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The enclosed series of papers on vinyl chloride and styrene came to my attention through Brian Bennett of ICI. They obviously will have to be included in the review by Sir Richard Doll and probably should be sent to Environmental Health Associates.

Sincerely yours,

Theodore R. Torkelson, Sc.D.
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Encs.

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Occupational Hazards of
Vinyl Chloride and Styrene

Trends in Cancer Mortality Among Workers in the Synthetic Polymers Industry

William J. Nicholson, Paul K. Henneberger
and Diane Tarr

Occupational Hazards in the VC-PVC Industry

William J. Nicholson, Paul K. Henneberger
and Herbert Seidman

Occupational Hazards in Production of Processing of Styrene Polymers - Epidemiologic Findings

William J. Nicholson and Diane Tarr

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ENVIRONMENTAL SCIENCES LABORATORY
MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

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TRENDS IN CANCER MORTALITY AMONG WORKERS IN THE SYNTHETIC POLYMERS INDUSTRY

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INTRODUCTION

The reactive double bonded structure of ethylene-like molecules allows a wide variety of chemicals to undergo polymerization. Unfortunately, this same structure has been found capable of transformation to an epoxide by the mammalian mixed function oxidase system (Bonse and Henschler, 1976). These epoxides or their reactive metabolites can bind to cellular macromolecules and may be responsible for the carcinogenicity of the parent molecule. Epoxide formation has been suggested as an intermediate in the carcinogenic action of vinyl chloride (Van Duuren, 1975) and vinylidene chloride (Maltoni, 1977), and in the mutagenic action of styrene (Milvy and Garro, 1976). The epoxides of ethylene, styrene and vinyl chloride have been shown to be carcinogenic, as well as directly mutagenic in bacterial test systems without the need for activation. The potential for conversion of ethylene-like molecules to the epoxides is greater for unsymmetrical structures such as vinyl chloride and vinylidene chloride than for symmetrical structures, such as ethylene, 1,2-dichloroethylene or tetrachloroethylene. It is beyond the scope of this review to discuss the structure-activity relationships of the monomers used in the plastics industry. Nevertheless, available data suggest that carcinogenicity depends on the metabolism of these monomers to reactive intermediates and that these reactions may be non-linear. However, when the metabolism of a compound is understood, a coherent picture of the dose and time dependence of cancer should emerge.

centrations. However, at concentrations of VC less than 500 ppm, a reasonably linear dose-response relationship obtains.

Gehring et al (1978) have explained the non-linearity in terms of Michaelis-Menten kinetics, in which the transformation of VC to a reactive intermediate follows the equation,

$$V = V_m S/(K_m + S) \qquad (1)$$

V and V_m are the rate and maximum rate, respectively, for the biotransformation of VC, S is the concentration of VC in inspired air, and K_m, the Michaelis constant. K_m was determined experimentally to be 860 µg/l and V_m to be 5,706 µg/4 hr. Figure 2A displays the dose-response relationship between the percentage of animals with liver HSA and the quantity of VC metabolized according to Eq. 1. As can be seen, a direct liner relationship exists with no evidence of a threshold or altered slope at low doses. The possibility of a non-linear dose-response relationship from detoxification kinetic steps has been postulated (Gehring and Blau, 1977); and discussed in detail (Hoel et al, 1983), but no evidence exists for such non-linearity in the data yet available. The unweighted least squares regression equation for the dose-response relationship is

$$\% \text{ HSA} = -0.066 + 0.0039\ V \qquad (2)$$

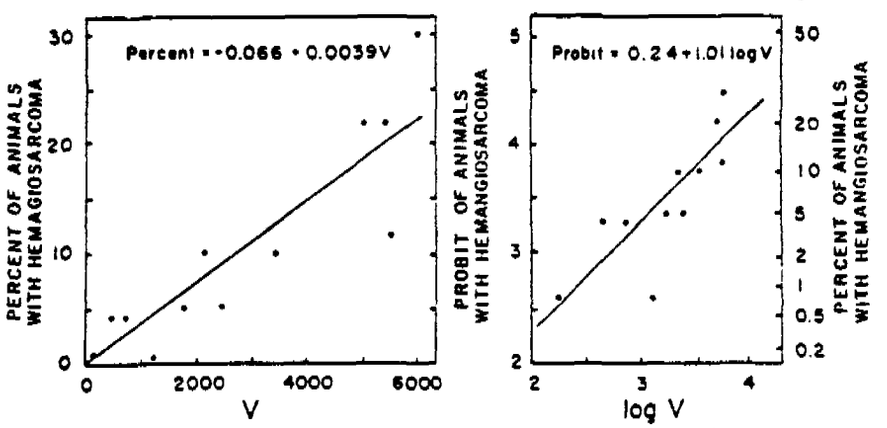

Figure 2. Linear and probit dose-response relationships for the quantity of VC metabolized/4 hr exposure (5 day/wk,52 wk).

