FILE: VINYL CHLORIDE – CARCINOGENICITY RISK ASSESSMENT

The Dow Chemical Company
Midland, Michigan 48674

REV'D

1803 BUILDING
May 28, 1991

Mr. David Hughes
Louisiana Department of Environmental Quality
Office of Air Quality and Radiation Protection
Enforcement and Regulatory Compliance Division
7290 Bluebonnet Boulevard
Fourth Floor
Baton Rouge, LA 70810

RE: COMMENTS ON AIR QUALITY REGULATIONS, LOG # AQ12

Dear Mr. Hughes:

We are pleased to submit the attached comments on the appropriate unit risk factor to be used in setting ambient guidelines for vinyl chloride monomer (VCM). We present two unit risk factors - one based on a pharmacokinetic animal model and the other based on an analysis of human epidemiology data. Use of either suggests that results based upon default cancer risk assessment procedures overestimate VCM cancer risk by two orders of magnitude or more. We suggest that Louisiana use a unit risk factor based on available scientific data rather than relying on standard default methodology.

We offer these comments in the spirit of advancing the science of evaluating air toxics and their potential health effects.

Thank you for your consideration.

Neil C. Hawkins, Sc.D.
Project Leader
Health and Environmental Sciences
1803 Building
517/636-8237

Ronald L. McCreedy
Development Leader
Chemicals and Metals TSD
2020 Building
517/636-1824

R&S147525

Summary: We propose a unit risk for vinyl chloride of 1.2×10^{-7} per ug/m^3 of lifetime average exposure. This unit risk is based upon an analysis of an extensive epidemiology study which showed excess liver and biliary tract cancer mortality and also possible brain and CNS cancer mortality. Because the unit risk is based on an analysis of an epidemiologic study, it is scientifically defensible and more appropriate than use of a unit risk based on default methodology, which is designed to be used when no human experience has been documented. Also presented in the paper, is a unit risk based on a one-hit linear model using an animal bioassay with low-dose pharmacokinetic adjustment. This is also a scientifically defensible departure from default methodology. This unit risk is approximately the same as that determined using the epidemiologic data. Using these unit risks and a 1/10,000 acceptable risk criterion, an ambient exposure guideline of 600 to 800 ug/m^3 was estimated. This range is at least two orders of magnitude greater than the current proposal of the State.

Derivation of a unit risk for Vinyl Chloride (CAS 75-01-4)

Vinyl chloride monomer (VCM) is clearly a rat and human carcinogen, causing liver angiosarcoma in both species and zymbal gland tumors in rats. Thus, for regulatory purposes, there is interest in deriving a quantitative estimate of a level of no significant risk. There are two general approaches to this problem. One approach has been the use of safety or uncertainty factors applied to no-observed-effect-levels (NOEL's) in animal studies to derive a safe level in humans. The other approach, which has been used more recently, has been the use of quantitative risk assessment to estimate levels of risk for any given exposure to a carcinogen. The risk assessment process involves a number of decision points for which there is no scientific consensus as to the correct approach. These areas of uncertainty, including the presence or absence of thresholds, the shape of the dose response model, and animal to man conversion factors, have been resolved within the regulatory agencies through the use of policy decisions as to a standardized default methodology. The default methodology is very conservative by design, so as to protect public health. *However, the EPA and OSTP guidelines on the use of risk assessment clearly state that the default methodology should not be used when other data are available.* In particular, epidemiology data and pharmacokinetic information should be incorporated into risk assessment when available.

In this document, we highlight the scientific information which should be examined in determining a unit risk factor for vinyl chloride ambient air exposures, and we propose a unit risk factor for VCM to be used in evaluating airborne emissions.

AN ANIMAL MODEL FOR DETERMINING THE UNIT RISK

Pharmacokinetic Information

Pharmacokinetic (PK) information can be used in two ways to augment risk assessments for vinyl chloride. PK data have been used to demonstrate and explain nonlinear behavior at both the high dose and low dose portions of the dose-response curve. The VCM bioassay data of Maltoni (1979) clearly indicated a plateau in the dose-response curve at high doses. This phenomenon has been explained by the use of Michaelis-Menton kinetics to calculate metabolite concentrations, as explored by Watanabe *et al.* (1976), and implemented by Gehring *et al.* (1978), Crump (1982) and USEPA (1987). However, this methodology only explains the high-dose results in the animal bioassay rather than addressing the problem of low-dose extrapolation. Low-dose risk assessments utilizing PK data have been discussed by Gehring *et al.* (1979) and Anderson *et al.* (1980).

