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OCCUPATIONAL HAZARDS IN THE VC-PVC INDUSTRY

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INTRODUCTION

On January 24, 1974, The Wall Street Journal published an article describing the occurrence of three deaths from hemangiosarcoma of the liver among polyvinyl chloride (PVC) production workers at the B.F. Goodrich Tire and Rubber Company plant in Louisville, Kentucky. This announcement shattered the relatively complacent view toward health effects associated with plastic production in general and PVC production in particular. At the time, U.S. and Western European production of vinyl chloride (VC) exceeded 6 x 10^6 metric tons. Numerous mortality and clinical studies were undertaken in the major producing countries in an attempt to establish the extent of the carcinogenic risk and to identify clinical parameters useful for surveillance of exposed groups. Because of the immediate concern in 1974, most of these studies were completed between 1974 and 1977. Several reviews and symposia on human health effects from VC exposure have been published recently. A superb one is by Lelbach and Marsteller (1981).

The exposures were high that led to the disease observed in these various studies. Typical concentrations in the industry were estimated to be about 1,000 ppm prior to 1955, from 300-500 during 1955-1970, and from 100-200 during 1970-1974 (Barnes, 1976). However, variations from such exposures would have occurred in specific plants (Rowe, 1975). While historical average exposures were generally less than 1,000 ppm, peak exposures often ex-

ceeded 5-10,000 ppm (where workers lost consciousness) and, on occasion, 40,000 ppm (where plants exploded). During 1974, exposures were reduced to about 10-20 ppm in the U.S. industry (Jones, 1981) and even further, following the promulgation of a 1 ppm standard by the Occupational Safety and Health Administration in 1974.

MORTALITY STUDIES OF VC-EXPOSED WORKERS

Table 1 shows the populations observed and the follow-up characteristics of twelve cohort studies of vinyl chloride exposed workers. The studies were independent with the exception that the portions of the population reported in the Equitable Environmental Health Study (1978) were included in some other U.S. studies. The proportionate mortality study of Monson et al (1974) is not included as the VC-exposed individuals studied therein were included in the cohort mortality study of Waxweiler et al (1976). The size of the cohorts varied greatly, from 255 in the study of Nicholson et al (1975) to 9,677 in the Equitable Environmental Health study. A notable feature of all of the studies is that the populations followed were relatively young or recently employed, even though many plants in the studies started production in the 1940s. Most workers were hired after 1950, when U.S. and Western European production increased sixfold in ten years (Nicholson and Henneberger, 1983). Thus, few deaths occurred among most of the groups observed and data on effects 25 or more years from onset of exposure are limited. The total mortality exceeded 10% of the observation cohort in only three studies. Further, the inclusion of recently employed individuals or those with short employment diluted the effects from VC exposure. Only five studies limited consideration to individuals with more than one year of exposure. In all cases, however, some individuals with more than 20 years from onset of employment were available for observation. The follow-up terminated in the mid-1970s for all studies.

Table 2 compares the results for cancer of all sites and chronic liver disease in all 12 studies. Cancer is elevated in most of the studies, although it does not achieve a 0.05 level of significance except in the studies by Waxweiler et al (1976) and Nicholson et al (1975). In the study by Ott et al (1975), a highly exposed subgroup with 15 years latency had 8 cancer deaths compared to 3.2

Table 1

Population and follow-up characteristics of twelve studies of vinyl chloride exposed workers

