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BEFORE THE
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

# CHEMICAL MANUFACTURERS ASSOCIATION VINYLIDENE CHLORIDE PROGRAM PANEL COMMENTS ON PROPOSED TEST RULE FOR 1,1-DICHLOROTHYLENE (VINYLIDENE CHLORIDE) OPTS-42082 51 Fed. Reg. 28840 (August 12, 1986)


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The Environmental Protection Agency has proposed that manufacturers and processors of vinylidene chloride ("VDC") (1,1-dichloroethylene) be required to conduct a two-year inhalation bioassay in mice, preceded by distribution, excretion and metabolism ("DEM") studies. The requirement is being proposed pursuant to Section 4(a)(1)(A) of the Toxic Substances Control Act ("TSCA"), 15 U.S.C. 2603(a)(1)(A). Toxic Substances, 1,1-Dichloroethylene; Proposed Test Rule (OPTS-42082), 51 Fed. Reg. 28840 (August 12, 1986) (the "proposed test rule").

The Chemical Manufacturers Association ("CMA") Vinylidene Chloride Program Panel ("VDC Panel") submits these comments on the proposed test rule. The VDC Panel is an industry group organized as a special program of CMA, representing all United States manufacturers of VDC and a substantial portion of the industry, both domestic and foreign, which converts VDC into other products. Its members are companies that would be required to conduct the testing of VDC if a final rule is issued.

## BACKGROUND AND SUMMARY

The proposed test rule for VDC, unlike other test rule proposals, was not initiated by an Interagency Testing Committee ("ITC") recommendation. The ITC has never included VDC among its "priority list" chemicals recommended for test rule consideration under Section 4(e) of TSCA.

Indeed, VDC does not fit the usual pattern of ITC-designated chemicals proposed for testing. VDC is unique in that it has been extensively studied in eighteen separate ~~oncogenicity~~ studies and in an abundance of acute and sub-chronic assays. The bioassays alone have utilized five routes of exposure in several strains of mouse, rat and hamster. Never before has the Agency proposed to require oncogenicity testing of a chemical that has already been so thoroughly tested.

Nor does VDC fit the usual pattern of potential exposure for ITC-designated chemicals. There is extremely little data regarding exposure to VDC, and what data exist show very little potential for exposure.

In this instance the test rule was prompted by the Agency's inability to regulate VDC under the Clean Air Act, despite the abundance of bioassay data and despite the Agency's use of worst-case assumptions regarding oncogenicity. The test rule was requested by the Office of Air Quality Planning and Standards, which had considered the regulation of

VDC as a hazardous air pollutant under Section 112 of the Clean Air Act, 42 U.S.C. § 7412. After reviewing all available data, the Agency announced on August 13, 1985 that the information currently available was not sufficient to support a decision to regulate VDC under any section of the Clean Air Act. 50 Fed. Reg. 32632, 34 (August 13, 1985). In its decision not to regulate VDC, the Agency concluded that the levels of human exposure are extremely low, even utilizing worst-case assumptions; that the evidence of carcinogenicity is limited; and that, even if carcinogenicity were assumed, the possible human risks are insufficient to justify regulation.

EPA is now proposing to issue a Section 4 test rule "to obtain data needed to better assess the oncogenic potential of [VDC]." These comments are submitted in response to that proposal.

The VDC Panel submits that the proposed rule is an entirely inappropriate use of Section 4(a) of TSCA. In view of the abundant bioassay and metabolism data regarding VDC, and in view of the absence of exposure data, no further oncogenicity study is needed. Indeed, the proposal is contrary to both the letter and the intent of TSCA. As these comments and the supplementary materials submitted for the record demonstrate, the proposed rule is without support in the record and should be withdrawn.

