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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,

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Encs.

Has Shah
VC Prog Panel
3/4/85

Toledo

Occupational Hazards of Vinyl Chloride and Styrene

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MOUNT SINAI SCHOOL OF MEDICINE OF THE CITY UNIVERSITY OF NEW YORK

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

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ENVIRONMENTAL SCIENCES LABORATORY
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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.

At this time, data are available on both experimental and human carcinogenesis from exposure to vinyl chloride (VC) and on its metabolism that provide information important for the understanding of observed dose-response relationships. This paper will consider these data on VC in detail as they provide estimates of the trends in future disease potential from past exposures and information on the efficacy of current occupational standards. As human and animal data accumulate on the effects of exposure to other monomers, the approach suggested by VC can be applied to their evaluation.

DOSE-RESPONSE RELATIONSHIPS

VC is one of the best studied chemicals in animal systems. The magnificent research by Maltoni and associates (1981) on nearly 7,000 animals over a ten year period is virtually unmatched in experimental carcinogenesis. A principal feature of their results is summarized in Figure 1 which shows the dose-response relationship for the percentage of animals that developed hemangiosarcoma (HSA) of the liver from 4 hr/day, 5 day/wk, 52 wk exposures to different concentrations of VC. As can be seen, the relationship is a non-linear one with evidence of saturation at high con-

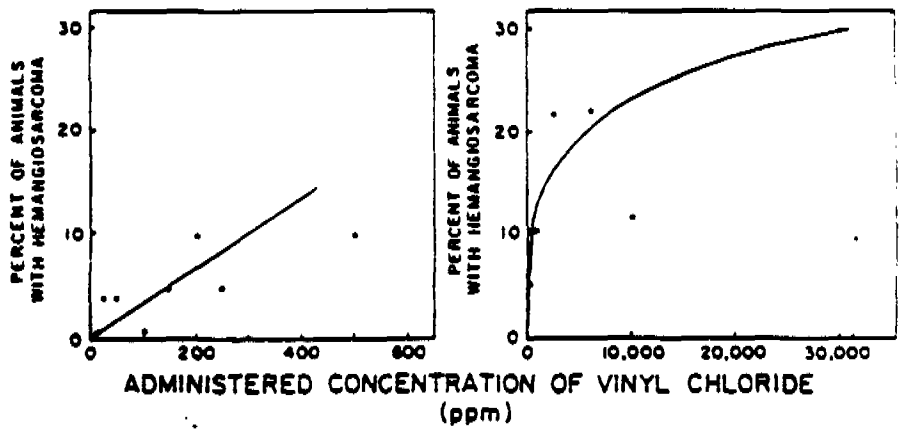

Figure 1. The percentage of rats developing liver hemangiosarcoma from 52 wk exposures to VC for 4 hr/day, 5 day/wk.

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

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

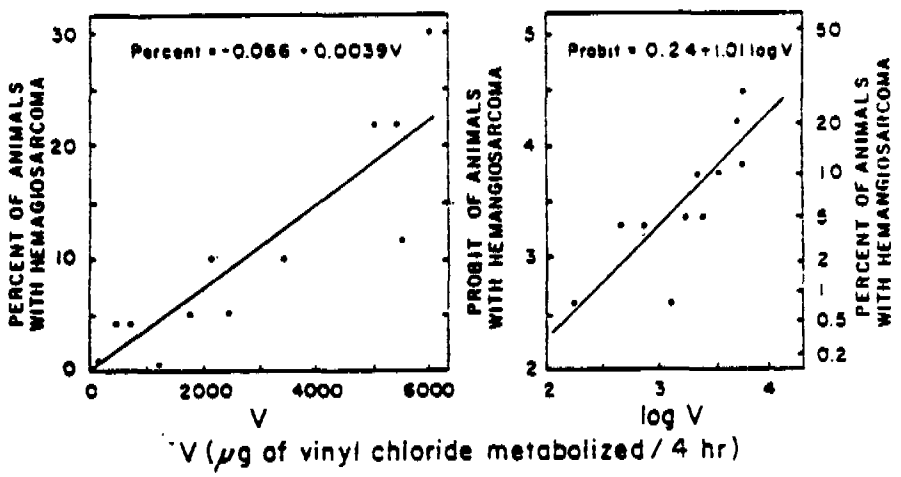

Figure 2. Linear and probit dose-response relationships for the quantity of VC metabolized/4 hr exposure (5 day/wk,52 wk).

