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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-

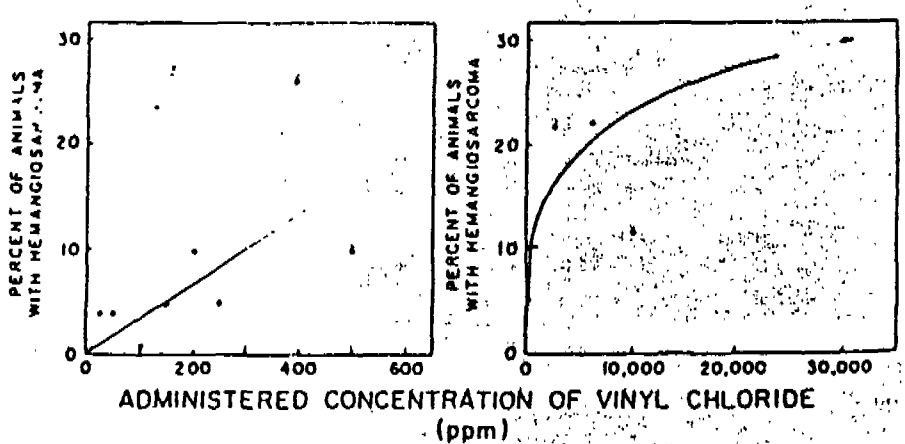

Figure 1. The percentage of rats developing liver hemangiosarcoma from 52 wk exposures to VC for 4 hr/day, 5 day/wk.

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

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

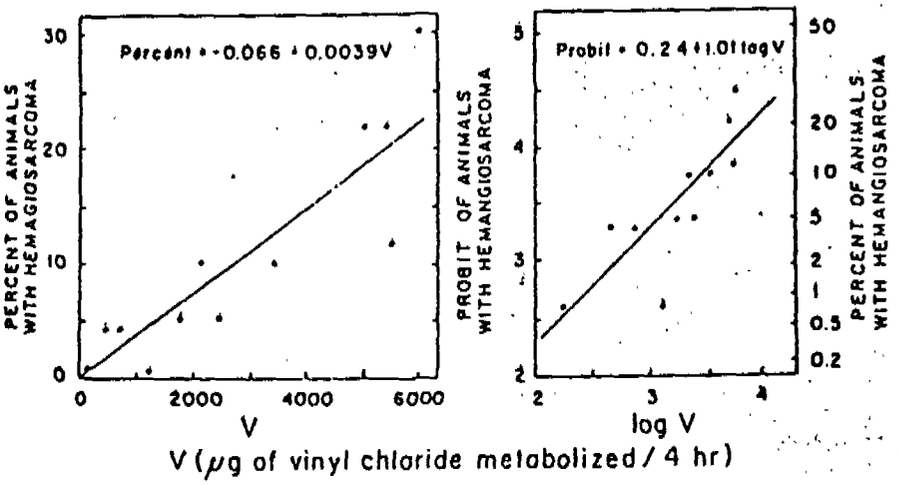

Figure 2. Linear and probit dose-response relationships for the quantity of VC metabolized/4 hr exposure (5 day/wk,52 wk).