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for a rare tumor, such as HSA, interactive effects may not be important and a power law relationship should adequately describe the time course of risk following exposure.

Some data are available from the use of Thorotrast in Japan and Denmark that indicate the incidence rate of HSA does follow Eq. 4 (Mori et al, 1979a; Mori et al, 1979b; Faber, 1978). The material was used in these countries over a limited period of time, so the incidence per calendar year and estimates of the population at risk can be used to estimate incidence rates by time from onset of exposure. While the data are very limited, they are consistent with a power law dependence of risk and suggest an exponent of approximately 3. Three is also compatible with the incidence of liver HSA in the mortality study of polymerization workers described elsewhere in this volume (Nicholson et al, 1983). However, only nine cases are available for analysis.

PROJECTIONS OF FUTURE MORTALITY FROM PAST VC EXPOSURE

Sufficient data have accumulated on the pattern of mortality from past VC exposures to allow an estimate future mortality from these exposures of using a linear dose-response relationship and a time course for risk of death from liver HSA given by Eq. 4. Figure 3 shows the number of cases of HSA according to various measures of time that have been identified in the United States, Western Europe and the world (NIOSH, 1982). The distributions shown in Figure 3 are the result of the exposure to VC of various groups of individuals in different periods of time since 1935. Equation 4 indicates that the incidences (not incidence rates) according to calendar year, year of exposure, and year from onset of exposure, respectively, are:

$$I_j = \sum_{i \leq j} C_i \, t_{j-i}^k \, F_j(\text{Mort}) \qquad (5a)$$

$$I_i = C_i \sum_{j \geq i} t_{j-i}^k \, F_j(\text{Mort}) \qquad (5b)$$

$$I_{j-i} = t_{j-i}^k \sum C_i \, F_j(\text{Mort}) \qquad (5c)$$

where i represents the quinquenium of exposure and j, the quinquenium of observation. i runs from 1 to 8, representing the years 1935-1974 and j from 1 to 9, extending the observations through 1979. The F_j(Mort) are the appropriate age and calendar year adjustments to the population in

Relative values for the C_i's can be determined from two sets of data. The first is the incidence of HSA according to calendar period of first exposure (I_i). Here the C_i's are directly proportional to the incidence in a given calendar period and available data are sufficient to establish reasonable values of C_i for the time period 1935-1955. Additional data on C_i can be developed from published data on the production of VC monomer. Figure 4 displays the available information on production in the United States (S.P.I., 1975-1978; U.S. Tariff Commission, 1948-1968) and Western Europe (O.E.C.D., 1971). A first approximation to the population exposure in different years would be to consider the C_i's to be proportional to VC production. However, average VC concentrations changed over the years of concern (Table 1) and an adjustment for the different relative exposures in different times must be made. This adjustment is indicated in Table 1 and on Figure 4. Further, an adjustment must be made to take into account the different number of workers required to produce a metric ton of VC in different time periods. As it would be expected that more workers were employed per tonne of VC produced during earlier years, an adjustment is required to account for productivity. Initial estimates of this factor are also indicated in Figure 4. The relative population exposure, taken to be the product of production, the workforce productivity adjustment, and the exposure adjustment is shown by the solid

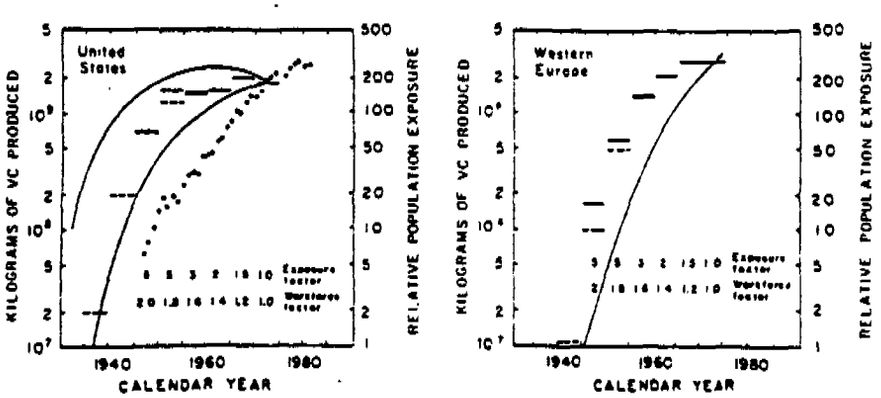

Figure 4. The production of VC in the U.S. and Western Europe along with estimates of the population exposures to VC polymerization workers in different calendar periods.