Gehring et al (1978) fitted the early data of Maltoni and Lefemine (1975) to a log-probit model. Figure 2B shows the log-probit plot using all available data from the studies from Maltoni et al (1981). The unweighted least squares regression line is

$$\text{Probit} = 0.24 + 1.01 \log V \qquad (3)$$

While such a plot fits the observable data ($r^2 = 0.68$), the linear dose-response relationship fits the data somewhat better ($r^2 = 0.77$). Further, there is very limited biological rationale for the use of a log-probit relationship in carcinogenesis and its use as a means of extrapolation to predict effects at very low exposures would appear to be more an act of faith than of science. On the other hand, a linear dose-response relationship between the incidence of HSA and the quantity of VC metabolized is biologically plausible and fits all available data. Its use is strongly suggested.

TIME COURSE OF CANCER

Much of human cancer has been found to follow a power law relationship with age (Armitage and Doll, 1961; Cook et al, 1969),

$$R = bt^k \qquad (4)$$

where R is the incidence rate of cancer at a specific site, t is age, and b and k are constants specific to site. In general, k is between 4 and 6 for most epithelial malignancies. While data for exposures to specific carcinogens are limited, bronchogenic carcinoma from cigarette smoking and mesothelioma from asbestos exposure also follow a power law of time from onset of exposure with an exponent between 3 and 5 (Doll and Peto, 1978; Newhouse and Berry, 1976; Peto et al, 1982). These findings have been interpreted in terms of a multistage model of carcinogenesis, the implications of which have been discussed by Peto (1977), Whittemore and Keller (1978), and Day and Brown (1980), among others. Deviations from the above time course occur with exposures to carcinogens that interact synergistically, such as asbestos and cigarette smoking in the production of lung cancer. This interaction can be incorporated in the multistage model, but a more complicated relationship obtains. However,

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:

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

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

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

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

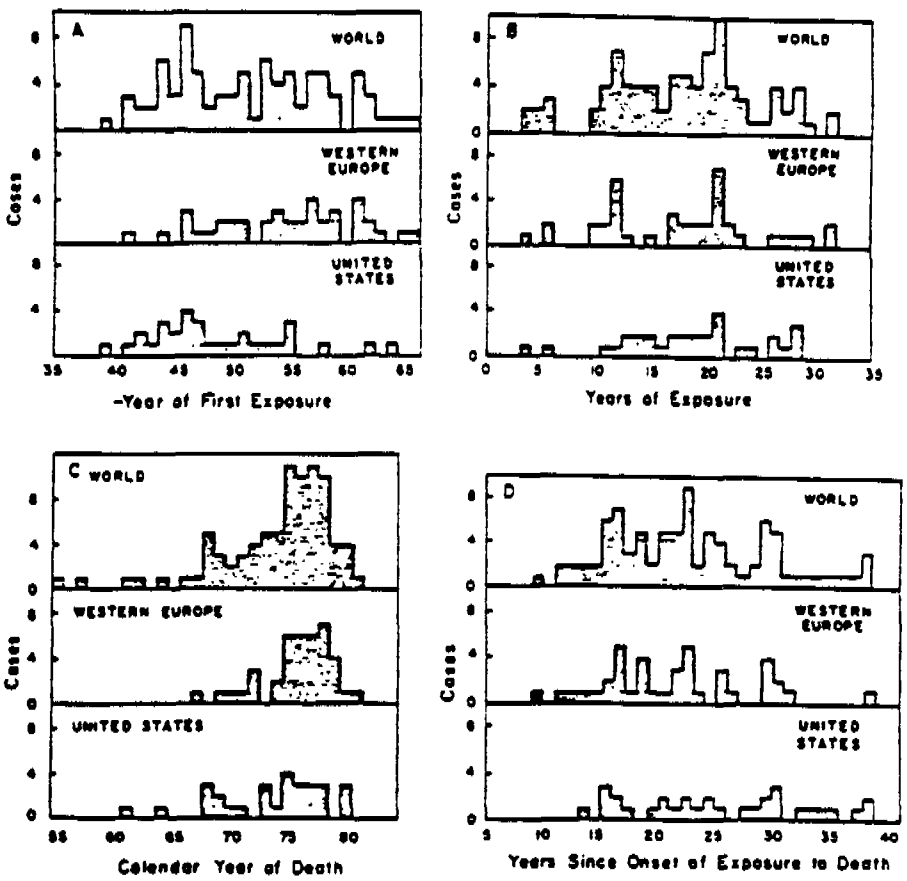

Figure 3. The number of cases of hemangiosarcoma of the liver in the U.S., Western Europe and the world according to several time criteria.