Study	Country	Analysis cohort size	Percent additional untraced	Number of deaths analyzed	Percent of total	Minimum exposure (years)	Minimum latency (years)	Earliest possible exposure	Maximum follow-up (years)	Last year of follow-up
Bertazzi et al. 1979	ITAL	4777	13.8	62	1.3	0.5	0.5	1952	22	1977
Buffler et al. 1979	USA	464	0.0	28	6.0	0.2	0.2[a]	1948	27	1975
Byren et al. 1976	SWED	750	low	38	7.7	>0	>0[a]	1945	28	1974
Duck et al. 1975	UK	2113	0.3	136	6.4	>0	>0[a]	1948	20	1975
Equitable Env. Health, 1978	USA	9677	4.9	707	7.3	1	1[a]	(1935)	25+	1972
Fox and Collier 1976, 1977	UK	7409	1.1	393	5.1	>0	>0[a]	1940	35	1974
Maeuda 1979	JAP	304	0.3	26	8.6	1	1	1949	20	1975
Nicholson et al. 1975	USA	255	0.8	24	9.4	5	10[a]	1947	25	1974
Ott et al. 1975	USA	522	0.0	79	15.1	>0	>0	1942	31	1973
Reinl et al. 1979	CZE	6544	7.3	414	6.3	>0	>0	NA	NA	1974
Theriault and Allard, 1981	CAN	451	2.8	59	13.1	5	5[a]	1943	30	1977
Waxweiler et al. 1976	USA	1287	0.5	136	10.6	5	10[a]	1940	22	1973

[a] Longer latencies considered for some causes of death.

Table 2

Observed and expected deaths among vinyl chloride exposed workers in twelve studies

Study	Cancer of all sites Deaths Obser.	Expec.	SMR	Chronic liver cancer Deaths Obser.	Expec.	SMR
Bertazzi et al	30	30.9	97	5	-	-
Buffler et al	8	5.19	154	0	-	-
5 yr. latency	6	4.34	138			
Byren et al	-	-	-	0	-	-
Duck et al	35	36.44	96	-	-	-
Equitable	139	141.39	104[a]	14	26.45	56††
Fox & Collier	115	126.77	91	1	2.68	37
Masuda	8	5.8	138	5	1.00	500[a]
Nicholson	9	3.9	230	1	(0.6)	167
Ott et al	13	16.0	81	3	2.7	111
15 yr. latency	9	9.2	98			
Reinl et al	94	90.6	112[a]	14	18.4	82
Theriault & Allard	20	16.37	122	-	-	-
Waxweiler et al	35	23.5	149†	2	4.0	50
15 yr. latency	31	16.9	184††			

[a] Adjusted for unknown causes of death
( ) = Estimated as a percentage of U.S. rates
† $p < 0.05$
†† $p < 0.01$
a SMR of control population equally high

expected ($p < 0.05$). The absence of significant findings in other studies may be attributed to their low power. The study of Bertazzi et al (1979) may be biased because of low follow-up in the group. Fourteen percent of the population were untraced and person-years at risk were calculated for these individuals as if they were alive. The low SMR of 44 for all causes of death suggests that proportionately more deaths occurred in untraced groups than in the traced. The studies by Buffler et al (1979), Byren et al (1976), Masuda (1979), and Theriault and Allard (1981) had very few deaths available for analysis. That of Ott et al (1975) also was limited by the number of deaths and further by virtue of a study group with relatively lower exposure (through better industrial hygiene control). While having more deaths available for analysis (136), the study by Duck et al (1975) was significantly

diluted by the inclusion of many individuals with very short and recent periods of exposure.

Turning to chronic liver disease, one remarkable finding is the absence of significantly elevated mortality from this cause in most of the populations under observation. The only study with a significant elevation is that of Masuda (1979) in which five deaths from chronic liver disease occurred where only one was expected. However, this must be considered in the light of an equally high mortality from liver disease (6 observed vs. 1.4 expected) in a comparison population followed for control purposes. Five of 62 deaths from chronic liver disease seen in the study by Bertazzi et al (1979) are unusual, but the limitations of this study and lack of details make evaluation difficult. The generally benign results in other studies contrast sharply with the severe liver disease from VC exposure documented in clinical studies (Marsteller et al, 1975). Hepatomegaly, hepatic fibrosis, portal hypertension, and bleeding esophageal varices have commonly been found in individuals heavily exposed to VC, even without concomitant exposure to alcohol.

