

of Laboratory Animal
isks for Man, 179-189.
itors). Carcinogenic
283 pages, IARC
International Agency

istics When Examining
Carcinogenicity. J.

ime Feeding Study in
Validity as a Bioassay
icol., 3:63-67.

affiotti, U. (1976).
Small Rodents. NCI
(), DHEW, Washington,

Trend in Life Table

ive Value of Rodent
ion of Human Risks.
O.

rrent Concepts and
esis. J. Supramol.

Industrial Hazards of Plastics and Synthetic Elastomers, pages 65-78
© 1984 Alan R. Liss, Inc., 150 Fifth Ave., New York, NY 10011

TRENDS IN CANCER MORTALITY AMONG WORKERS IN THE SYNTHETIC POLYMERS INDUSTRY

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

Environmental Sciences Laboratory, Mount Sinai
School of Medicine, City University of New York
New York, New York 10029, U.S.A.

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-

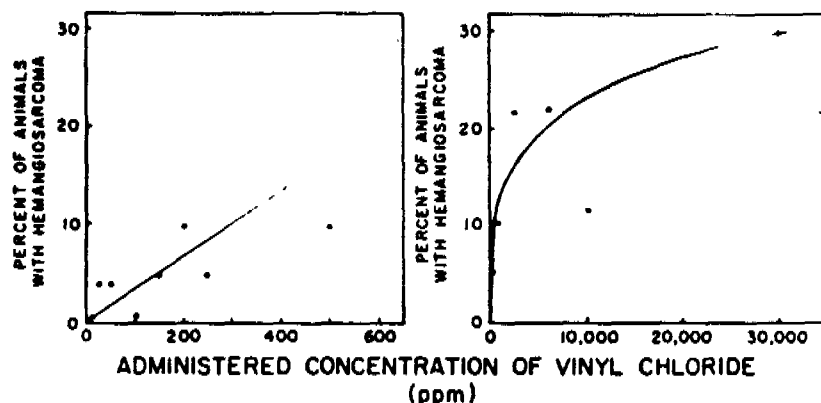
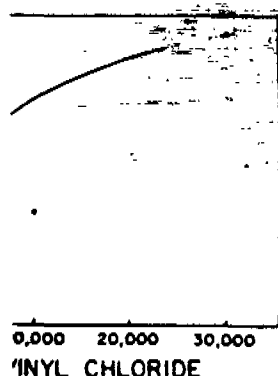


Figure 1. The percentage of rats developing liver hemangiosarcoma from 52 wk exposures to VC for 4 hr/day, 5 day/wk.

on both experimental
to vinyl chloride
information import-
dose-response rela-
these data on VC in
ie trends in future
d information on the
rds. As human, and
f exposure to other
can be applied to

chemicals in animal
ltoni and associates
ten year period is
carcinogenesis. A
marized in Figure 1
ip for the percent-
arcoma (HSA) of the
osures to different
ie relationship is a
ation at high con-



ing liver hemangio-
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,

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

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 $\mu\text{g/l}$ and V_m to be 5,706 $\mu\text{g/4 hr}$. 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 linear 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

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

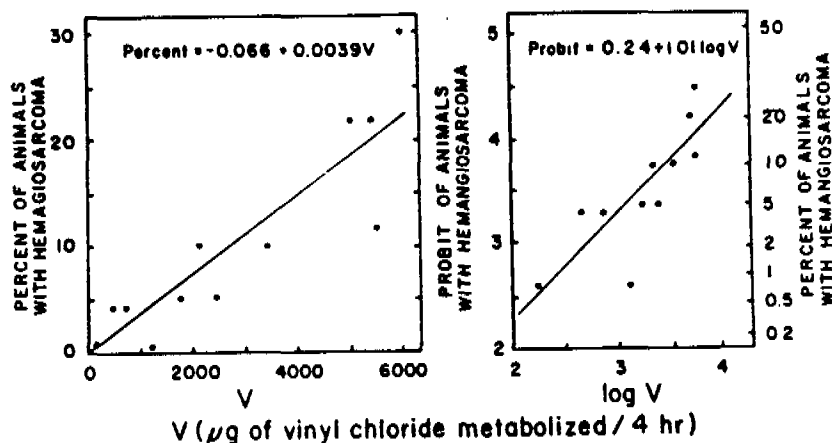


Figure 2. Linear and probit dose-response relationships for the quantity of VC metabolized/4 hr exposure (5 day/wk, 52 wk).