United States and Western Europe. The results of this procedure, combining the data for the United States and Western Europe, are shown in Figure 5. As can be seen I_{j-i}, the incidence according to years from onset of exposure is best fit by a value of k = 2. A value of 3 is compatible with the data, but values greater than 4 can be ruled out. I_j is relatively insensitive to the choice of k, but a value of 4 fits the data best.

An interesting feature of this calculation is that the separate determination of the C_i's for Western Europe and the United States indicates that the population exposures per tonne of VC produced were approximately four times greater in Western Europe than the United States. This would suggest that more intense exposures occurred in some European plants or that more workers were exposed per tonne of VC produced.

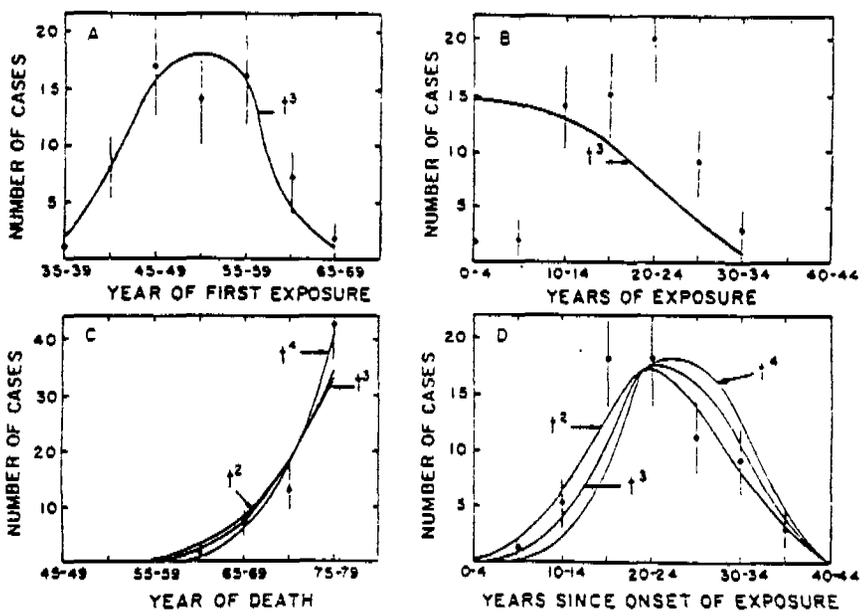

Figure 5. A comparison of the calculated incidence of hemangiosarcoma of the liver with that observed in the U.S. and Western Europe according to several time criteria and models for calculation.

jected numbers of HSA for the United States range from 200 to 600 and, for Western Europe, from 550 to 2,800. (The greater range for Europe is the result of the more recent usage of pattern.) The most probable projection for future disease is felt to be that represented by a power of 3, a choice suggested by Thoratrast data and the very limited mortality data on HSA in the study by Nicholson et al (1983). Lower values are also reasonable, but the fit to the data would suggest that the use of a power of 4 may be inappropriate.

Obviously, many caveats exist in the consideration of these projections. The estimates strongly depend upon a reasonable ascertainment of cases through 1979. The concerns for VC-induced HSA in recent years would suggest that ascertainment was fairly good, at least for long term employees and pensioners. However, some cases in short term workers may have been missed. The projections also depend on the choices of the C_i and the k. We have projected mortality based on reasonable choices for these parameters. However, other choices cannot be absolutely excluded. While these uncertainties exist, the data indicate that, within a factor of 2 or 3, future HSA mortality from exposures prior to 1975 will be about 350 deaths in the United States and 1,200 in Western Europe. Further, these deaths will occur in a relatively small population. In the United States, the group at highest risk would be comprised of fewer than 5,000 individuals. Among this heavily exposed group, HSA may account for 10% of all deaths (Nicholson et al, 1983). Clearly, any intervention techniques that might be developed to reduce this projected risk could be efficiently applied.