Purchase *et al.* (1987) reviewed risk assessments for VCM and showed that, among the linear models used, risk estimates vary widely from a unit risk of approximately 7.8×10^{-5} per ug/m^3 downwards (less risk) by at least a factor of 100-fold. The different values derived from animal models vary primarily on the basis of whether or not pharmacokinetic information has been utilized in the assessment. In evaluating the use of pharmacokinetic data, Anderson *et al.* (1980) conclude that: "Based on the present understanding of the mechanism of carcinogenesis, we believe this to be a more rational approach to the low-dose extrapolation problem." Clearly, the scientific consensus is that VCM is one of the chemicals which should be evaluated using PK data rather than using the standardized default methodology.

Gehring *et al.* (1979) fit a number of low dose extrapolation models to the metabolized dose of VCM, and showed that risk estimates derived without consideration of low-dose metabolite formation potentially overestimate risk by at least an order of magnitude.

A Unit Risk Factor Based on Animal Data

A unit risk can be adapted from the 1979 Gehring, Watanabe, and Park peer-reviewed, technical paper on the incorporation of pharmacokinetic information into risk assessment models. The Maltoni study (1979) was selected as an appropriate bioassay for building an animal model for human risk assessment. Additionally, the pharmacokinetic studies of Gehring, Watanabe, and others were used to estimate effective metabolite dose both in the animal and human risk models. The procedures for accomplishing this are described in the Gehring et al., 1979 paper. If the one-hit model is selected, which represents a conservative model choice and is similar to the linearized

multistage model used by the EPA, the approximate unit risk would be 1.5 x 10^{-7} per ug/m^3 of continuous vinyl chloride exposure (one in ten thousand cancer risk would be associated with lifetime average exposure of 670 ug/m^3). This unit risk, derived using the one hit model and Michaelis-Menton kinetics, is scientifically rigorous and defensible. While this unit risk is more appropriate because it incorporates pharmacokinetic information, the most appropriate unit risk for vinyl chloride would be based on epidemiology studies, since extensive results are available.

A UNIT RISK BASED ON EPIDEMIOLOGY DATA

In the early 1970's, vinyl chloride was reported to cause a rare form of cancer, angiosarcoma of the liver, among workers who had been exposed at extremely high levels for many years in polyvinyl chloride (PVC) polymerization plants. Since this discovery, there have been approximately 50-60 angiosarcoma of the liver deaths reported throughout the United States and Canada which have been associated with previous vinyl chloride exposure. Eighty percent of these deaths occurred in four PVC plants where exposures to vinyl chloride were known to have been over 500 ppm in the 1950's and 1960's. Today, there are strict emission limitations under the NESHAP regulation, and the OSHA regulated 8-hour time weighted average for vinyl chloride is 1 ppm. It is particularly noteworthy that there has never been a reported death from angiosarcoma of the liver among Louisiana chemical workers who have worked with vinyl chloride (Forman *et al.*, 1985).

Vinyl chloride has not been definitively shown to cause cancer at any other anatomical site in humans, although some studies have suggested that brain and CNS cancers are associated with high levels of VCM exposure. Epidemiologic studies conducted in the 1970's suggested that there may be an association with brain and lung cancer, however, recent updates of these studies have reported either no association, or associations only at a much lower statistical level of significance.