Table 3 lists the mortality data for primary cancer of the liver and biliary passages and for cancer of the lung, trachea and bronchus. In the case of liver cancer, the overall data are consistent and dramatic. Hemangiosarcomas of the liver were found in eight of the twelve studies. In each of the eight, a very large and highly significant SMR for liver cancer was seen. Methodological limitations can account for negative data in the other four studies. The large SMR's observed, however, are largely the result of low values for the expected number of cases rather than a high incidence of observed cases. Only 28 separate liver hemangiosarcomas were identified in all twelve studies. As the overall excess number of deaths from liver and biliary cancer in all studies was 47, some hemangiosarcomas may not have been identified. The low numbers must also be considered in light of the limited follow-up times in most studies.

The evidence for lung cancer is less clear. There is an elevation in some studies, but at a level that does not achieve statistical significance, except in the 15 year latency population of Waxweiler et al (1976). This, in part, may be the result of the low power of many of the

Table 3

Observed and expected deaths from selected causes among vinyl chloride-exposed workers

	Cancer of the liver and biliary passages				Cancer of the lung, trachea and bronchus		
	Obs.[a]	Exp.	SMR	Hemangio-sarcomas	Obs.	Exp.	SMR
Bertazzi	8	(1.0)[b]	(800)†††	3	7	(7.7)[c]	(91)
Buffler	0	(0.17)	—	0	5	1.73	289†
5 yr. latency					4	1.49	268
Byren	4	0.97	413†	2	3	1.78	168
10 yr. latency	4	0.68	589††	2			
Duck	—	—	—	0	16	15.53	103
19 yr. latency					14	10.69	131
Equitable	10	(4.5)	(224)†	5	45	44.29	107
15 yr. latency					41	37.0	111
Fox and Collier	4	0.71	563††	2	46	51.23	90
15 yr. latency					28	26.0	108
Maguda	1	0.6	167	0	1	(0.8)	(125)
Nicholson	3	(0.12)	(2500)†††	3	0	(1.1)	--
Ott	0	(0.5)	—	0	4(5?)	5.2	??(96?)
Reinl	12	0.9	1523†††	4	22	24.6	95[b]
Theriault	8	(0.5)	(1600)†††	8	2	5.78	35
15 yr. latency					2	4.25	47
Waxweiler	7	0.6	1155†††	6	12	7.7	156
15 yr. latency	7	0.4	1606†††	6	11	5.7	194†
Total of nonduplicated hemangiosarcomas							29

† < 0.05
†† < 0.01
††† < 0.001

a All verified liver cancer deaths, including those established by review of all available information.

b ( ) = Expected deaths estimated on the basis of 1950-1969 U.S. adjusted rates, ICD 155/ICD 140-205.

c ( ) = Expected deaths estimated on the basis of national age adjusted rates, ICD 162-163/ICD 140-205.

d One hemangiosarcoma occurred in a PVC fabricator.

e Includes cancer of the pancreas.

studies. Only two have an 80% power to detect an overall risk of 1.5 (Beaumont and Breslow, 1981). Of significance, however, are the very low SMR's in the groups studied by Theriault and Allard (1981), Reinl, et al (1979), and Nicholson et al (1975), cohorts that would be expected to manifest a high risk on the basis of the many hemangiosarcomas that were found. The four largest studies, although in some cases limited by inclusion of short-term and recently employed workers, also are noteworthy for the SMR's close to 100. Where available, data on subcohorts with longer latency (> 15 yr) suggest some increased risk.

Waxweiler et al (1981) undertook a detailed analysis of the exposure of those with lung cancer in their previously published study (Waxweiler et al, 1976) in an attempt to identify particular etiological agents. The analysis used a serially additive expected dose model (Smith et al, 1980) in which a dose measure during each year of exposure was accumulated for each study individual for a variety of potentially carcinogenic agents. The cumulative doses for those with lung cancer were compared with those of other individuals in the plant under study. The results showed that the greatest correlation of lung cancer was with exposure to PVC dust. Secondarily, exposure to vinylidene chloride appeared to be important, but only for large cell and adenocarcinoma. The serially additive dose for VC monomer differed little in those with lung cancer compared to others in the plant, except, possibly, for large cell cancers.

