August 27, 1991

Ms. Meredith Scheck
Assistant Director
The Vinyl Institute
Wayne Interchange Plaza
155 Route 46 West
Wayne, NJ 07470

Dear Ms. Scheck:

Joe Ledvina informed me of the potential interest that the Vinyl Institute has in a new quantitative cancer risk assessment for vinyl chloride. He also stated that you need more definitive information on what I am proposing to do, its importance, and how it could be used by the Vinyl Institute.

In August last year I was contacted by Vista Chemicals to evaluate why the State of Mississippi was using a more stringent ambient air emission standard for vinyl chloride than had been used previously. The former number was based on an EPA report dated 1984. The more recent stringent number which resulted in a 12 fold higher risk was taken from a more recent 1985 EPA publication. Both documents were prepared by contractors for EPA and neither really underwent a good scientific peer review. Apparently EPA's regional office in Atlanta is recommending states use the quantitative risk assessment methodology in the 1985 document. I found several errors in the 1985 risk assessment procedure and discussed these errors with EPA's Hazard Assessment Group (formerly Cancer Assessment Group). They agreed that the quantitative risk assessment was in error and thought until new data become available, the quantitative risk assessment procedure in the 1984 document should be used.

EPA has not conducted a recent comprehensive review on vinyl chloride but is aware of new data and risk modeling tools that may be useful in conducting a new quantitative cancer assessment. Although conducting a new risk assessment for vinyl chloride is not currently on their high priority work agenda, at least two staff members in the Hazard Assessment Group are continuing to conduct work on vinyl chloride. Now that EPA is devoting so little time to this work, it is an opportune time to do an independent, thorough examination of the recent data and risk assessment methods that would be applicable to a new quantitative assessment. Such an assessment would most likely improve on the current simplistic and conservative vinyl chloride model currently in use. Because of EPA's current workload, they do not have the time or expertise to improve on the existing methodology and would be receptive to having an independent scientific assessment performed.

BACKGROUND

Vinyl chloride is a category A carcinogen (a known human carcinogen), however, the epidemiology data have not been of sufficient quality to use to quantitate risk. In lieu of this, EPA used rat studies where the exposures were adequately known, in order to establish a relationship between cancer incidence and exposure in the high exposure range. The linearized multistage model was employed to extrapolate to exposures and cancer incidences that were about 100,000 less then observed in the study. It is assumed that the same relationship between exposure and cancer at very high levels of vinyl chloride holds for very low levels of vinyl chloride and cancer incidence. This assumption has always been criticized by the scientific community. The linearized multistage model fits the observable data to a quadratic relationship and essentially is a curve fitting exercise (no biological information concerning cancer mechanisms or pharmacokinetic data on vinyl chloride was/can be used in this model). A statistical 95% upper bound of the linear term of the quadratic is employed (q1*), which at low concentrations results in a simple linear relationship

cancer incidence = q1*(exposure)

Usually a lifetime cancer incidence of 1 in 1,000,000 is considered acceptable and the exposure that is determined from the above equation results in this risk. For vinyl chloride this exposure is 0.00015 ppm using the current EPA methodology. Because of criticisms from the scientific community and recommendations from EPA's science advisory board, the agency is becoming more receptive to alternative cancer models for the linearized multistage (personal communication with Dorthy Patton, EPA Risk Assessment Forum, Chairperson). Therefore, the development of new more scientifically justifiable quantitative risk assessment methodology using biological data is both timely and needed and can result in lower risk estimates than the conservative model now in use.

Chemicals can initiate and/or promote cancer. Initiators are agents that interact with DNA in some manner to cause a change in the sequencing that results in a mutation. Recent studies have shown that for many cancers to develop more than one mutation must occur. This is in contrast to the "one hit" theory of carcinogenesis on which regulatory agencies base their current model. The cancer incidence would be nonlinear with respect to exposure concentration and would suggest that the currently used linear model overestimates the risk at low concentrations. Pure promoters such as dioxin are not mutagenic, rather they influence the proliferation of cells such as preneoplastic cells or clones that have already undergone one mutation (transformation). The relationship between promoter concentration and cancer is also likely to be nonlinear.

Vinyl chloride is an initiator but has to be metabolized to an active form in order to cause a mutation. This active form is also deactivated in the body

and excreted. Therefore, there is a balance between formation of the active carcinogen and its deactivation that is dependent on exposure concentrations. Establishing a relationship between external exposure and active carcinogen in the body. and then between active carcinogen and cancer incidence would result in a more accurate cancer model than the current model, where only the relationship between external concentration and cancer incidence is used to estimate risk.