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

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

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),

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

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,

ly data of Maltoni
1. Figure 2B shows
data from the stud-
ghted least squares

(3)

ta ($r^2 = 0.68$), the
the data somewhat
ry limited biologi-
it relationship in
of extrapolation to
ould appear to be
the other hand, a
n the incidence of
is biologically
its use is strongly

to follow a power
oll, 1961; Cook et

(4)

at a specific site,
cific to site. In
ithelial malignan-
ic carcinogens are
arete smoking and
follow a power law
exponent between 3
Berry, 1976; Peto
interpreted in terms
he implications of
'), Whittemore and
0), among others.
cur with exposures
ly, such as asbes-
on of lung cancer.
the multistage mo-
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:

$$I_j = \sum_i C_i t_{j-i}^k F_j(\text{Mort}) \quad (5a)$$

$$I_i = C_i \sum_j t_{j-i}^k F_j(\text{Mort}) \quad (5b)$$

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

where i represents the quinquennium of exposure and j , the quinquennium 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 $F_j(\text{Mort})$ are the appropriate age and calendar year adjustments to the population in

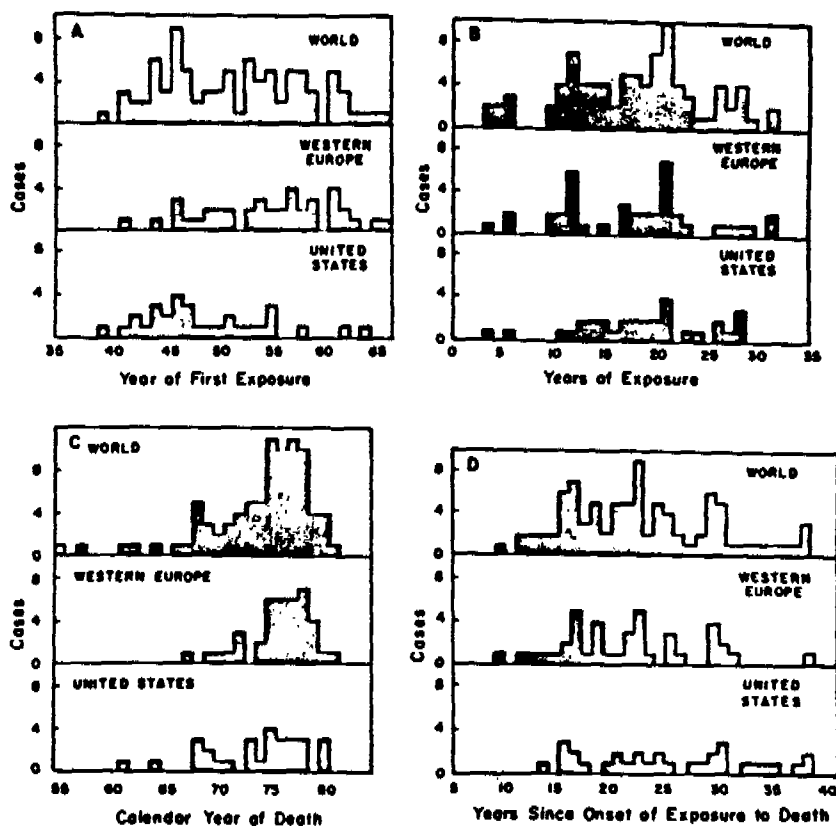
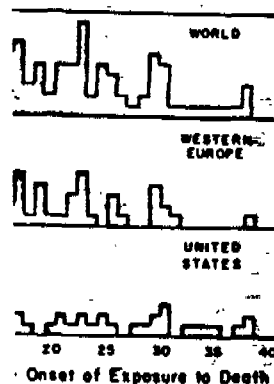
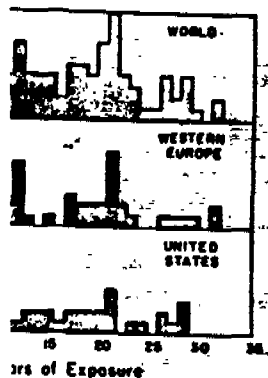


Figure 3. The number of cases of hemangiosarcoma of the liver in the U.S., Western Europe and the world according to several time criteria.

quinquennium 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.



osarcoma of the liver
according to seve-

ne C_i 's are propor-
tional, i.e., the average
time period times the
response relation-
ship. VC is linear in the
incidence of HSA is propor-
tional. One need not know
the air vinyl chloride

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

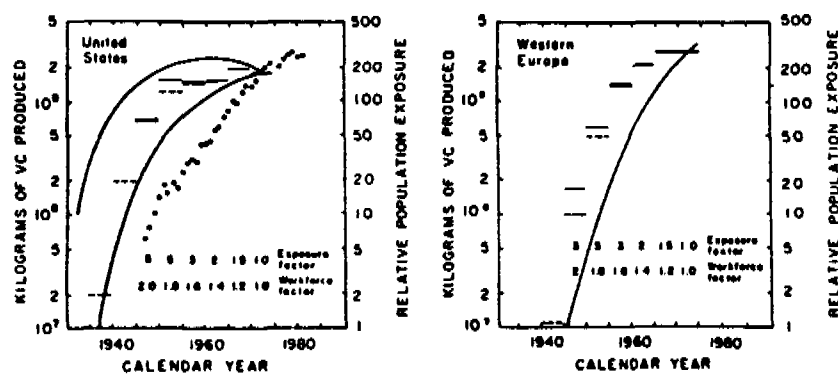


Figure 4. The production of VC in the U.S. and Western Europe along with estimates of the population exposures to VC polymerization workers in different calendar periods.