Thus, evidence to date does not establish that VC monomer is an important lung carcinogen in exposed worker populations, although it is recognized that limited long-term observation has so far been available. In all studies considered here, a slight deficit of cases was seen compared to the number expected. In the subcohorts with more than 15 years from onset of exposure, an overall excess of 10% was observed. If, in addition, one considers a "healthy worker effect," any excess lung cancer would still be considerably less than the excess of liver cancer. A qualification to this conclusion is that no study specifically considered cigarette usage. If cigarette smoking was much less common among VC workers than the general population, higher SMR's would have been seen if smoking specific data were available. However, this

possibility is unlikely, considering the many different populations studied. The uncertainty in human data is also reflected in animal studies. Increased lung cancers have been seen in mice but not in rats or hamsters (Maltoni et al, 1981).

Table 4 shows the results for brain and central nervous system cancers and for cancers of the lymphatic and hematopoietic systems. Cancers of the brain and central nervous system were significantly elevated in a number of studies, although the results differed considerably across studies. Again, negative data may be simply the result of limited long-term follow-up or the low power of the study. In such cases the information is only sufficient to set an upper limit on relative risk of brain cancer. In contrast to lung cancer, however, the largest study group has a significantly elevated risk of brain and central nervous system malignancy. As with lung cancer, the data on brain and CNS cancer in animals are equivocal. Neuroblastomas and brain malignancies are observed in rats exposed to VC, but not among mice or hamsters (Maltoni et al, 1981). The human data are also mitigated by the recent finding of brain and central nervous system tumors in a variety of chemical plant exposure circumstances (Alexander et al, 1980; Selikoff et al, 1982). Excess brain malignancies, but not the etiological agents, have been identified in several Texas and Louisiana chemical/petrochemical plants. VC exposure was documented for some cases, but it could not explain the overall findings. As individuals in many of the VC studies considered here were exposed to other chemicals and petrochemicals, the possible role of these agents cannot be excluded. Further, it has been suggested that some working groups, with employer-paid medical plans, may have better case ascertainment than is generally available (Greenwald et al, 1981) and, thus, more brain malignancies identified. In any case, the number of excess malignancies of the brain and central nervous system (approximately 10) in all studies is considerably less than the number of hemangiosarcomas identified in the same populations.

Similar results are obtained for malignancies of the lymphatic and hematopoietic system. Here again, the analysis is limited by the few deaths and disparate results which occurred in different studies. Overall, there would appear to be an elevated risk, but the influence of

Table 4

Observed and expected deaths from selected causes among vinyl chloride exposed workers

	Cancer of the brain & central nervous system			Cancer of the lymphatic and hematopoietic system		
	Obser.	Expect.	SMR	Obser.	Expect.	SMR
Bertazzi	1	(0.8)[a]	125	4	(3.0)[b]	(133)
Buffler	0	(0.1)	-	0	(0.5)	-
Byren	2	0.33	612†	0	-	-
Duck	-	-	-	-	-	-
Equitable	12	5.90	203†	20	17.01	124
Fox & Collier	2	3.66	55	9	9.01	100
Hasuda	0	(0.15)	-	0	(0.5)	-
Nicholson	1	(0.1)	(1000)	2	(0.4)	(500)
Ott	1	0.4	(250)	1	(1.6)	(63)
Reinl	2	1.3	162	15	7.7	216††
Theriault	0	0.6	-	1	1.67	60
Waxweiler	3	0.9	329	4	2.5	159
15 yr. latency	3	0.6	498†			

† < 0.05

†† < 0.01

[a] ( ) = Expected estimated from the ratio of age standardized U.S. rates ICD 193/ICD 140-205.

[b] ( ) = Expected estimated from the ratio of 1950-1969 U.S. rates ICD 200-205/ICD 140-250.

confounding exposures precludes definitive statements. The overall excess of such malignancies (about 10) is also much less than those from primary hemangiosarcomas of the liver.