A world-recognized expert in epidemiology, Sir Richard Doll, recently reviewed the existing vinyl chloride literature as it pertains to cancer in humans. He concluded that vinyl chloride is a known occupational carcinogen (only for angiosarcoma of the liver) which is due to high occupational exposure levels which have not existed since this association was reported in the early 1970's. According to Doll, the risk for cancer in communities surrounding vinyl chloride production plants from environmental emissions in today's tightly controlled and well-regulated environment "must be negligible." (Doll, 1988)

Generally, risk assessments utilize animal data as the basis for quantification of risk. Human epidemiology data often do not have sufficiently precise

exposure estimates or sufficiently well-defined populations to be of quantitative value. Human results are clearly preferred, when available, however, and should be included in any risk assessment review. In the case of VCM there are at least three assessments of sufficient precision which utilize the human database to estimate risk. In one analysis (Barr, 1982), negative epidemiological studies of people living near VCM production facilities have been used to estimate human potency. Barr estimates that 256 ug/m^3 is the approximate lifetime dose corresponding to a human risk of 10^{-6} (25600 ug/m3 assuming linearity and a 1/10,000 criterion). Purchase *et al.* (1987) note that Barr's estimate is similar to the highest estimates of 10^{-6} dose levels derived from animal data and are orders of magnitude higher than the conservative dose estimates which do not take into account low dose PK. This result is consistent with other observations that humans may be less sensitive than animals to the carcinogenic effects of VCM.

In an independent review of VCM, the National Health Council of the Netherlands (1987) derived ambient exposure levels corresponding to risk levels of 10^{-6} in humans. Their estimates were derived from both animal data and from epidemiological human data. While noting that the estimates did not differ greatly, they expressed a preference for the human data and reported a value of 1 μg/cubic meter as corresponding to a risk of 10^{-6} (100 ug/m3 assuming linearity and a 1/10,000 risk criterion). This value is approximately 80 times higher than the exposure level derived using the default procedure unit risk of 7.8×10^{-5} per ug/m^3.

A PROPOSED UNIT RISK USING EPIDEMIOLOGY DATA

The Chemical Manufacturers Association had a study of vinyl chloride exposed workers performed (first completed in 1972 and updated in the 1982 Wong (1986) study). This study included 37 plants and more than 10,000 workers. The study confirmed that these vinyl chloride workers experienced significant mortality excesses in cancer of the liver and biliary tract and possibly cancer of the brain and other central nervous system components. Using the Wong study, these cancer sites were selected for use in estimating a human potency for vinyl chloride environmental exposure. When human epidemiology data are available it is preferable to base unit risk estimates on these data. The details of the calculation are presented in Appendix A, and a manuscript fully describing the calculation is in preparation.

The limitations of using the Wong data need to be explicitly stated:

The mean durations of exposure are rough estimates

The analysis assumes that all workers were exposed at an average

concentration of 250 ppm for the time they were on the job (differences in lifetime exposures are due to differences in exposure durations). However, based on a review of papers summarizing vinyl chloride exposures of that era, the estimate of 250 ppm is probably off by no more than a factor of 2 or 3.

Liver, brain and CNS sites were all combined, although the mechanisms for causation are not likely to be the same.

The GLOBAL82 program was used to fit a multistage model for estimating risk per unit dose. This approach assumes a linear, non-threshold low dose response to vinyl chloride. This is a conservative assumption, which may not be true. In fact, the USEPA describes the methodology as one for setting upper bounds with the added caveat that "the true value of the risk is unknown and may be as low as zero" (Federal Register, 1986).

The correction of the risk estimate for latency assumes that all survivors are 54 years old and that they are expected to die at approximately 70 years old. 54 is the average age although there is a distribution around that value.

Having given these limitations, we believe that a unit risk estimate based on this analysis is the most scientifically defensible and credible as it is based on actual human experience and involves no extrapolation from animal to man. A unit risk estimate of 1.2×10^{-7} per ug/m^3 is recommended. This estimate is the unit risk based on the upper 95% confidence limit predicted using the linearized multistage model as described by the USEPA in its 1986 Carcinogen Assessment Guidelines. It adds an additional level of conservatism relative to using the maximum likelihood estimate, which is five-fold lower. Using our recommended unit risk, the estimated average lifetime exposure corresponding to a one in ten thousand additional cancer risk would be approximately 800 ug/m^3.

Table I summarizes the ambient concentrations corresponding to 1 in ten thousand risk using several epidemiology studies, our proposed unit risk factor based on the Wong epidemiology study, a one-hit unit risk using PK data, and a unit risk of 7.8×10^{-5} per ug/m^3, which would reflect use of the most conservative default methodology without consideration of low dose pharmacokinetics.