At higher concentrations used to detect cancer in experimental animals, vinyl chloride may also act as a promoter by causing proliferation of liver cells. Current models used by regulatory agencies do not account for promotional activity, but treat all carcinogens as initiators. By not addressing the promotional component would likely lead to overestimating the risks at lower exposure levels. If adequate data are available to demonstrate that vinyl chloride has promotional activity it could be used in the development of a new quantitative model.

Epidemiology studies on vinyl chloride have been updated (personal communication with Charles Risk of EPA's Hazard Assessment Group). These studies should be evaluated to determine if a dose related response can now be attained. If so, it may be possible to use the human data for a quantitative assessment. Also, a determination can be made to see if the current linearized multistage model (rat studies) discussed above accurately predicts the observed cancer incidence using the updated epidemiology studies. For benzene, the animal studies overpredicted the leukemogenic risk in the human epidemiology studies (personal communication with Todd Thorslund).

I have learned from EPA that they have data on vinyl chloride that indicate young rats are more susceptible to vinyl chloride toxicity than adult animals. These data have not been published but should be evaluated. EPA is concerned that their current risk assessment may underestimate the cancer risk, because the risk assessment to set ambient levels was performed on adult animals to set ambient levels and may not sufficiently protect sensitive young individuals. They verbally agreed to give me the data to review.

PROPOSAL

There are essentially two parts to any quantitative risk assessment. The first part is to assess and organize the data available to determine if dose response relationships can be developed. The second part involves taking the data and modeling it using statistical techniques to best describe the biological results. Depending upon the data available, certain conservative assumptions have to be made in order to err on the side of protecting public health. Usually, quantitative assessments performed on limited data result in a more conservative risk assessment (e.g., the 1984 risk assessment for vinyl chloride).

This proposal deals only with the first part of the quantitative risk assessment as first the data available for vinyl chloride must be assessed and

organized to determine if the new data are of sufficient quality to develop a new quantitative model. This initial assessment should provide indications as to whether the development of a new quantitative model will result in a more or less conservative prediction of risks at ambient levels compared to the existing EPA model. The four parts of the initial assessment are:

a) a complete review of the pharmacokinetics (metabolism) of vinyl chloride

b)conduct a complete review of information pertaining to the multistage process of carcinogenesis as it pertains to vinyl chloride and an assessment of the potential for vinyl chloride to act as a promoter

c) obtain and review the updated epidemiology data on vinyl chloride and compare it with the animal studies. Determine if the human data are sufficient to quantitate risk

d) obtain and review data regarding the greater sensitivity of young animals to vinyl chloride toxicity

A decision can then be made if the development of a new model is worthwhile. Each of a these points is described in more detail below.

A. Pharmacokinetic review

Below is the current concept behind EPA's 1984 risk assessment. It essentially curve fits the experimentally high external vinyl chloride concentrations with cancer incidence and extrapolates orders of magnitude downward to a risk of 1 in a 1,000,000.

vinyl chloride(external exposure concentration) + normal cell ------> cancer

The actual cancer risk can be more accurately determined from the relationship between activated carcinogen and cancer incidence.

vinyl chloride---------->activated carcinogen + normal cell------> cancer
(external exposure) (internal concentration)

:
:
:
v

inactivation of carcinogen

:
:
:
v

excretion of metabolites

To evaluate this more accurate model a critical review of the pharmacokinetic

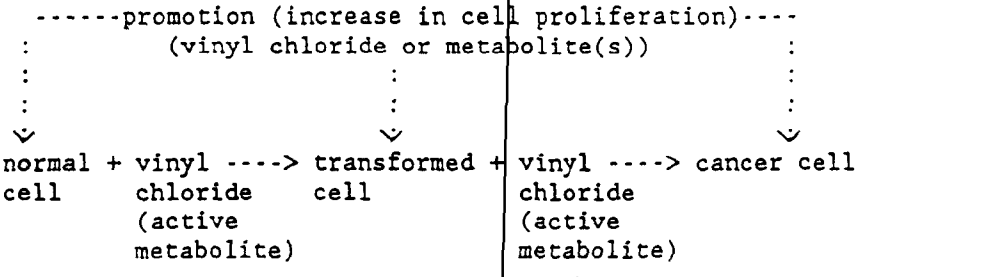
data on vinyl chloride will be made to determine if the current data base will allow establishing a relationship between external vinyl chloride concentration and internal activated carcinogen levels, particularly at low levels where the formation of active carcinogens is not saturated and deactivation may be more prominent. If possible, a qualitative assess will be made if the use of the relationship is likely to result in an over- or under-prediction of the current risk used by EPA. If the data base is inadequate the research needs will be provided to establish a relationship that can be used in a quantitative assessment.