EFFECT OF REDUCTION OF EXPOSURE TO VC

As mentioned previously, most mortality studies followed populations only to the 1972-1975 period. No data exist on the risk to previously exposed populations after cessation of exposure in 1974, although hemangiosarcomas have been noted among retirees. We have recently completed a follow-up through 1981 of the population reported in 1975 (Nicholson et al, 1975) to determine whether a high risk of liver cancer continues, following significant reduction in exposure. The original group employed at a VC polymer-

ization plant in Niagara Falls, New York, has been expanded by 40 additional workers, all exposed for five years, who achieved ten years from onset of exposure subsequent to April 1974. Additionally, 195 individuals employed at a VC polymerization plant in South Charleston, West Virginia, with five years of exposure and ten years from onset in December, 1966, were identified and traced through 1980.

Table 5 lists the observed and expected deaths by cause for both groups with the deaths occurring after 1974 separately identified. (These are preliminary data; full

Table 5

Observed and expected deaths among vinyl chloride polymerization workers

Niagara Falls, NY (N = 296)
(January 1, 1956 - December 31, 1981)

Cause of death	Observed 56-74	74-81	Total	Expected	SMR
All causes	23	21	44	40.87	108
All cancer	8	8	16	9.01	177[a]
Lung	0	2	2	3.25	62
Colon/rectum	1	2	3	1.39	216
Brain	1	0	1	0.33	303
Liver	3	3	6	0.19	3158[b]
Lymphoma	2	1	3	0.55	545[a]
Pancreas	1	0	1	0.50	200
Cirrhosis of liver	1	1	2	1.41	142
Cardiovascular disease	13	6	21	19.88	106

South Charleston, WV (N = 195)
(December 1, 1966 - December 31, 1980)

Cause of death	Observed 66-73	74-80	Total	Expected	SMR
All causes	12	24	36	44.74	80
All cancer	2	10	12	10.65	113
Lung	1	1	2	4.07	49
Colon/rectum	0	0	0	1.89	—
Brain	0	0	0	0.43	—
Liver	0	4	4	0.23	1739[c]
Lymphoma	0	0	0	0.59	—
Pancreas	0	0	0	0.67	—
Cirrhosis of liver	0	1	1	1.81	55
Cardiovascular disease	8	12	20	27.24	73

a $p < 0.05$
b $p < 0.001$
c $p < 0.0005$

pathological review of all available specimens has not been completed.) Among the 44 deaths that occurred in the Niagara Falls cohort, 6 were from primary cancer of the liver, including 5 hemangiosarcomas. Three of the hemangiosarcomas occurred in the period prior to 1974 and 2 subsequently. Similar findings occurred among the smaller group in West Virginia. Here, of 36 deaths, 4 were from hemangiosarcoma, all of which occurred subsequent to 1974. Thus, the risk of neoplastic VC disease continues undiminished, even though exposures to the monomer have been significantly reduced. The combined data from both groups are shown in Table 6 and demonstrate an excess risk of cancer, which is totally accounted for by the enormously increased risk of liver malignancy observed in each time from onset of exposure category. The excess lymphomas which achieved significance at the $p < 0.05$ level in the Niagara Falls group lose significance when combined with the data from South Charleston. A deficit of lung cancer was observed in both study groups and brain malignancies were about equal to the number expected.

It is not certain whether the results of these two plants will be reflected in the results of other plants in future years. The South Charleston plant was the first facility to commercially produce VC. The New York plant opened immediately following the cessation of World War II. Thus, we are observing effects in populations that include many individuals with long times from onset of exposure. There is no information on whether the exposures in these two plants were significantly different from those of the majority of other VC polymerization facilities. It is known that pre-1974 exposures in the New York plant were sufficiently high to cause loss of consciousness to some individuals (4.5% of those examined in the clinical survey of 1974) (Lilis et al, 1975).