The unit risk based on the Wong epidemiology study and that based on the one-hit animal model incorporating PK data are quite similar. Since both are derived scientifically and are appropriate departures from default methodology, we feel strongly that any unit risk estimate used in regulation

of vinyl chloride should be in the range of 10^{-7} per ug/m^3. Unit risk estimates more conservative than this would not be appropriate based on scientific analyses of available data.

In summary, we recommend the use of the unit risk derived based on the Wong epidemiologic study. While it has the limitations given, for example, approximate exposure estimates, we feel the potential errors are small relative to use of default methodology, which involves extrapolation from animal to man, and that the predicted unit risk is more accurate and is compatible with other epidemiologic studies and risk estimates base on scientific principles.

TABLE 1. Comparison of ambient concentrations for predicted risk of one in ten thousand -- vinyl chloride monomer.*

Source of Estimate	VCM Concentration (ug/m^3) for 1 in 10,000 risk
Sir Richard Doll	Risks from environmental emissions "must be negligible"
Barr (epidemiology)	25,000
Unit Risk based on Wong Epi study (1.2×10^{-7} per ug/m^3)	830
One hit unit risk (One hit model using PK data, 1.5×10^{-7} per ug/m^3)	670
Netherlands Study (epidemiology and animal data)	100
Default methodology (linearized multistage, 7.8×10^{-5} per ug/m^3) (animal data, no PK data)	1.3

* Estimates assume linearity in the dose response.

R&S147531

REFERENCES

Anderson, M.W., Hoel, D.G., and Kaplan, N.L. A General Scheme for the Incorporation of Pharmacokinetics in Low-Dose Risk Estimation for Chemical Carcinogenesis: Example-Vinyl Chloride. *Toxicology and Applied Pharmacology 55, 154-161 (1980).*

Barnes, A.W. Vinyl Chloride and the Production of PVC. *Proc. R. Soc. Med.* 69: 277 (1976).

Barr, J.T. Risk Assessment for Vinyl Chloride in Perspective. Presented at the 75th Annual Meeting of the Air Pollution Control Association, New Orleans, USA, *(June 1982).*

California Air Resources Board (CARB), Draft Technical Support Document, Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant. May, 1990.

Crump, K.S. Quantitative Assessment of Human Risk From Exposure to Carcinogens with Special Reference to Vinyl Chloride. Contract for Occupational Health and Safety Division, Ontario Ministry of Labour (1982).

Doll, R. Effects of Exposure to Vinyl Chloride: An Assessment of the Evidence, *Scand J Work Environment Health 14 (1988) 61-78.*

EPA. Incorporation of Biological Information in Cancer Risk Assessment: Example Vinyl Chloride. Office of Environmental Health and Assessment, U.S. Environmental Protection Agency. EPA/600/d-87/188 (1987).

Forman, D., B. Bennett, J. Stafford, and R. Doll. Exposure to Vinyl Chloride and Angiosarcoma of the Liver: A Report of the Register of Cases. *British Journal of Industrial Medicine.* 42: 750-753 (1985).

Gehring, P.J., Watanabe, P.G., and Park, C.N. Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted from Studies in Rats *Toxicology and Applied Pharmacology. Vol. 49, No. 1 (June 15, 1979).*

Gehring, P.J., Watanabe, P.G. and Park, C.N. Resolution of Dose-Response Toxicity Data for Chemicals Requiring Metabolic Activation: Example - Vinyl Chloride. *Toxicology and Applied Pharmacology 44, 581-591 (1978).*

Maltoni, C. and G. Lefemine. *Annals of N.Y. Academy of Sciences.* 246: 195-218 (1979).

