there is no evidence to support it, namely, that of vinyl chloride as a cause of any cancer of the digestive tract other than angiosarcoma of the liver. Two hazards (of melanoma and cancer of the thyroid) have been suggested only very recently, and few of the available studies have provided information about them. There is no good theoretical reason or laboratory evidence to suggest that either should be produced by

[5] The deaths attributed to different groups of respiratory diseases and the corresponding SMR values that are cited in this section for the US study are as given by the Environmental Health Associates (14) and have not been adjusted to account for the number of deaths from an unknown cause. To take account of these deaths, the observed deaths and SMR values can both be multiplied by 1.0674.

vinyl chloride, and, in light of present evidence, the simplest explanation is that the reported excesses are the chance effects that must be expected when many different types of cancer are studied in several different populations. So far as melanoma is concerned, it has to be remembered that the disease has become much more common in recent years in Scandinavia (where the excess was reported) due, it is believed, to the popularity of sunbathing and the increased opportunities for Scandinavians to travel to the warmer parts of Southern Europe and North Africa. The extent to which this change may have affected the observation in Norway needs to be examined.

Two other hazards (of lymphoma and brain cancer) were suggested by the early results of some of the US studies. That vinyl chloride might produce a hazard of lymphoma was initially supported by the preliminary results of animal studies, but the complete results of the many investigations that have been undertaken (see reference 29) do not suggest that lymphoma or any other cancer of the hematopoietic system is liable to be produced. There is, however, some evidence that brain tumors can be produced in rats (29). The hypotheses that lymphomas and brain cancers might be produced by vinyl chloride have been supported by the observation that both these types of cancer have caused death more often than might be expected from national mortality rates, but the excesses observed in the combined data from the four principal studies in this review are small and not statistically significant, and the hypotheses remain unproved. The small excess of brain cancer is particularly difficult to evaluate, as mortality rates from this disease have changed rapidly over time as methods of diagnosis have improved and the suspicion of an occupational hazard (which was raised in 1975) could have influenced the findings. What excess has occurred has been limited to the US and Germany, and the German findings carry little weight, as the excess was found in each of the three occupational groups studied, irrespective of the chemicals to which they were exposed. The supplementary data from the German study showing an increased mortality from lymphatic and hematopoietic cancers are more impressive, particularly as the excess was the most marked for men who had been employed for at least five years. In these circumstances, judgment must still be suspended until the data for each study are analyzed for each specific type of cancer, by intensity and duration of exposure, and by time since exposure began.

There remains the suggestion that vinyl chloride might cause lung cancer. At first sight, this possibility is ruled out by the SMR of 97 for the combined data for respiratory cancer for the four principal studies. Lung cancer is, however, normally so common (accounting for about 8 % of the expected deaths) that an increase in mortality that was half as important (numerically) as the increase in mortality from angiosarcoma of the liver might easily be overlooked (95 % confidence limits of the SMR 85—112). The incidence of the disease varies moreover within a country, and there must be doubts as to whether the national experience provides a suitable reference for men employed in plants that are not evenly distributed about the country. In these circumstances one cannot exclude an occupational hazard unless it can be shown that the mortality of the exposed men is independent of the factors that might be expected to influence it if some of it were occupational in origin, namely, the intensity and duration of exposure and the time since exposure began. It is not possible to examine these relationships in detail, as the reports do not provide all the necessary information. Such information as they do provide, which was summarized in table 6, supports the idea that exposure to vinyl chloride involves a small hazard of lung cancer. Taken in conjunction with the knowledge that lung tumors have been produced in several species of animals exposed to vinyl chloride by inhalation (29), it would seem that a small hazard of lung cancer probably did occur. The evidence is not, however, strong enough to conclude that it definitely did. If it did, the hazard was evident only for men who had been employed for many years at a time when exposures of several hundred parts per million or more were common, and any persisting risk can be only minute and incapable of detection.

The questions that have been left unanswered by this discussion might well be answered definitely if (i) all the exposed men could be followed to (say) the end of 1984, (ii) the investigators could present their data in comparable ways, taking account of duration of employment and time since first employment and presenting data separately for men first employed before (say) 1965 and between 1965 and 1974, and (iii) estimates could be made of the effect of correcting the results for each group of employees for the locality in which they lived and worked.

