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Written

THE DOW CHEMICAL COMPANY

MIDLAND, MICHIGAN 48674

1803 BUILDING
July 3, 1990

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Ms. Barbara Cook
Project Manager
California Air Resources Board
1102 Q Street
Sacramento, CA 95814

Dear Ms. Cook:

Attached are our comments on the unit risk derivation presented in the May, 1990 Draft Technical Support Document, Proposed Identification of Vinyl Chloride as a Toxic Air Contaminant.

We appreciate your accepting our comments, which have been submitted to promote the best possible science in the performance of health risk assessments.

Pleased call on us should you require additional information.

Sincerely,

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Attachments

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COMMENT: DRAFT TECHNICAL SUPPORT DOCUMENT, MAY, 1990, "PROPOSED IDENTIFICATION OF VINYL CHLORIDE AS A TOXIC AIR CONTAMINANT"

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

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 factors or uncertainty factors applied to no-observed-effect-levels (NOEL's) in animals to derive a safe level in humans. The other general approach, which has been used more recently by regulatory agencies, has been the use of quantitative risk assessment to estimate levels of risk for any given exposure. 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 agencies through the use of policy decisions as to a default methodology. The default methodology is conservative in nature, so as to protect public health. However, the State of California Cancer Risk Assessment Guidelines as well as 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 the appropriate data are available. The DHS unit risk for vinyl chloride of 20 x 10(-5) per ppb, as cited in the CARB Draft Technical Document (CARB, 1990), does not utilize the available pharmacokinetic or epidemiological information.

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 bioassay data of Maltoni (1979) clearly indicated a plateau in the dose-response curve at high doses. This phenomenon can be explained by the use of a Michaelis-Menton function to calculate metabolite concentrations, as suggested 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.* (1980) reviewed risk assessments for VCM and showed that, among the linear models used, risk estimates varied from the current DHS value, (equivalent to a unit risk of 20 x 10(-5) per ppb), upwards (less risk) 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."

Gehring *et al.* (1979) fit a number of 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. For example, the one-hit model applied to metabolized dose predicts a risk of 189 per million at 1 ppm for an occupational exposure (Gehring, 1979). By comparison, use of nominal dose (air concentration), predicts upper bound "risks" of 37,000 per million using the unit risk of 20 x 10(-5) per ppb. Other viable dose response models predict much lower risk.

Not withstanding the fact that the health criteria represent one aspect of many inputs considered in the standard setting process, we submit it is essential to base any proposed regulation on the most complete information possible. For this reason we believe that risk assessments for vinyl chloride should include PK data, or preferably, the use of actual human data.

Risk assessments derived from 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 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.

Vinyl chloride has not been shown to cause cancer at any other anatomical site in humans. 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 100 ppb is the approximate lifetime dose corresponding to a human risk of 10(-6). 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.

Gehring *et al.* (1979) compared the results of an epidemiological study of approximately 10,000 occupationally exposed workers to the values predicted by four different mathematical models derived from animal data. They conclude that the observed human results are <u>inconsistent</u> with the two linear non-threshold models used, and are <u>consistent</u> with both the probit model and a linear threshold model. The latter two models predict 10^{-6} risk levels at <u>occupational</u> exposure levels in excess of 1 ppm.

These analyses by no means prove the validity of the two models and undoubtedly numerous other models would fit and give quite different results for predicting the ambient level corresponding to a 10^{-6} risk level. However, these analyses <u>do</u> show that human epidemiology data can be used to derive risk estimates for VCM exposures and that the models indicate that the linear non-threshold models are conservative by a substantial margin. This is to be expected in light of the well known conservativeness of the models. U.S. EPA, for instance, when presenting risks estimates describes them as upper bounds and notes that: "the true value of the risk is unknown and may be as low as zero" (Federal Register, 1986).

In an analysis of alternative modeling assumptions for animal to human extrapolation, Elizabeth Anderson, (1984) as head of the U.S. EPA Cancer

Assessment Group found that alternative plausible modeling assumptions would lead to risk estimates that were 15-fold to 10,000-fold lower than the standard LMS procedure. Thus it is essential to use the available human data to place some perspective on the results predicted solely from animal data.

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). This value is approximately 80 times higher than the exposure level derived using the DHS unit risk of 20 x 10(-5) per ppb.

The over prediction of the models can be further demonstrated for VCM by comparing predictions of risk utilizing the DHS unit risk with human exposure scenarios. To make this comparison, Table 1 shows the "risk" predicted from the DHS model for a number of occupational exposure situations. The relevance of the specific exposure scenarios are also discussed below.

The specific exposure scenarios used in Table 1 were based upon a retrospective study (Barnes, 1976), in which past typical VCM exposures in PVC plants were estimated as: 1000 ppm in 1945-1955, 400-500 ppm in 1955-1960, 300-400 ppm in 1960-1970, 150 ppm in mid-1973 and considerably lower afterwards. Considering the latency of carcinogenesis in general, and for VCM in particular, tumor incidence rates noted in the 1980's reflect exposures from the 1960's.

It can be seen from Table 1 that incidence rates predicted from the linear animal model are completely incompatible with that observed in actual human studies. For example, in the study examined by Gehring (1970) there were only 5 observed cases in 9677 workers. This is approximately three orders of magnitude less than that which would be predicted by the DHS model.

Thus, there are a number of assessments based upon human epidemiological data which would indicate that linear models utilizing animal data overpredict risk by at least one to two orders of magnitude. In the interests of assuring that any proposed regulation is supported by as comprehensive a review of the available health data as possible, we submit these assessments should be incorporated into any risk assessments which will be used for regulatory control. This is particularly important in view of the fact that they are based upon human data rather than on laboratory animal results.

It can be seen from the above analysis that standard risk assessment methodology and the use of reported literature results lead to orders of magnitude over-estimates of the predicted risk from emissions of VCM from

existing facilities. We recommend that these inconsistencies in the risk estimates be resolved if they are to be used as the basis for any proposed regulation.

TABLE 1. "RISK" PREDICTED FROM LMS MODEL
(using unit risk of 20×10^{-5} per ppb)

Occupational Exposure Scenario	Upper Bound on "Risk" (Cases Per 10,000)
400 ppm 30 years	9999
400 ppm 20 years	9995
300 ppm 30 years	9998
300 ppm 20 years	9964
200 ppm 30 years	9960
200 ppm 20 years	9770
100 ppm 30 years	9400
100 ppm 10 years	6090
100 ppm 5 years	3750

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