MORBIDITY AND CLINICAL FINDINGS AMONG VC-EXPOSED WORKERS

Clinical abnormalities from VC exposure predated by 25 years the documentation of its carcinogenicity. Various VC-related abnormalities were reported in Eastern European literature, including hepatomegaly (Tribukh et al, 1949), angioneurosis (Filatova and Gronsberg, 1957), osteolytic lesions of distal phalanges (Smirnova, 1961), Raynaud's phenomenon and sclerodermalike skin lesions (Suciu et al, 1963). However, VC disease was not seri-

Table 6

Observed and expected deaths among vinyl chloride exposed workers in two polymerization facilities by time from onset of exposure

Cause of death	Years since onset of exposure: 10 - 19 Obs.	10 - 19 Exp.	20 - 29 Obs.	20 - 29 Exp.	30+ Obs.	30+ Exp.	Total Obs.	Total Exp.	SMR
All causes	24	19.13	30	34.63	26	31.64	80	85.61	93
All cancer	7	3.72	9	7.98	12	8.03	28	19.66	142
Lung	1	1.26	1	2.96	2	3.08	4	7.31	55
Liver	2[a]	0.08	3[a]	0.18	5[b]	0.17	10	0.42	2381
Brain	1		0		0		1	0.76	132
Lymphoma	2	0.27	1	0.46	0	0.41	3	1.14	263
Cirrhosis of liver	0	0.76	3	1.24	0	0.87	3	2.85	105
Cardiovascular disease	14	8.74	15	17.58	12	16.40	41	42.73	96
Person years	2924		2734		1404				

a. hemangiosarcoma
b. 4 hemangiosarcomas and 1 hepatoma

ously considered in the West until the published description of Raynaud's syndrome, acroosteolysis, and pseudoscleroderma in two Belgium VC reactor cleaners (Cordier et al, 1966). Additional cases were soon noted (Wilson et al, 1967) and a comprehensive epidemiological study of 5,011 U.S. workers employed in production and polymerization was undertaken. It showed that 11.9% had possible X-ray signs of acroosteolysis, compared with 3.2% in a Michigan general population control group, with 2% definitely having Raynaud's phenomenon or X-ray evidence of acroosteolysis (Dinman et al, 1971). The conditions were clearly associated with the cleaning of reactors, in which a heavy exposure to VC occurred. Only one case of Raynaud's phenomenon occurred among 557 workers employed in PVC fabrication.

During the early 1970's, VC liver disease was described in detail by Marsteller et al (1973, 1975). Observations on selected workers showed hepato- and splenomegaly to be common. Peritoneoscopy and guided liver biopsy identified severe portal hypertension in some, generally without cirrhotic fibrosis, although perisinusoidal and focal or diffuse capsular fibrosis were commonly seen. The portal hypertension could lead to bleeding esophageal varices, with possible fatal consequences. In

heavily exposed individuals, the portal hypertension and hepatic fibrosis often progressed after cessation of exposure (Martin et al, 1974). The histology of malignant and nonmalignant liver disease has been well described by Popper and Thomas (1975; Thomas et al, 1975), who suggested the possibility of an interrelationship between hemangiosarcoma and the proliferation of sinusoidal lining cells and hepatocytes seen in VC fibrosis. Lelbach and Marsteller (1981) have also noted that the vast majority of hemangiosarcoma cases have appeared on a background of some degree of hepatic fibrosis. The implications of these suggestions for a hemangiosarcoma dose-response relation are uncertain.

During 1974, extensive studies were undertaken by the Environmental Sciences Laboratory of the total workforces of three polymerization plants in the states of New York, Michigan and West Virginia. The results from the New York plant (Lilis et al, 1975) indicated the presence of acroosteolysis in heavily exposed individuals. Hepato- and splenomegaly or hepatic tenderness was commonly observed and associated with duration of exposure and elevated alkaline phosphatase levels. Sixty-four of 354 had an enlarged or tender liver or spleen and of these, 41% had elevated alkaline phosphatase. Liver function tests were not particularly revealing, except for a correlation of elevated alkaline phosphatase levels with duration of exposure. Additionally, carcinogenic embryonic antigen titers were slightly higher among vinyl chloride exposed groups than in a smoking matched control population (Anderson et al, 1978).