OCCUPATIONAL STANDARDS FOR VC

Nicholson et al (1983) have shown that liver HSA accounts for at least 50% of all VC-induced malignancies. Thus, it would appear that average exposures of 200-500 ppm in previous years will lead to 1,000-4,000 excess cancer deaths in all workers exposed to VC in Western Europe and the United States prior to 1975. If a standard of 1 ppm is met, the average exposure of all the workers would be between 0.2-0.5 ppm, 1,000 times less than that which existed previously. One would expect the VC-induced malignant risk to be reduced by a corresponding amount. This implies that, <u>if the VC industry complies with a 1 ppm standard</u>, cancer from employ-

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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-

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*	1948	27	1975
Byren et al. 1976	SWED	750	low	58	7.7	>0	>0*	1945	28	1974
Duck et al. 1975	UK	2113	0.3	136	6.4	>0	>0*	1948	20	1975
Equitable Env. Health, 1978	USA	9677	4.9	707	7.3	1	1*	(1935)	25+	1972
Fox and Collier 1976, 1977	UK	7409	1.1	393	5.1	>0	>0*	1940	35	1974
Hanuda 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*	1947	25	1974
Ott et al. 1975	USA	522	0.0	79	15.1	>0	>0	1942	31	1973
Reinl et al. 1979	GER	6544	7.3	414	6.3	>0	>0	NA	NA	1974
Theriault and Allard, 1981	CAN	451	2.8	59	13.1	5	5*	1943	30	1977
Waxweiler et al. 1976	USA	1287	0.5	136	10.6	5	10*	1940	22	1973

* Longer latencies considered for some causes of death.

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 29 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

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

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
Masuda	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	214††
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

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-

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.

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 were 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

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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OCCUPATIONAL HAZARDS IN PRODUCTION AND PROCESSING OF STYRENE POLYMERS - EPIDEMIOLOGIC FINDINGS

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INTRODUCTION

Of the major plastic monomers, styrene is exceeded only by ethylene, propylene and vinyl chloride in terms of production. In 1977, approximately 3 x 10^6 metric tons were produced in the United States and 7 x 10^6 metric tons worldwide (IARC, 1979). Approximately 60% of the monomer produced was used in homopolymers, largely for the packaging industry. Other important uses of styrene are in the production of copolymers with acrylonitrile (SAN) and acrylonitrile and butadiene (ABS). Styrene also finds widespread use as a copolymer with butadiene in the production of the synthetic elastomer, styrene-butadiene rubber (SBR), which forms the basis of approximately 80% of U.S. rubber products. Finally, it is extensively used as a solvent and cross-linking agent for polyester resins in the fiber reinforced plastic (FRP) industry. Estimates of the number of workers employed in the various industries using styrene-based polymers are given in Table 1 along with typical exposure levels (Tossavainen, 1978). In addition to occupational exposure, low-level environmental contamination can occur from combustion of styrene-based products, as the thermal decomposition of polystyrene leads to evolution of the monomer, in contrast to other polymer materials.

MORTALITY STUDIES OF STYRENE-EXPOSED WORKERS

Studies on the mortality of populations exposed to styrene are fraught with difficulty because of confound-

Table 2

Population and follow-up characteristics of three studies of styrene exposed workers

Study	Country	Analysis cohort size	Percent traced	Number of deaths analyzed	Percent of total
Ott et al. 1980	USA	2904	97.4	303	10.4
Nicholson et al. 1978	USA	560	100.0	83	14.8
Frentzel-Beyme et al. 1978	GER	1960	93.0Ger 29.0For	73	3.7

	Minimum exposure (years)	Minimum latency (years)	Years follow-up	Exposures
Ott et al. 1980	1	1	1940-1975	<10 ppm (3)[a]
Nicholson et al. 1978	5	10	1960-1975	<20 ppm (5)
Frentzel-Beyme et al. 1978	1 mo.	1 mo	1956-1976	< 1 ppm[b]

[a] ( ) = Estimated average exposure
[b] Current measurement after installation of controls

The study of Nicholson et al (1978) successfully traced all of 563 men employed in styrene production, polymerization and polymer processing who had 5 years of employment on May 1, 1960 and were 10 years from onset of work in a large U.S. production facility. The basic mortality data are shown in Table 3 and demonstrate no excess mortality from any cause of death. Analyses according to years from onset of exposure and calendar years of observation did not reveal any pattern of excess mortality. However, because of the limited number of deaths, the data can be used only to establish upper limits of risk. For example, the data are only sufficient to indicate that the SMR for lymphoma or leukemia is less than 280 at the 0.05 level of significance and that of lung cancer, less than 220. While no excess mortality was identified in the cohort observed, the above publication mentioned the existence of 7 deaths from leukemia and 5 of malignancy of the lymphatic system among 444 deaths known to have occurred in the plant workforce. While the ages of death were not available for exact proportionate mortality calculations, the number of lymphomas is in line with expectations, while leukemia appears to be in excess by as much as a factor of two. However, the possibility of high exposures to benzene in the facility during earlier years weakens the likelihood