Hazards to the general population

As vinyl chloride has been proved to cause cancer in man and is a mutagen in laboratory experiments, it must be presumed that even the minute doses that escaped into the general environment from production plants or (in the early days of manufacture) from PVC materials will have caused some risk of cancer to the general public. These risks must, however, have been very small, as air concentrations of vinyl chloride, even within a kilometer of plants handling vinyl chloride, used to be (in or around 1975) of the order of 10 to 40 ppb (1, 3, 15), and this level is about one-ten thousandth of the concentration that has caused an occupational hazard. It is obvious, therefore, that it would be impossible to detect the risk of any cancer that might be produced by vinyl chloride other than a risk of angiosarcoma of the liver, as it has proved so difficult to detect any other risk among men who were exposed occupationally. The position with regard to an-

giosarcoma of the liver is different. This disease is normally so rare that, in the absence of specific exposure to one of the known causes (vinyl chloride, thorium dioxide, and arsenic in pesticides and medicines), the annual incidence is on the order of $1—2 \cdot 10^{-7}$ (5, 8).[6] In these circumstances the discovery of even one case in a man living close to a factory in which vinyl chloride was used in the days before exposure was tightly controlled may be regarded as presumptive evidence of the effect of environmental pollution.

Several surveys have been undertaken to determine whether any such cases have occurred. Saric et al (43) and Elinder & Pershagen (13) sought for cases in the vicinity of plants handling vinyl chloride in Yugoslavia and Sweden and found none. In Holland Dalderup et al (11) found eight confirmed cases not attributable to thorotrast or arsenic and could trace "no contact with vinyl chloride," but they made no specific mention of the patient's place of residence. Baxter et al (3) found 14 confirmed cases in Great Britain over a 12-year period, one of which was in a man who had lived half a kilometer from a PVC manufacturing plant, and, in New York State over an 18-year period, Brady et al (5) found 19 cases that could not be attributed to any known cause, five of which were in people living within a mile of plants manufacturing or using vinyl chloride. The overall incidence rates in these last two studies were not unduly high, but the occurrence of as many as six cases among people living so close to manufacturing plants is surprising. Brady and his colleagues, moreover, compared their series of patients with matched referents and found that none of the referents lived equally close to a plant. Two of these six neighborhood cases (one in England and one in New York State) cannot be attributed to environmental pollution with vinyl chloride, as the men who developed the disease had lived near the plants for six and eight years, respectively, before developing the disease, and this period is too short to allow for the necessary latency. The other four cases, however, all occurred after 15 or more years of local residence, and the discovery of these cases strongly suggests that pollution of the environment around plants manufacturing VCM or PVC may have caused a minute hazard to the general public.

Current concentrations around plants handling vinyl chloride are certainly much lower than those reported previously by the US Environmental Protection Agency. Recent British measurements made within a few hundred meters of the VCM areas have given average values below the daily limit of detection (5 ppb) for three of five plants, the readings at the two others being 20 ppb (100 m outside the boundary fence) and 88 ppb (just inside it) (47), although substantially higher values were recorded on two occasions associated with putting one plant into operation and with an accident at the other. According to any reasonable criterion the hazard to the general public (if there is any at all) must be negligible (42).

No other hazard to the general population, other than a hazard of cancer, can reasonably be postulated.

Summary

This paper reviews (i) the possible effects of vinyl chloride on the personal health of men exposed by virtue of their occupation (other than the early effects of the very high concentrations to which men were exposed when the industry was first developed — unconsciousness, cardiac arrhythmia, and the characteristic "vinyl chloride illness") and (ii) the carcinogenic effects that might conceivably be observed in the general population as a result of the widespread distribution of vinyl chloride as a pollutant. The possibility that vinyl chloride might act as a teratogen or might cause mutations in the germ cells has not been examined, as the little evidence that has been adduced relating to such possible effects has been reviewed elsewhere and the conclusion was reached that no such effects have been demonstrated.

Many groups of workers exposed to vinyl chloride in the manufacture of VCM or PVC have been studied since the carcinogenic potential of vinyl chloride was first recognized. Some results have shown that occupational exposure can cause angiosarcoma of the liver, and others have suggested that it may cause several other types of cancer as well. The actual situation can be determined only in an examination of all the evidence, especially the combined results of those studies that include a substantial proportion of observations on men more than 25 years after their first exposure and cover a long enough period for more than 10 % of the employees to have been expected to die.