Tamburro and Greenberg (1981) have evaluated the effectiveness of federally mandated screening tests for vinyl chloride exposed workers. Figure 1 shows the results on specificity and sensitivity for 78 individuals with hepatic status determined by biopsy. ICG clearance had the highest combined sensitivity and specificity, with SGPT the second most useful test. Elevated alkaline phosphatase had the greatest specificity of all tests, particularly for chemically-induced liver injury, but was lacking in sensitivity. SGOT and GGPT were of limited use because of their low specificity for chronic liver disease. They recommended the use of ICG clearance for screening, to be followed with alkaline phosphatase determinations for those with altered clearance.

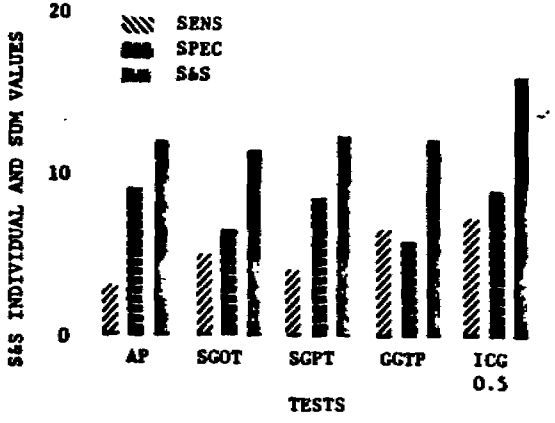

Figure 1: Sensitivity and specificity of various biochemical screening tests and their sensitivity and specificity sum values (S & S) based on 78 with biopsy documentation of their hepatic status.

Three of the seven individuals who died after 1974 with hemangiosarcoma in the previously described mortality followup were examined in 1976. One, who died 22 months after examination, had no noteworthy abnormalities on examination (alkaline phosphatase was 88, slightly high). A second, who died three yesrs after examination, had a slightly enlarged, palpable liver (11 x 6 cm) with normal blood counts and chemistry. Only one of the above drank alcohol at all and he only drank 2-3 beers/month. The third, who died 22 months after examination, had a slightly enlarged liver (11 x 8 cm) and spleen (13 x 8 cm), and slightly elevated alkaline phosphatase (93), SGOT (52) and CEA (4.7). Thrombocytopenia was also present (75,000). No data are available on later clinical parameters, but the above results are clearly not sufficiently specific for identification of a special risk.

Pulmonary abnormalities also have been associated with VC/PVC exposure. Small opacities, predominantly irregular, of profusion 1/0 or greater were found in 20 of 1,216 workers employed at PVC production in an Italian plant (Mastrangelo et al, 1981). All had been exposed to high levels of PVC dust (>10 mg/m^3). Lilis et al (1976) reported that approximately 20% of VC/PVC workers with high exposures to PVC dust had abnormal X-rays, which correlated with duration of exposure and, also, with cigarette smoking. In contrast, only 4.7% of individuals in a PVC plant with low dust levels had abnormal X-rays. In addition to "typical pneumoconiosis," a granulatomous reaction to PVC dust has been reported (Arnaud et al, 1978). Miller et al (1975) have observed pulmonary function abnormalities (a reduction in the ratios FEV$_1$/FVC and MMF/predicted MMF) in both smokers and non-smokers heavily exposed to PVC dust (and also to VC monomer). Maltoni and Lodi (1981), observed greater percentage of abnormal sputum cytological results among VC exposed workers compared to several other groups of manufacturing workers or miners. Only workers in the chromium industry demonstrated a greater proportion of abnormal cells.