Table 1
Measured and estimated exposures to vinyl chloride
to polymerization workers in various time periods

Calendar Period	Vinyl chloride exposures (ppm)			Approximate relative exposure
	Barnes (1976)	Ott et al (1975)	Suciu et al (1975)	
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 quinquennium. The dashed lines across each quinquennium 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 quinquennium 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 quinquennia 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

vinyl chloride
time periods

Approximate
relative
exposure

	5
	5
	3
900	2
50	1.5
60	1

lines across each
case determined by
5a and matched to
in the quinquennium
of the two sets
sure prior to 1960
that estimated by
ted in Figure 4.

ive values for C_1 ,
early an approxi-
y projections of
 C_1 's, alternate
es, Figure 4a.
e between the two

calculated using
e 4, values of k
mined by matching
Figure 3. In this
or time of first
5-29, 26%; 30-34,
0-54, 2.5%. This
examined by Meunt
974. The pattern
be a decreasing
ime of 12 years.
f employment for
(Nicholson et al,
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_{1-1} , 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_1 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_1 '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.

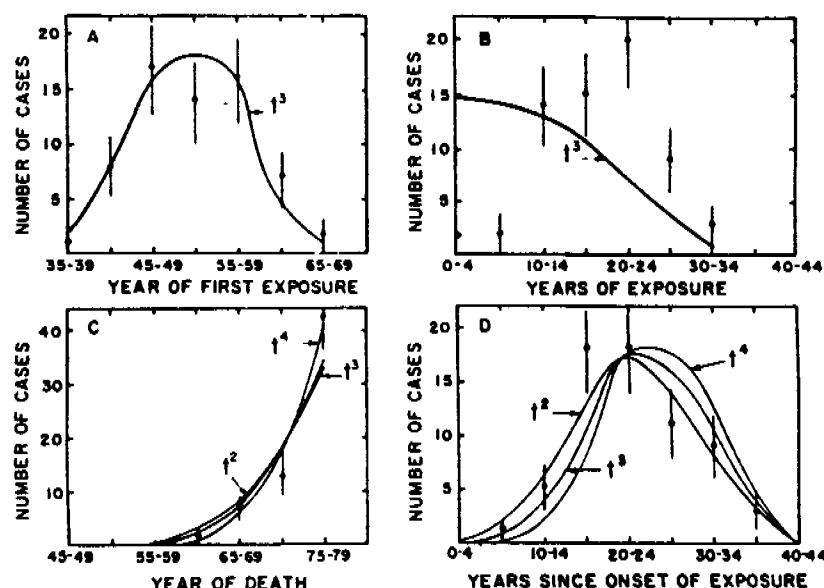


Figure 5. A comparison of the calculated incidence of hemangiosarcoma of the liver with that observed in the U.S. and Western Europe according to several time criteria and models for calculation.

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 ^a	260	

^a 26 deaths have occurred through 1979

^b 39 deaths have occurred through 1979

ificantly from that according to years y, we assumed the industry would be employment time of 12 s with employment available information correct, that our error, that there shorter exposures, risk for shorter near dose-response at duration of em- assessment of popu- could have required exposure would be

by the preceding the mortality from 40, using Eq. 4a. ately for Western n in the data for lues of C's indi- projections assum- quadratically with suggested by expe- We also considered for only 45 years be seen, the pro-

ed States
0 from
to 1975

ected Mortality
as^a Western Europe^b

540
1190
2780
1120

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 Thoratrat 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-

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.

REFERENCES

- Armitage P, Doll R (1961). Stochastic models for carcinogenesis. In: Proceedings of the Fourth Berkeley Symposium on Mathematical Statistics and Probability. (Ed. Neyman J) Univ Calif Press, Berkeley pp. 19-38.
- Barnes AW (1976). Vinyl chloride and the production of PVC. Proc Roy Soc Med 69:277-280.
- Bonse G, Henschler D (1976). Chemical reactivity, biotransformation and toxicity of polychlorinated aliphatic compounds. CRC Crit Rev Toxicol 5:395.
- Cook PJ, Doll R, Fellingham SA (1969). A mathematical model for the age distribution of cancer in man. Int J Cancer 4:93-112.
- Day NE, Brown CC (1980). Multistage models and primary prevention of cancer. J Natl Cancer Inst 64:977-989.
- Doll R, Peto R (1978). Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J Epidem Comm Health 32:303-313.
- Faber M (1978). Malignancies in Danish Thorotrast patients. Health Physics 35:153-158.
- Gehring PJ, Blau GE (1977). Mechanisms of carcinogenesis: dose response. J Environ Path Toxicol 1:163-179.