quinquenium j from normal mortality. The C_i's are proportional to the total population exposure, i.e., the average number of workers exposed in a given time period times the average VC concentration. Since the dose-response relationship for both inspired and metabolized VC is linear in the range of most worker exposures, the risk of HSA is proportional to the total population exposure; one need not know the number of workers exposed and their vinyl chloride exposure separately.

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

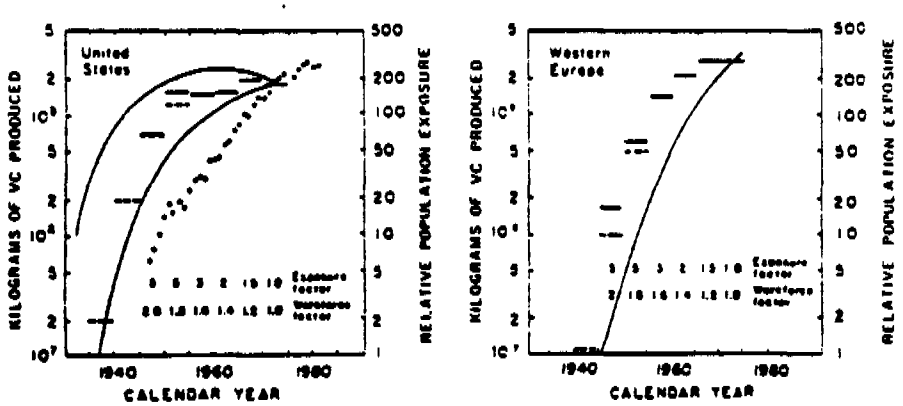

Figure 4. The production of VC in the U.S. and Western Europe along with estimates of the population exposures to VC polymerization workers in different calendar periods.

Table 1

Measured and estimated exposures to vinyl chloride to polymerization workers in various time periods

Calendar Period	Vinyl chloride exposures (ppm) Barnes (1976)	Ott et al (1975)	Suciu et al (1975)	Approximate relative exposure
Before 1950	1000			5
1950-54	1000	100 - 400		5
1955-59	400 - 500	100 - 400		3
1960-64	300 - 400	20 - 80	200 - 900	2
1965-69	300 - 400	20 - 80	40 - 50	1.5
1970-74	150 - 300		40 - 60	1

lines across each quinquenium. The dashed lines across each quinquenium during earlier years are those determined by fitting the observed HSA incidence to Eq. 5a and matched to the value estimated from production data in the quinquenium 1955-1959. As can be seen, the comparison of the two sets of data suggested that the population exposure prior to 1960 was slightly less in some quinquenia than that estimated by the use of the adjustment factors indicated in Figure 4.

The procedure of estimating the relative values for C_i, particularly in the years after 1960, is clearly an approximate one. To consider how sensitive any projections of future mortality are to the choices of C_i's, alternate choices are shown by the light solid lines in Figure 4a. Any realistic estimates of the C_i's must lie between the two lines.

Relative values of I_i, and I_{j-i} were calculated using the relative values of C_i shown in Figure 4, values of k between 2 and 4, and absolute values determined by matching to the incidence data of HSA found in Figure 3. In this calculation, the age distribution used for time of first exposure was: 15-19, 8.5%; 20-24, 26%; 25-29, 26%; 30-34, 15%; 35-39, 11%; 40-44, 7%; 45-49, 4%; 50-54, 2.5%. This distribution was that of 740 VC workers examined by Mount Sinai School of Medicine personnel during 1974. The pattern of duration of employment was assumed to be a decreasing exponential with an average employment time of 12 years. This corresponds to typical patterns of employment for long-term workers in the chemical industry (Nicholson et al, 1982; Wong, 1982). Separate calculations were made for the

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.