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

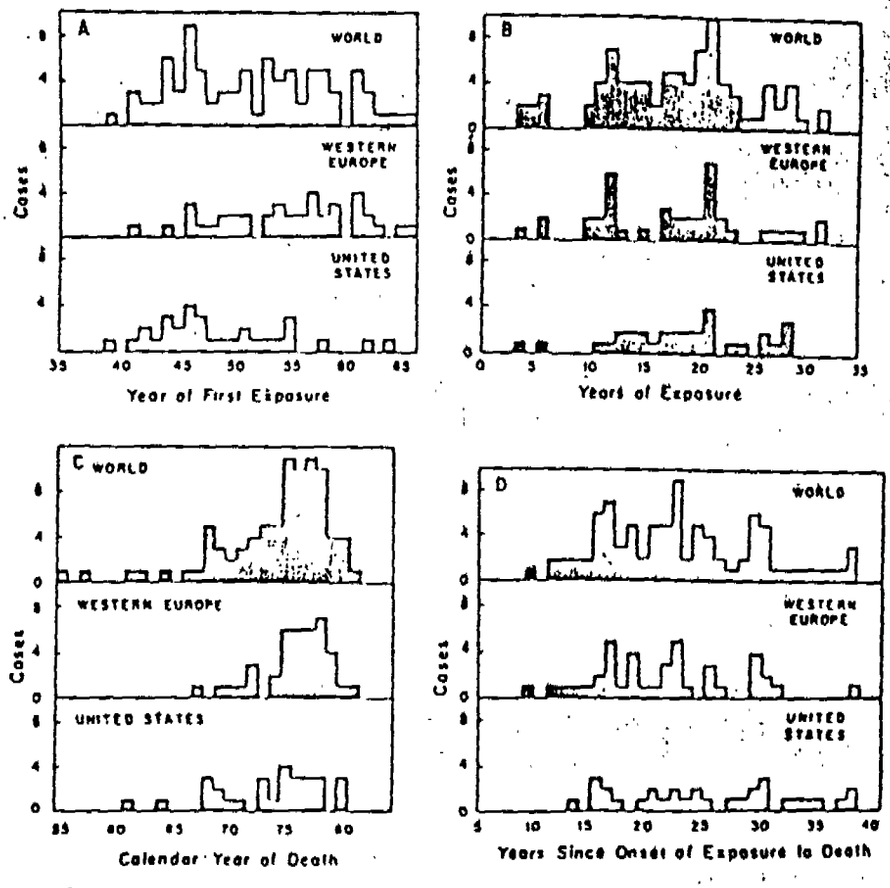

Figure 3. The number of cases of hemangiosarcoma of the liver in the U.S., Western Europe and the world according to several time criteria.

quinquenium j from normal mortality. The C_j'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

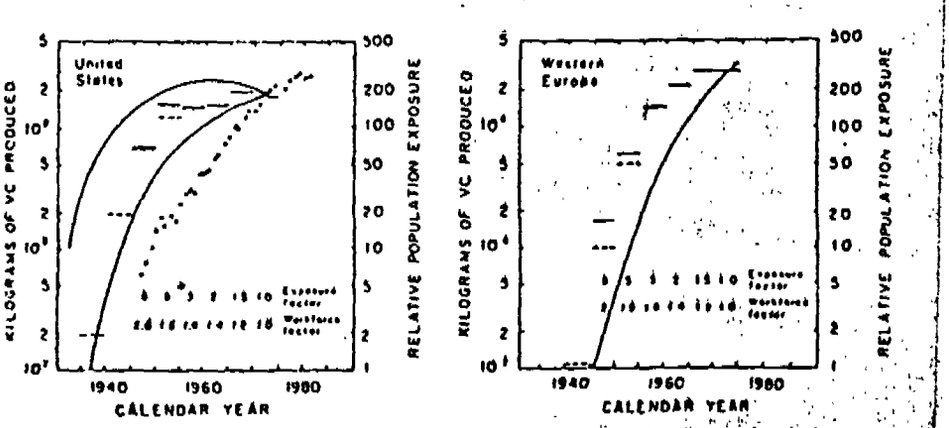

Figure 4. The production of VC in the U.S. and Western Europe along with estimates of the population exposures to VC polymerization workers in different calendar periods.

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 $I_{i,i}$ and $I_{i,i-i}$ 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.

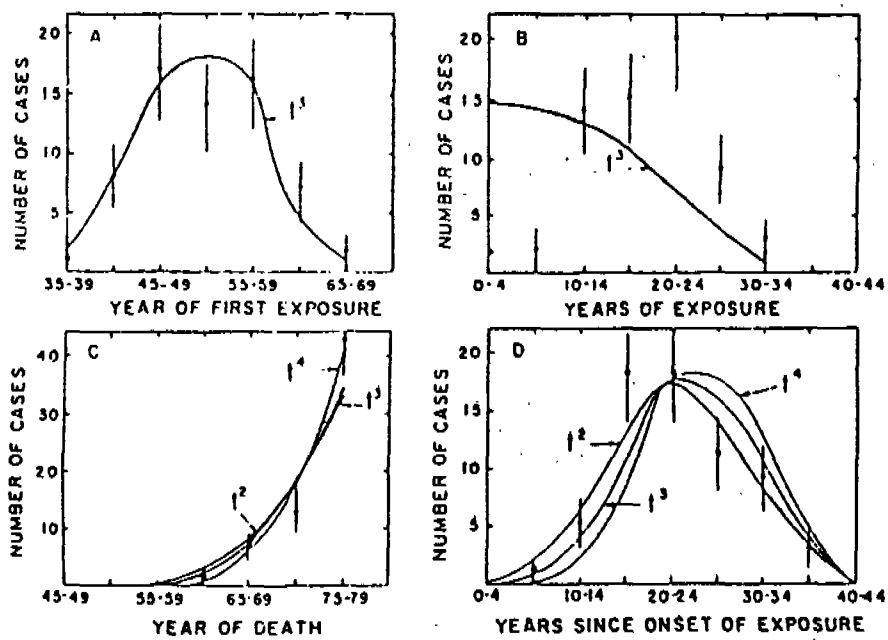

Figure 5. A comparison of the calculated incidence of hemangiosarcoma of the liver with that observed in the U.S. and Western Europe according to several time criteria and models for calculation.

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 suggest 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. 4a. 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[4]	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, 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, if the VC industry complies with a 1 ppm standard, cancer from employ-

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