Table 4

Observed and expected deaths by cause for total production and non-professional research employees (2310 men), 1940-1976

Causes	Observed deaths	Expected deaths US white males	SMR	Expected deaths, Company comparison	SMR
All causes	282	357.8	79	287.6	98
Malignant neoplasms	55	64.2	87	65.0	85
Respiratory system	14	20.8	67	23.9	59
Digestive system	16	18.0	89	21.2	67
Lymphatic and hematopoietic system except leukemia	6	4.5	133	2.6	230
Leukemia	6	2.9	207	1.6	375
Other sites	13	18.0	72	15.7	83
Cardiovascular disease	143	172.4	83	141.5	101
Nonmalignant respiratory dis.	12	14.3	84	10.0	120
All other causes	72	106.9	67	71.1	101

From Ott et al. 1980

concentrations of styrene (5-9 ppm). Because of a lack of a definitive exposure-response-relationship and the presence of possible confounding exposures, the authors refrained from drawing any conclusions on an etiological relationship.

In 1976, nine cases of various types of leukemia were identified in two SBR plants and reported to the U.S. National Institute for Occupational Safety and Health (Meinhardt et al, 1978). All occurred after 1971 in a population of 5,600 workers. No data were presented on the expected numbers of deaths from leukemia in the group. Concern generated by the findings in the two plants led to reports on the leukemias present in two large ongoing studies of rubber workers. McMichael et al (1976) reported a relative risk of 6.2 for lymphatic and hematopoietic malignancies among employees producing elastomers, including SBR. However, this was based upon only 6 cases, 3 leukemias and 3 lymphomas. In a subsequent case control study of the same plant, a relative risk of 2.4 was found for the same exposure group (Spirtas et al, 1976). The difference in the two values reflect the uncertainties associated with small numbers of cases. A similar investigation by Monson et al (1978) showed an excess of leukemia to be present in calendering, extrusion, tire building and rubberized fabrics. However, the excess was associated with exposure to solvents and not to styrene.

various respiratory symptoms, and gastrointestinal disturbances, such as nausea, vomiting and loss of appetite, are commonly reported by styrene-exposed workers. Other abnormalities reported include headaches, tiredness and sleep disturbance. After a period of exposure, adaptation may occur and there can be a decrease in the various symptoms. Nevertheless, significant alterations still exist among currently employed workers.

Several systematic studies of the various clinical effects from styrene exposure have been conducted in recent years. Many of these focused on possible neurological alterations and clearly demonstrated adverse findings at moderate styrene exposures (less than most national standards). The most extensive of these is that by investigators from the Institute of Occupational Health of Finland (Seppäläinen and Härkönen, 1976; Lindström et al, 1976; Härkönen, 1977; Härkönen et al, 1978). They examined 98 workers employed at 24 plants manufacturing FRP products. Air concentrations were sampled and ranged from 5 to 300 ppm. The means of five post-workday urine mandalic acid (MA) concentrations ranged from 7 to 4,700 mg/l with a linear relationship existing between the log of the MA concentration and the log of the styrene concentration. The mean value of MA in the population was 808 mg/l and corresponded to an exposure of about 40 ppm of styrene. Abnormal EEG's were found in 30% of those with MA in excess of 700 mg/l, compared to about 10% for those with lower MA values and normal controls (Seppäläinen and Härkönen, 1976). Lindström et al (1976) noted increased visuomotor inaccuracy (symmetry drawing and Bourdon-Wiersma tests) and lowered psychomotor performance (Mira test) for various MA concentrations ranging from 800-2,000 mg/l (See also: Härkönen et al, 1978). Fatigue, irritation, difficulty in concentration, nausea, dizziness, and lightheadedness were more frequently reported by the styrene-exposed workers than by unexposed controls (Härkönen, 1977).

A deteriorating EEG among styrene workers has also been described by Klimkova-Deutschova et al (1973). Alterations of nerve conduction have been documented by Rosén et al (1978) who observed an increased duration and decreased amplitude of sensory action potentials. Lilis et al (1978) suggested the possibility of a decrease in peroneal nerve conduction velocity. The decrease, however, was only associated with length of employment and not intensity of expo-

to other chemicals, such as benzene. The studies are severely limited because of the relatively low styrene exposure of the groups studied. They provide no guidance on carcinogenic risk in populations much more heavily exposed as in the FRP industry. The significant clinical findings among styrene-exposed workers are largely limited to abnormalities of the central nervous system, where a variety of objective and subjective symptoms have been reported in the FRP industry. Concern for long-term degnerative neurological disease exists for continued long-term exposure in this industry. The possibility of pulmonary effects from styrene exposure has also been noted.

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