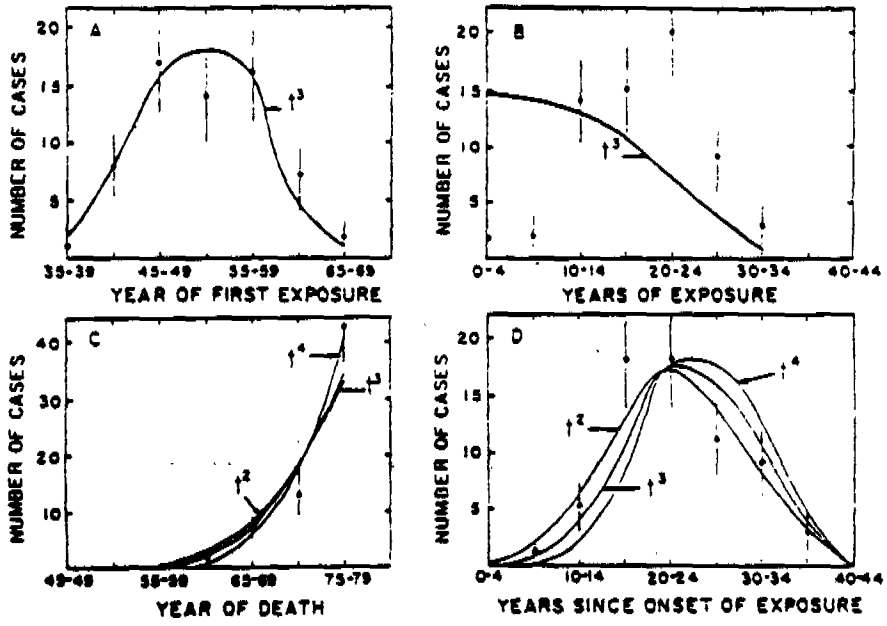

Figure 5. A comparison of the calculated incidence of hemangiosarcoma of the liver with that observed in the U.S. and Western Europe according to several time criteria and models for calculation.

One set of data that differs significantly from that calculated is the distribution of cases according to years of VC exposure. As mentioned previously, we assumed the distribution of employment times in the VC industry would be a decreasing exponential with a mean employment time of 12 years. The significant deficit of cases with employment times less than 10 years suggests that the available information on duration of VC exposure may not be correct, that our assumed employment distribution may be in error, that there may be an underascertainment of cases with shorter exposures, or that there may be proportionately less risk for shorter exposures than would be predicted on a linear dose-response relationship. It should be mentioned that duration of employment is not an important variable in assessment of population risk. Shorter employment times would have required more men to be exposed, but their average exposure would be proportionately lower.

Using the values of C_i's determined by the preceding analysis and values of k from 2 to 4, the mortality from liver HSA is calculated to the year 2040, using Eq. 5a. These data are listed in Table 2, separately for Western Europe and the United States. Also shown in the data for the United States are projections using values of C_i's indicated by the solid curves of Figure 4 and projections assuming that the risk of HSA will increase quadratically with age of exposure. This age dependence was suggested by experimental results of Groth et al (1981). We also considered a time course for HSA that increased as t^3 for only 45 years and remained constant thereafter. As can be seen, the pro-

Table 2

Projections of mortality in the United States and Western Europe to the year 2040 from exposures to vinyl chloride prior to 1975

Model	Total Projected Mortality	
	United States[a]	Western Europe[b]
t^2	190	540
t^3	340	1190
t^4	630	2780
t^3, to 45 years from onset of exposure	310	1120
t^3, upper exposure curve, Fig. 4	240	
t^3, lower exposure curve, Fig. 4	450	
t^3, + Age[5]	260	

[a] 26 deaths have occurred through 1979
[b] 39 deaths have occurred through 1979

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_1 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-

ment therein would be virtually eliminated. However, there will still remain a risk of developing HSA of the order of 10^{-4} per individual for a working lifetime, based on a United States or European workforce of about 10,000 workers.

SUMMARY

A high risk of death from liver HSA has been documented from past exposures to VC. Similar to other carcinogens, the risk of VC-induced liver HSA appears to increase as the second or third power of time from onset of exposure. It is possible to project future mortality using this power relationship, estimates of VC exposure, and observed mortality to 1980. These projections suggest that 200-600 deaths may occur in the United States and 550-2,800 in Western Europe from liver HSA. These projections also suggest that a 1 ppm standard in the VC industry will go far to protecting workers from future malignant disease.