National Health Council of The Netherlands. A Scientific Basis for the Risk Assessment of Vinyl Chloride. *Regulatory Toxicology and Pharmacology 7, 120-127 (1987).*

Purchase, I.F.H., Stafford, J., and Paddle, G.M. Vinyl Chloride: An Assessment of the Risk of Occupational Exposure. *Fd. Chem. Toxic. Vol. 25, No. 2, pp. 187-202, 1987.*

Watanabe, P.G., McGowan, G.R., and Gehring, P.J. Fate of [^{14}C] Vinyl Chloride After Single Oral Administration in Rats. *Toxicology and Applied Pharmacology 36, 339-352 (1976).*

Wong, Otto. Final Report: An Update of An Epidemiologic Study of Vinyl Chloride Workers, 1942-1982. Prepared for the Chemical Manufacturers Association by Environmental Health Associates, 520 third Street, Suite 208, Oakland, CA 94607. October 17, 1986.

Appendix A

Derivation Of An Upper Bound Unit Risk Using The Wong Epidemiology Study

A. Study Population

10,173	Total
- 973	Not followed up on in 1982 study
9,200	Workers, Total

B. Study Population Broken Down By Duration of Exposure

Exposure Duration	Mean Duration	Number of Workers
<10 years	4.2 years	3094
10-20 years	14.1 years	2777
20+ years	28.2 years	3329

C. Assuming Workplace Average Exposures Were at 1/2 of TLV During Period, Calculate Lifetime Mean Exposure Levels For Each Category

TLV (pre 1970's) = 500 ppm
1/2 TLV = 250 ppm

1/2 TLV		Correction For Years Exposed		Correction For Days Worked Per Year		Correction For Breathing Rates	=	Lifetime Average Exposure
	X		X		X			

Calculation by Category:

<10 years exposure:

$$250 \text{ ppm} \times \frac{4.2 \text{ years}}{70 \text{ years}} \times \frac{240 \text{ days}}{365 \text{ days}} \times \frac{10 \text{ m}^3/\text{day}}{20 \text{m}^3/\text{day}} = 4.9 \text{ ppm}$$

10-20 Years Exposure:

$$250 \text{ ppm} \times \frac{14.1}{70} \times \frac{240}{365} \times \frac{10}{20} = 16.6 \text{ ppm}$$

>20 Years Exposure:

$$250 \text{ ppm} \times \frac{28.2}{70} \times \frac{240}{365} \times \frac{10}{20} = 33.1 \text{ ppm}$$

D. CALCULATE EXCESS NUMBER OF CANCER DEATHS FOR EACH EXPOSURE DURATION CATEGORY

EXCESS = Observed - Expected

Category	Liver			Brain/CNS		
	Obs.	Exp.	Excess	Obs.	Exp.	Excess
<10 years	6	3.29	2.7	13	7.89	5.1
10-20 years	20	1.62	18.4	4	3.31	.69
>20 years	11	.86	10.1	3	1.56	1.4

E. SUMMARY TABLE FOR UNIT RISK MODELING

Category	Mean Lifetime Exposure	Combined Excess Deaths/Liver, Brain, & CNS	Total Workers
<10 years	4.9 ppm	8	3094
10-20 years	16.6 ppm	19	2777
20+ years	33.1 ppm	12	3329

F. FITTING OF MULTISTAGE MODEL USING GLOBAL 82 TO SUMMARY DATA SET

$R(d) = 1 - EXP[-0.00376 - .264 \times 10^{-4}d]$

(note that Q_2 term equaled zero in the model)

MLE on Linear Term = $.264 \times 10^{-4}$/ppm

Upper 95% Confidence Limit on Linear Term = $.139 \times 10^{-3}$/ppm
(Linearized Mulstistage Model Estimate)

G. CORRECTION OF UNIT RISKS FOR LESS THAN LIFETIME FOLLOW UP FOR SURVIVORS AMONG THE STUDY COHORT

$$\text{Correction Factor} = \left(\frac{\text{Average Life Expectancy}}{\text{Average Age of Surviving Cohort Members}}\right)^3$$

$$= \left(\frac{70}{54}\right)^3 = 2.18$$

Unit Risks:

MLE = $2.18 \times .264 \times 10^{-4}$/ppm = $\frac{6 \times 10^{-5}}{\text{ppm}}$ or 2.3×10^{-8} per ug/m^3

Linearized Multistage = $2.18 \times .139 \times 10^{-3}$/ppm = $\frac{3 \times 10^{-4}}{\text{ppm}}$ or 1.2×10^{-7} per ug/m^3