ted. However, there
HSA of the order of
fetime, based on a
out 10,000 workers.

been documented from
er carcinogens, the
to increase as the
of exposure. It is
ng this power rela-
observed mortality
200-600 deaths may
in Western Europe
uggest that a 1 ppm
o protecting workers

dels for carcinoge-
Berkeley Symposium
ility. (Ed. Neyman
production of PVC.

activity, biotrans-
ated aliphatic com-

mathematical model
man. Int J Cancer

models and primary
Inst 64:977-989.
cing and bronchial
ips among regular
Epidem Comm Health

horotrast patients.

of carcinogenesis:
1:163-179.

Gehring PJ, Watanabe PG, Park CN (1978). Resolution of dose-response toxicity data for chemicals requiring metabolic activation: example - vinyl chloride. *J Toxicol Appl Pharmacol* 44:581-591.

Groth DH, Coate WB, Ulland BM, Hornung, RW (1981). Effects of aging on the induction of angiosarcoma. *Environ Health Persp* 41:53-57.

Hoel DG, Kaplan NL, Anderson MW (1983). Implication of non-linear kinetics on risk estimation in carcinogenesis. *Sci* 219:1032-1037.

Maltoni C, Lefemine G (1975). Carcinogenicity assays of vinyl chloride: current results. *Ann NY Acad Sci* 246: 195-224.

Maltoni, C (1977). Recent findings on the carcinogenicity of chlorinated olefins. *Environ Health Persp* 21:1-5.

Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D (1981). Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. *Environ Health Persp* 41:3-29.

Milvy P., Garro AJ (1976). Mutagenic activity of styrene oxide (1,2-epoxyethylbenzene), a presumed styrene metabolite. *Mutat Res* 40:15-18.

Mori T, Kato Y, Shimamine T, Watanabe S (1979a). Statistical analysis of Japanese Thorotrast-administered autopsy cases. *Environ Res* 18:231-244.

Mori T, Maruyama T, Kato Y, Tahashashi S (1979a). Epidemiological follow-up study of Japanese Thorotrast cases. *Environ Res* 18:44-54.

National Institute of Occupational Safety and Health (U.S.) (October, 1982). Reported cases of angiosarcoma of the liver among vinyl chloride polymerization workers.

Newhouse ML, Berry G (1976). Prediction of mortality from mesothelial tumors in asbestos factory workers. *Brit J Indus Med* 33:147-151.

Nicholson WJ, Perkel G, Selikoff IJ (1982). Occupational exposure to asbestos: population at risk and projected mortality - 1980-2030. *Am J Indust Med* 3:259-311.

Nicholson WJ, Henneberger P, Seidman H. Occupational hazards in the VC-PVC industry. This volume.

Organization for Economic Cooperation and Development, Chemical Industry (1971). Quoted in: Levinson C. Work hazard: vinyl chloride. ICF Geneva.

Ott MG, Langner RR, Holder BB (1975). Vinyl chloride exposure in a controlled industrial environment. *Arch Environ Health* 30:333-339.

- Peto R (1977). Epidemiology, multistage models and short-term mutagenicity tests. In: Origins of Human Cancer (Eds. Hiatt HH, Watson JD, Winsten JA). Cold Spring Harbor Laboratory pp. 1403-1430.
- The Society of the Plastics Industry, Inc (1975-1982). Facts and Figures of the U.S. Plastics Industry, New York.
- Suciu I, Prodan EI, Paduraru A, Pascu L (1975). Clinical manifestations in vinyl chloride poisoning. Ann NY Acad Sci 246:53-69.
- U.S. Tariff Commission (1948-1968). Polyvinyl chloride and copolymer production data.
- Van Duuren B (1975). On the possible mechanism of carcinogenic action of vinyl chloride. Ann NY Acad Sci 246:258-267.
- Whittemore AS, Keller JB (1978). Quantitative theories of carcinogenesis. Society for Industrial and Applied Mathematics Review 20:1-30.
- Wong O (1981). An epidemiologic study of workers potentially exposed to brominated chemicals: with a discussion of a multifactor adjustment. In: Quantification of Occupational Cancer (Eds. Peto R, Schneiderman M). Banbury Report 9 Cold Spring Harbor Laboratory pp. 359-378.

REPI

Intr

last
beca
ized
plas
know
pers

publ
empl
are
ether
in pl
incl
offsp

Publi

effec
frequ
on sp
husba
pater
vinyl
the ei