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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
Beffler 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	7489	1.1	393	5.1	>0	>0*	1940	35	1974
Maguda 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
Reini 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

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* 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 disease 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*	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*	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††			

* 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 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

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[d]	7	(7.7)[c]	(91)
Bufflar	0	(0.17)	—	0	5	1.73	289*
5 yr. latency					4	1.49	268
Byren	4	0.97[e]	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[f]
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
Masuda	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	77(96?)
Reinl	12	0.9	1323 $^{+++}$	4	22	24.6	95[f]
Theriault	8	(0.5)	(1600)$^{+++}$	8	2	5.78	35
15 yr. latency					2	4.25	47
Waxweiler	7	0.6	1135 $^{+++}$	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.

f Adjusted for unknown causes of death.

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
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
Wanweiler	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 polymerization 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 56-73	74-81	Total	Expected	SMR
All causes	24	20	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[c]
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	8	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	14	22	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	0.63	—
Liver	0	4	4	0.23	1739[b]
Lymphoma	0	0	0	0.59	—
Pancreas	0	1	1	0.67	150
Cirrhosis of liver	0	1	1	1.81	55
Cardiovascular disease	10	10	20	27.24	73

a $p < 0.05$
b $p < 0.001$
c $p < 0.0001$

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	34.83	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.

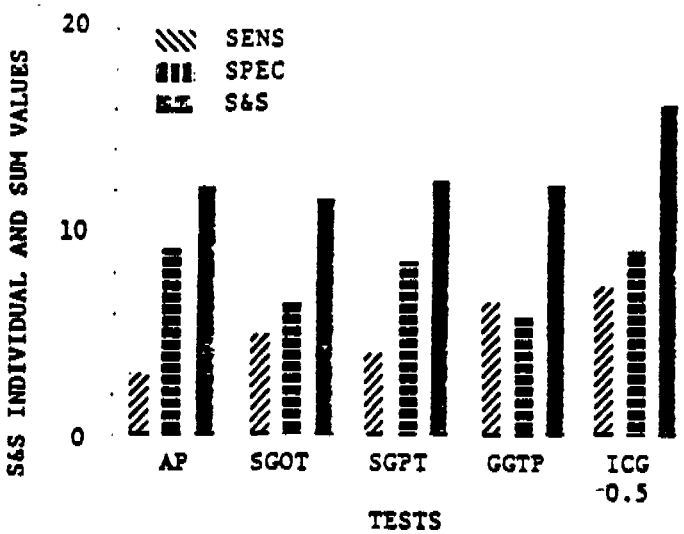

Figure 1: Sensitivity and specificity of various biochemical screening tests and their sensitivity and specificity sum values (S & S) based on 78 with biopsy documentation of their hepatic status.

Three of the seven individuals who died after 1974 with hemangiosarcoma in the previously described mortality followup were examined in 1974. One, who died 22 months after examination, had no noteworthy abnormalities on examination (alkaline phosphatase was 88, slightly high). A second, who died three years 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 (Maatrangelo 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 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

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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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 1

Occupational exposures to styrene

Process	Percent of styrene production	Number of workers involved	Typical exposure (ppm)
Monomer production	100	10,000	1 - 20
Polymer production (PS,ABS,SBR)	60 - 70	50,000	1 - 20
Reinforced plastics production (FRP)	20 - 30	200,000	20 - 300
Polymer processing (PS,ABS,SBR)	5 - 10	1,000,000	0.01 - 1

From Tossavainen, 1978

ing exposures to other known carcinogenic materials. Benzene exposures can occur in the production of styrene monomer, as the principal production process utilizes benzene to produce ethylbenzene, which, in turn, is dehydrogenated to form styrene. Copolymerization involves exposures to acrylonitrile and/or butadiene, which are carcinogenic in animals (Huff, 1983). Finally, some of the additives used in styrene products may be carcinogenic, as well as other chemicals used in facilities producing styrene or polystyrene.

Only three studies provide data on possible human carcinogenicity of styrene, each having some of the confounding exposures mentioned above. All were of groups of individuals employed in monomer production, polymerization or polymer fabrication, where exposures were relatively limited. No data exist on the mortality of individuals employed in the FRP industry, where styrene concentrations were (and are) commonly ten times higher. Table 2 lists the cohorts observed and some of the characteristics of the three studies.