The results of four studies can be usefully combined for this purpose. They are two national studies, one from the US and the other from the UK, and two studies of employees in one plant in Canada and two plants in Italy. The results of other studies from the Federal Republic of Germany, Norway, Sweden, Italy, France, and Japan can be used only to provide supplementary information. The many earlier reports of exposed workers in the US and the UK concern men covered more completely in the two recent national studies, and their results serve only as sources of hypotheses.

Minor criticisms can be made of three of the four most useful studies. They do not seriously affect the value of the results, except that allowance has to be made for the failure to determine the cause of 6.3 % of the deaths recorded in the US study. Three of the studies use national rates to estimate the numbers of deaths that might have been expected to occur in the absence of any special occupational hazard, and the fourth (Canadian) uses rates for the province in which

[6] The figure of $1.4 \cdot 10^{-6}$ cited by Heath et al (21) seems to have been a misprint for $1.4 \cdot 10^{-7}$.

the plant was situated. It must, therefore, be kept in mind that the rates used may not have been wholly appropriate for the localities in which the plants were situated. This circumstance is potentially important for the US study, which covered workers in 37 plants, 22 of which were situated in the southern part of the country. The other less informative studies are, for the most part, open to more serious criticism, and the value of each set of results needs to be assessed separately in relation to each disease.

The combined results of the four principal studies show that the SMR values, reflecting the ratios between the numbers of deaths observed and those expected in the absence of an occupational hazard multiplied by 100, have been (i) 77 for accidents and other violence, (ii) 84 for diseases other than cancer, and (iii) 102 for cancers other than cancer of the liver. All these results are what might be anticipated for an industry devoid of any specific occupational hazard. The low ratio for diseases other than cancer reflects the "healthy worker effect," which results from the selection process that inevitably excludes some of the less healthy members of the population from industrial employment and is compatible with a higher ratio for cancer, as the mortality from cancer is not normally subject to such an effect, apart from the first two or three years immediately following the start of employment.

The mortality from cancer of the liver was nearly seven times that expected. Most of the 51 excess deaths were known to be due to angiosarcoma, even though this diagnosis was not recorded on the death certificate. The excess corresponds closely with the 49 deaths due to angiosarcoma reported to the International Register of Angiosarcoma Cases as occurring in employees of the plants concerned during the periods under observation. All the men who developed the disease were likely to have been exposed to concentrations of vinyl chloride of several hundred parts per million or more.

Three other types of cancer which have been suggested to occur as a result of exposure to vinyl chloride are cancers of the lung, brain, and lymphatic and hematopoietic systems. The combined data for the mortality from respiratory cancer fail, at first sight, to support the hypothesis regarding lung cancer (SMR 97). Higher ratios for lung cancer have, however, been observed consistently in the subgroups in which the effect of an occupational hazard would be most likely to be seen (that is, men employed for more than 10 years, exposed to higher than average concentrations, or observed more than 20 years after first exposure). In two of the supplementary studies it was also noted that the mortality from lung cancer was specifically increased among the most heavily exposed workers. The combined data show small excesses in the mortality from cancers of the brain and of the lymphatic and hematopoietic systems. The excesses are, however, not statistically significant, and there is nothing to suggest that they are occupational in origin. An exception is the observation of an increased mortality from cancers of the lymphatic and hematopoietic systems in the supplementary study from the Federal Republic of Germany.

Two types of cancer were reported to be in excess in the Norwegian study, namely, thyroid cancer and melanoma. The significance of this finding is difficult to assess because very little information about these cancers has been provided by other studies.

Suggestions that vinyl chloride might cause cancers of the digestive tract have failed to account for the contribution of angiosarcoma of the liver. When this disease is excluded, the mortality from digestive tract cancer decreases to below the average (SMR 82 for the four principal studies).

A small excess mortality from the heterogeneous group of "other cancers" in the combined results of the four principal studies was statistically marginally significant (83 deaths against 65.25 expected, $P<0.05$). Some of the excess was likely to have been due to the misclassification of angiosarcomas as secondary cancers of the liver or carcinomatosis, site unknown.

The following three nonmalignant causes of death have required special examination: cirrhosis of the liver because of damage to the liver in "vinyl chloride illness," myocardial infarction (from analogy with the effect of other halogenated hydrocarbons and because of some observations from Swedish PVC fabricators), and nonmalignant respiratory disease because of changes in lung function and the radiographic appearance of the lungs observed in men exposed to PVC dust. Far from being raised, the mortality from cirrhosis of the liver was less than expected in the three principal studies and in one of the two supplementary studies which gave separate figures for the disease (SMR values of 69, based on 46 deaths, and 82, based on 15 deaths), while in the other supplementary study the increase was trivial.