Ducatman et al (1975) have observed an increased frequency of chromosome abnormalities in the lymphocyte cultures of VC workers. Most of the abnormalities were "unstable" changes, such as fragments, dicentrics, and rings. This was confirmed by Purchase et al (1978), among others. Some of the group studied by Purchase was resampled 18 and 42 months later (Anderson et al, 1980). In those studied during January 1976, the frequency of abnormalities was increased in those who continued VC/PVC employment, but decreased in those who left the industry. In January 1978, no increased frequency was found in any worker. The authors attributed the decrease to the reduction in VC exposure.

HEALTH HAZARDS IN THE PVC PROCESSING INDUSTRY

Prior to identification of hemangiosarcoma in VC polymerization workers, little effort was made to control either the concentration of residual monomer in PVC dust or exposures to dust and VC that occurred in the various forming operations of the PVC fabricating industry. VC concentrations in excess of 10 ppm occurred frequently. While these concentrations were significantly lower than those of the polymerization industry, the much greater employment in the processing industry (hundreds of thousands vs. tens of thousands in the polymerization work) raised concern for population health effects, particularly for malignant disease for which no threshold was known. However, only two hemangiosarcomas have been documented in

the PVC processing industry, one in an accountant in a plant making PVC fabric and one in an Italian plant making PVC sacks. A third case may have occurred in an electrical wire insulator, but the pathological diagnosis is uncertain (Lloyd, 1975). This is in contrast to 85 cases known to have occurred among polymerization workers (NIOSH, 1982). This is somewhat comforting and indicates a significantly lower total VC-related neoplastic risk among fabrication workers. However, it should be noted that case finding is likely to be poorer in this group than in polymerization workers.

A proportionate mortality study has been conducted of 4,341 deaths of former employees of 17 PVC fabricators (Chiazze Jr., et al, 1977). The direct PMR's suggested an excess in total cancer mortality among both white men and white women with the major excesses concentrated in cancers of the digestive organs. An excess of breast cancer was also seen in women, but not confirmed in a case-control study (which was of very low power and could only detect a threefold increased risk) (Chiazze, Jr. et al, 1980). The results of the proportionate mortality study must be considered cautiously. In such studies, elevated cancer risks and are typically seen because of a "healthy worker effect," which leads to a reduction in cardiovascular deaths relative to those of cancer. If PCMR's (proportionate cancer mortality ratios) had been calculated, rather than PMR's, digestive cancer would still be elevated but not at an 0.05 level of significance. Interestingly, an excess of stomach cancer was seen in the proportional mortality study of Baxter and Fox (1976).

SUMMARY

Overall, the results of the analysis of 12 studies of VC production and polymerization workers demonstrate an enormously elevated risk of liver malignancies, the possibility of a twofold increased risk of brain and central nervous system tumors and perhaps, also, of malignancies of the lymphatic and hematopoietic system. However, the role of other agents cannot be excluded in the etiology of nonhepatic malignancies. Bronchogenic carcinoma does not appear to be increased from exposures to VC monomer, although a relationship to PVC dust was suggested in one study. These conclusions must be considered in light of limited data on workers followed more than 25 years from

onset of exposure. Considering the numbers of observed and expected deaths in all studies, it would appear that the excess of malignancies at nonhepatic sites is less than the excess of liver tumors. Data presented elsewhere in this volume (Nicholson and Henneberger, 1983) suggest that exposure reductions in 1974 may have virtually eliminated the VC-associated risk of liver cancer if the current U.S. standard is met. To the extent that VC exposure is associated with other cancers, a similar risk reduction would be expected.

Raynaud's phenomenon, acroosteolysis, sclerodermalike skin lesions, hepato- and splenomegaly with noncirrhotic hepatic fibrosis, and severe portal hypertension have been associated with past heavy exposures to VC. Evidence exists that the liver disease and portal hypertension may progress following cessation of exposure. However, all of the above syndromes were found largely in heavily exposed individuals. Their occurrence would be much less likely in workers exposed only to concentrations currently allowed. Pulmonary deficits, X-ray abnormalities, and, perhaps, lung cancer have been associated with VC/PVC exposure. Because of the possible contribution of PVC dust to these findings, engineering controls during polymer drying, bagging and usage are warranted.

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