As can be seen from Table 2, the large number of individuals lost to follow-up in the study by Frentzel-Beyme et al (1978) severely limits its usefulness. Of those exposed, 7% of the German workers and 71% of foreign "guest workers" were untraced. Of those traced, 74 had died, 12 from cancer. Only 37 deaths occurred in those with five or more years of exposure. The overall result did not demonstrate excess mortality for any cause of death. However, the limitations of the study are clear.

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 3

Expected and observed mortality experiences of 360 individuals employed in styrene production and polymerization prior to 1 May 1955, followed ten years after onset of exposure (1 May 1960 — 31 December 1973)

Cause of Death	Expected	Observed	SMR
All causes	106.41	83	78
Cancer	21.01	17	81
Cancer of the lung	6.99	6	117
Leukemia	0.79	1	126
Lymphomas	1.25	1	80
Other cancer	11.98	9	75
Heart and circulatory dis.	56.35	52	92
Respiratory diseases	6.64	1	15
Other causes of death	22.41	13	58

From Nicholson et al, 1978

of association of any possible excess of leukemia with styrene exposure.

The final study of styrene mortality is that of Ott et al (1980) who described the experience of 2,904 individuals with potential exposure to styrene prior to January 1, 1976. Three hundred three deaths occurred, 292 among production and nonprofessional research employees. The mortality experience for this latter group is shown in Table 4 and is compared to the expected deaths calculated from U.S. white male rates and rates from observations on other company employees. As can be seen, the mortality of styrene-exposed individuals compares favorably with each group; the only excess of note being six leukemias compared to 2.9 expected using U.S. rates and 1.6 from company rates. Lymphomas were also elevated, but not at an 0.05 level of significance. The excess leukemia was further investigated in an analyis of cancer incidence in the styrene-exposed population compared to that expected from rates of the Third National Cancer Survey. In this analysis, it was found that a significant number of lymphatic leukemias (5 observed vs. 0.26 expected) occurred in individuals who were exposed to styrene (< 5 ppm), ethylbenzene (< 5 ppm), polystyrene extrusion fumes, and colorants. Indeed, four of the five cases worked in the same general area during the period of time, 1947-1948, although their dates of death and other exposures varied widely. Interestingly, there were no deaths of lymphocytic leukemia among 442 individuals exposed to higher

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.

Since 1976, considerable interest has existed in potential carcinogenicity of styrene. This has been heightened by the data on mutagenicity and possible carcinogenicity of styrene and styrene oxide (Huff, 1983). Some suggestive human data are available from studies of polymerization workers and SBR production facilities. The irony of the situation is that no studies have been conducted of groups exposed to the enormously higher concentrations found in the FRP industry. The data available on styrene carcinogenicity are such that they can provide no assurance of safety at these higher exposures.

CARCINOGENIC RISK FROM COMONOMERS USED WITH STYRENE

The two principal comonomers used in styrene-based copolymers have each been shown to be carcinogenic in animals. Of these, acrylonitrile has also been associated with lung cancer in humans. In a group of 1,345 male employees, with potential exposure to acrylonitrile and followed from 1956 through 1976, 8 cases of lung cancer occurred compared with 4.4 expected from company rates (O'Berg, 1980). Further, there was a correlation of increased risk with intensity and duration of exposure. Among production workers employed between 1950 and 1952, 6 lung cancer deaths were observed vs. 1.5 expected ($p < 0.01$). A second study of 327 employees of a rubber chemicals plant with potential exposure to acrylonitrile identified 9 deaths of lung cancer compared to 5.9 expected, based on mortality rates for U.S. white males (4.7 based on mortality rates for other rubber workers from the same city) (Delzell and Monson, 1982). The excess was greatest among those who had worked for more than 5 years in the facility. These data, while limited by the small numbers, strongly suggest that acrylonitrile is carcinogenic for humans.

While butadiene has been demonstrably carcinogenic in animals (Huff, 1983), no data are available from human exposures.

CLINICAL FINDINGS AMONG STYRENE-EXPOSED WORKERS

A variety of symptoms have been reported from styrene exposure, dating from the rapid increase in production during World War II. Eye, nose and throat irritation,