Data for myocardial infarction have not been reported separately. But myocardial infarction accounts for most of the deaths attributed to ischemic heart disease, and there is no evidence that either ischemic heart disease or cardiovascular disease as a whole was unduly common (SMR values of 90 and 92, respectively) or related to occupational exposure.

The data for the third category of nonmalignant disease (nonmalignant respiratory disease) are confusing, because the two large national studies give conflicting results. The combined data for the four principal studies show the low mortality that is commonly found in healthy industrial populations (SMR 80). This figure hides, however, an increased mortality from chronic obstructive lung disease (SMR 120), which includes emphysema and is due to a grossly increased mortality attributed to emphysema in the US study (SMR 193). The corresponding mortality in the British study, which was preferentially described as due to bronchitis, was less than expected (SMR 82), as was the mortality from pneumonia (SMR 50) and other res-

piratory diseases (SMR 46) in the US study. There is no consistent evidence that the mortality from emphysema or bronchitis was specifically occupational, and it seems possible that the reported excess in the US study was an artifact due to nosological difficulties with the use of the seventh revision of the ICD.

Review of the massive data now available on the long-term health of men occupationally exposed to vinyl chloride leads to two clear conclusions. First the men have experienced a specific hazard of the normally extremely rare angiosarcoma of the liver. Approximately 1 in 335 of the men exposed in the 49 plants studied died of the disease, and approximately 2 % of the observed deaths were attributed to it. In the course of time the numbers of cases of angiosarcoma must be expected to increase two to three times. Second, the mortality from all other causes has been typical of that of normally healthy industrial workers. If any hazard has existed, its effect has been small.

The data provide no reason to think that any hazard other than one of cancer has been overlooked. It is, however, still difficult to decide whether vinyl chloride produces small risks of cancer, compared to those due to nonoccupational causes, at sites other than the liver, and, if so, whether, in total, these risks might cause almost as many deaths as angiosarcoma of the liver.

There is too little evidence either to confirm or refute the suggestion that vinyl chloride might cause melanoma or cancers of the thyroid, brain, and lymphatic and hematopoietic systems. None of the small excesses that have been recorded point specifically to an occupational hazard, apart from that attributable to cancers of the lymphatic and hematopoietic systems in the German study reviewed, and most are likely to be the sort of chance effect that is certain to be observed when many types of cancer are examined in many different studies.

The lack of any increased mortality from lung cancer in the combined results of the four principal studies reviewed does not exclude the possibility that there may have been a small occupational hazard of developing the disease, as geographic variations in the incidence of the disease throw doubt on the validity of using national rates for estimating the expected numbers of deaths. The greater mortality in groups of workers who would be more likely to show an occupational hazard than other groups suggests that a small hazard may have existed. The evidence is, however, weak, and the existence of a hazard has not been proved.

Clearer answers to some of the questions that have been posed in this review might be obtained if the various groups of investigators could present their results in more appropriate and comparable ways.

As vinyl chloride is a mutagen in laboratory experiments and a proved human carcinogen, the minute doses that have escaped into the general environment as pollutants must be presumed to have caused comparably minute risks to the general public. No such risk could possibly be detected, other than one of angiosarcoma of the liver which is normally an extremely rare disease. Several surveys have sought evidence of the existence of such an effect, and suggestive evidence that such an effect may have occurred at a time when environmental pollution was much greater than it is now has been found in one.