B. *Multistage process review*

current model

normal cell + vinyl chloride ----> cancer cell ONE STAGE LINEAR RELATIONSHIP

two stage model



TWO STAGE NON-LINEAR RELATIONSHIP

The two stage carcinogenic model is a function of the square of the concentration of the internal active carcinogen (metabolite). The promotional effect is likely to be nonlinear and may have a threshold.

A review of the literature will be performed to determine if data are available which indicate that the cancers induced by vinyl chloride (e.g., angiosarcomas) are multistage involving the mutation of more than one oncogene and/or regulatory gene and whether vinyl chloride has promotional activity. If the process is multistage then the current EPA method of estimating the vinyl chloride cancer risk is likely to overestimate the risk.

C. Updated Epidemiology data review

This part involves:

1. Acquire the updated data from EPA and determine its adequacy to establish a dose-response relationship.

2. If the data are good enough, the current EPA quantitative risk assessment procedure (rat data) will be used to determine if it accurately predicts the risks in the updated human epidemiology study.

D. Review the vinyl chloride toxicity data for young animals

This part involves:

1. Acquire the unpublished data from EPA scientists.

2. Determine whether the data can be used to show that young rats are more susceptible to vinyl chloride toxicity than adult animals.

3. If young animals are more susceptible, assess whether this data can be used in a quantitative risk assessment and can be extrapolated to humans.

A report will be written that will contain an introduction describing the purpose of the qualitative assessment, four sections (A,B,C,D) that will be organized into an assessment review of the data with references, and conclusions based on the assessment. A discussion covering all sections will follow that describes how the assessments in A, B, C, and D are likely to influence a new quantitative cancer assessment for vinyl chloride, along with recommendations whether new studies and/or a new quantitative assessment is justifiable. This constitutes the first part of the proposal. A proposal for the second part (modeling and statistical analysis) depends on the findings in part 1 and can not be written at this time.

It is possible, depending on the needs of the Vinyl Institute and the findings, to publish the first part of the proposal in a peer reviewed journal. Regulatory agencies find published results more convincing and useable (to be decided after completion of Part I).

Costs of PART 1

$29,000

Time to complete project

The project can be completed within 6 months, and could be initiated this November. A monthly progress report will be provided to the Vinyl Institute until the project is completed. Travel (e.g., meetings with the Vinyl Institute) is not included in this cost.

I hope this provides you with sufficient information to initiate the first part of the proposal in order to determine if a new quantitative cancer risk assessment for vinyl chloride is warranted and beneficial to the Vinyl Institute. It has been my experience that regulatory agencies like EPA find it difficult to change from established procedures. However, their established procedures are being criticized by the scientific community, and because of this EPA is likely to be more receptive to alternative scientifically justifiable models. One cannot predict if a new model will be more or less conservative than the existing model, but since the existing models are so conservative, it seems unlikely that any new model will result in lowering existing standards.

If you need any additional information or wish to address any points that I overlooked, please call me at 703-934-3126. I have enclosed my resume and Dr. Suresh Moolgavkar's resume. Suresh is a member of the Fred Hutchinson Cancer Research Center and professor of Epidemiology at the University of Washington. He would be involved in the epidemiology review in the first part of the proposal and would have a major role in part 2. I have also enclosed a recent workshop review paper on benzene that will be published this Fall, as well as a previous publication concerning different mechanisms of asbestos carcinogenicity.

Sincerely,

Peter Voytek

Enclosures

PETER E. VOYTEK

EDUCATION

1963	B.A., Chemistry, University of Vermont
1969	PhD., Biochemistry, University of Vermont
1980	Program in Environmental Policy and Management, Harvard University

POSITIONS AND AFFILIATIONS

Senior Science Advisor and Vice President, Clement International

Consultant to the Center for Environmental Health and Human Toxicology, affiliated with Georgetown and George Washington Universities

Guest research scientist, Laboratory of Molecular Microbiology, NIAID,NIH

Member of the Senior Executive Service, Acting Deputy Director of EPA's Office of Health and Environmental Assessment; Director of EPA's Reproductive Effects Assessment Group

Senior Toxicologist/Pharmacologist and Science Advisor to the Deputy Assistant Administrator for the Office of Toxic Substances, EPA

Senior Toxicologist in the Criteria and Standards Division, Water office, EPA

Senior Research Fellow at NIEHS, NCI, NIH

Research Associate/Instructor, Department of Pharmacology, Yale University

AWARDS

Selected into the Federal government senior executive service 1980, EPA.

Bonus for Outstanding Achievement, 1980.

NSF undergraduate summer grant for research in Physical Chemistry 1962.