References

1. Air Products and Chemicals, Inc. Comments on the proposed standard for vinyl chloride. Letter to DR Goodwin, Environmental Protection Agency, Washington, DC 23 September 1976. (Cited in an unpublished report by Barr to Air Products and Chemicals, Inc, in 1981).
2. Baser ME, Tockman MS, Kennedy TP. Pulmonary function and respiratory symptoms in polyvinyl chloride fabrication workers. Am Rev Respir Dis 131 (1985) 203—208.
3. Baxter PJ, Anthony PP, MacSween NM, Scheuer PJ. Angiosarcoma of the liver in Great Britain, 1963—73. Br Med J 2 (1977) 919—921.
4. Belli S, Bertazzi PA, Comba P, Foa V, Maltoni C, Masina A, Pirastu R, Regianni A, Vigotti MA. Indagine sulla mortalita dei produttori di PVC in Italia: Disegno dello studio e primi risultoti. Cancer Lett (in press).
5. Brady J, Liberatore F, Harper P, Greenwald P, Burnett W, Davies TN, Bishop M, Polan A, Vianna N. Angiosarcoma of the liver: An epidemiologic survey. J Natl Cancer Inst 59 (1977) 1383—1385.
6. Buffler PA, Wood S, Eifler C, Suarez L, Kiliane DJ. Mortality experience of workers in a vinyl chloride monomer production plant. J Occup Med 21 (1979) 195—203.
7. Byren D, Engholm G, Englund A, Westerholm P. Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. Environ Health Perspect 17 (1976) 167—170.
8. Byren D, Holmberg B. Two possible cases of angiosarcoma of the liver in a group of Swedish vinyl chloride workers. Ann NY Acad Sci 246 (1975) 249—250.
9. Cooper WC. Epidemiologic study of vinyl chloride workers: Mortality through December 31, 1972. Environ Health Perspect, 41 (1981) 101—106.
10. Creech JL, Johnson MN. Angiosarcoma of liver in the manufacture of polyvinyl chloride. J Occup Med 16 (1974) 150—151.
11. Dalderup LM, Freni SC, Bras G, Bronckhurst FB. Angiosarcoma of the liver. Lancet 1 (1976) 246.
12. Duck BW, Carter JT, Coombes EJ. Mortality study of workers in a polyvinylchloride production plant. Lancet 2 (1975) 1197—1199.
13. Elinder CG, Pershagen G. Pilot study concerning the mortality in Njurunda Community. Swedish Nature Conservancy Board, 1978. (Cited in an unpublished report by Barr to Air Products and Chemicals, Inc, in 1981).
14. Environmental Health Associates. An update of an epidemiological study of vinyl chloride workers 1942—82: Final report to the Chemical Manufacturers Association. Environmental Health Associates, Oakland, CA 1986.
15. Environmental Protection Agency. Standard support document and environmental impact statement: Emission standard for vinyl chloride. Environmental Protection Agency, Washington, DC 1975. (EPA 450/2-75-009).
16. Equitable Environmental Health. Epidemiological study of vinyl chloride workers: Final report to Manufacturing Chemists Association. Rockville, MD 1978.

17. Falk H, Telles NC, Ishak KG, Thomas LB, Popper H. Epidemiology of thorotrast-induced hepatic angiosarcomas. Environ Res 18 (1979) 65—73.
18. Fiechtner J, Reyes C, Rentmerster K, et al. Epidemiologic notes and reports: Angiosarcoma of the liver — Wisconsin. Morb Mortal Wkly Rep 25 (1976) 57—58.
19. Forman D, Bennett B, Stafford J, Doll R. Exposure to vinyl chloride and angiosarcoma of the liver: A report of the register of cases. Br J Ind Med 42 (1985) 750—753.
20. Fox AJ, Collier PF. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br J Ind Med 34 (1977) 1—10.
21. Heath GW, Falk H, Creech JL. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. Ann NY Acad Sci 246 (1975) 231—236.
22. Heldaas SS, Langard SL, Andersen A. Incidence of cancer among vinyl chloride and polyvinyl chloride workers. Br J Ind Med 41 (1984) 25—40.
23. International Agency for Research on Cancer. Some monomers, plastics and synthetic elastomers and acrolein. Lyon 1979, pp 377—438. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans, volume 19).
24. Jones DP, Smith PM. Progression of vinyl chloride induced hepatic fibrosis to angiosarcoma of the liver. Br J Ind Med 39 (1982) 306—307.
25. Jones RD. A mortality study of vinyl chloride monomer workers employed in the United Kingdom in 1940—1984. Scand J Work Environ Health (in press).
26. Lilis R, Anderson H, Miller A, Selikoff I. Pulmonary changes among vinyl chloride polymerisation workers. Chest 2 (1976): suppl, 299—305.
27. Lloyd MH, Gauld S, Copland L, Soutar CA. Epidemiological study of lung function of workers at a factory manufacturing polyvinyl chloride. Br J Ind Med 41 (1985) 328—333.
28. Maltoni C, Ciliberti A, Gianni L, Chieco P. Vinyl chloride carcinogenesis: Current results and perspectives. Med Lav 65 (1974) 421—444.
29. Maltoni C, Lefemine G. Carcinogenicity bioassays of vinyl chloride: Current results. Ann NY Acad Sci 246 (1975) 195—218.
30. Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D. Experimental research on vinyl chloride carcinogenesis. In: Maltoni C, Mehlman MA, ed. Archives of research on industrial carcinogenesis. Volume 2. Princeton Scientific Publishers, Princeton, NJ 1984.
31. Marsteller HJ, Delbach WK, Muller R, Gedigk P. Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. Ann NY Acad Sci 246 (1975) 95—134.
32. Marsteller HJ, Delbach WK Muller R, Juhe S, Lange CE, Rohner HG, Veltman G. Chronisch-toxische Leberschäden bei Arbeitern in der PVC-Produktion. Dtsch Med Wochenschr 98 (1973) 2311—2314.
33. Masuda Y. Long term mortality study of vinyl chloride and polyvinyl chloride workers in a Japanese plant. Arch Ind Hyg Toxicol 30 (1979): suppl, 403—409.
34. Mirkova E, Mihailova A, Nosko M. Embriotakrichno i teratogenno destuige no vinilkhloride. Khig Zdraveopaz 21 (1978) 440. (Cited in an unpublished report by Barr to Air Products and Chemicals, Inc, in 1981).
35. Molan I, Molan G, Holmberg B, Elofsson S, Holmund L, Moosing R, Westerholm P. Mortality and cancer rates among workers in the Swedish PVC processing industry. Environ Health Perspect 41 (1981) 145—151.
36. Monson RR, Peters JM, Johnson MN. Proportional mortality among vinyl-chloride workers. Lancet 2 (1974) 397—398.
37. Nakamura K. A mortality study of vinyl chloride workers in Japan. Sangyo Ika Diaguka Zasshi 5 (1983): suppl, 49—57.
38. Nicholson WH, Henneberger PK, Tarr D. Trends in cancer mortality among workers in the synthetic polymers industry. In: Industrial hazards of plastics and synthetic elastimers. Liss, New York, NY 1984, pp 65—78.
39. Nicholson WJ, Hammond EC, Seidman H, Selikoff IJ. Mortality experience of a cohort of vinyl chloride-polyvinyl chloride workers. Ann NY Acad Sci 246 (1975) 225—230.
40. Ott MJ, Langner RR, Holder PB. Vinyl chloride exposure in a controlled industrial environment. Arch Environ Health 30 (1975) 333—339.
41. Pierre C, Tassignon JP, Pernin H, Spelkens J. Etude de la mortalite chez des travailleurs exposes au chlorure de vinyle. Arch Mal Prof Med Trav Secur Soc 40 (1979) 1131—1145.
42. Royal Society Study Group. Risk assessment: Report by a study group. Royal Society, London 1983.
43. Saric M, Kulcar Z, Zorica M, Gelic J. Malignant tumors of the liver and lungs in an area with a PVC industry. Environ Health Perspect 17 (1976) 189—192.
44. Soutar CA. Epidemiological study of respiratory diseases in workers exposed to polyvinyl chloride dust. Thorax 35 (1980) 644—652.
45. Tabershaw IR, Gaffey WR. Mortality study of workers in the manufacture of vinyl chloride and its polymers. J Occup Med 16 (1974) 509—518.
46. Thériault G, Allard P. Cancer mortality of a group of Canadian workers exposed to vinylchloride monomer. J Occup Med 23 (1981) 671—676.
47. Turner CA, Payne AP, Bushby BR. Determination of ambient levels of vinyl chloride monomer (VCM) around manufacturers in the UK: Part 7. Warren Spring Laboratory, Department of Trade and Industry, Stevenage (United Kingdom) 1984.
48. Viola PL, Bigotti A, Caputo A. Ontogenic response of rat skin, lungs, and bones to vinyl chloride. Cancer Res 31 (1971) 516—519.
49. von Greiser E, Reinl W, Weber H. Vinyl-chlorid exposition und mortalitat deutscher chemiearbeiter im vergleich zur mortalität nichtexponierter chemiearbeiter und PVC-verarbeiter. Zentralbl Arbeitsmed Arbeitssch Prophyl Ergonomie 32 (1982) 44—62.
50. Waxweiler RJ, Stringer W, Wagoner JK, Jones J, Falk H, Carter C. Neoplastic risk among workers exposed to vinyl chloride. Ann NY Acad Sci 271 (1976) 40—48.

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