Part I of these comments provides a brief summary of the extensive data base relevant to an assessment of VDC's potential carcinogenicity. There are presently a total of eighteen animal bioassays using VDC. Because of the inconsistent results, substantial research has been conducted into the metabolic pathways and pharmacokinetic changes encountered in various species and strains exposed to VDC. Toxicologists now have a sound scientific basis to explain the single positive mouse study and the negative studies in other species. Because the mechanism of tumor formation in the Swiss mouse is inapplicable to humans, toxicologists also are able to make a reasonable prediction that VDC is unlikely to pose a carcinogenic risk to humans. In order to complete the record, copies of most of the relevant VDC studies are being submitted by the Panel in a supplemental submission accompanying these comments.

Part II of the comments describes the legal standard under which a test rule may be issued and circumstances under which a reviewing court must overturn a test rule. Under th heavy burden which Congress placed upon EPA rulemaking under TSCA, the Agency's findings must be supported by substantial evidence in the rulemaking record taken as a whole. When all available data are included, the record fails to support the proposed findings under Section 4(a)(1)(A).

The record demonstrates that VDC does not present an unreasonable risk -- a conclusion supported by the Agency's decision that VDC could not be regulated under the Clean Air Act even if carcinogenicity were assumed. The total lack of exposure data, the abundant negative oncogenicity test data, the negative epidemiology data and information regarding inter-species metabolic differences demonstrate that the Agency may not make the requisite "may present" findings for VDC under Section 4(a)(1)(A)(i).

Similarly, the proposed finding under Section 4(a)(1)(A)(ii) -- that the record contains insufficient data upon which the effects of manufacture or processing can reasonably be determined -- is contradicted by the record itself. Existing information permits the reasonable determination or prediction of possible health effects of VDC manufacture or processing.

Finally, the likelihood that the proposed testing will significantly improve the Agency's ability to assess potential human risks arising from manufacture and processing is extremely remote. The record does not substantiate EPA's proposed finding under Section 4(a)(1)(A)(iii) that the nineteenth ~~oncogenicity~~ long term study is necessary to develop data upon which the effects of VDC manufacture or processing can reasonably be determined or predicted.

Part III of these comments addresses the six issues raised for comment in the preamble to the proposal. In several instances, the issues are also addressed elsewhere in the comments.

For the reasons discussed in these comments, and as demonstrated in the health effects data being submitted for the record, the proposed rule is not supported by the record and should not be adopted.

## I. THE EXTENSIVE DATA BASE FOR VDC DEMONSTRATES THAT VDC IS UNLIKELY TO POSE ANY ONCOGENIC RISK TO HUMANS

The potential oncogenicity of VDC and relevant metabolic and pharmacokinetic differences among animal species have been studied extensively. A consensus has developed among scientists who have studied the matter regarding the mechanism by which tumors were produced in the single positive study. The response seen in the Maltoni Swiss mouse study (Maltoni, C., 1985) can be understood as an effect of certain metabolic characteristics of the laboratory species and strain studied -- characteristics that are not found in other species that have been studied and that are not present in humans.

A. Toxicology Data Suggest that VDC Oncogenicity is Directly Related To the Saturation of Metabolic Pathways in Mice in a Way That is Not Likely to Occur in Humans.

Animal bioassays with VDC have been uniformly negative, with the one noteworthy exception cited by the Agency. It was only when Swiss mice were exposed for one year in the Maltoni inhalation study to concentrations of VDC that were notably toxic and near the acutely lethal level that tumors could be produced. However, the record contains abundant evidence of the extreme sensitivity of this strain of mouse to VDC and of the mechanism whereby that sensitivity is expressed. The single positive oncogenicity study appears to be directly related to the significant tissue injury in male mice exposed to VDC, which is associated with the well-documented saturation of certain metabolic pathways.

Attached as Appendix A is a summary of existing data entitled "Interpretive Review of the Animal Toxicological, Pharmacokinetic/Metabolism, Biomolecular and In-Vitro Mutagenicity Studies on Vinylidene Chloride and the Significance of the Findings for Man" by J.M. Norris and R.H. Reitz ("Interpretive Review"). The Interpretive Review contains a comprehensive overview of data relevant to an effort to extrapolate from existing animal data for human risk assessment purposes.

EPA scientists have also recognized how well-characterized the mechanism of VDC toxicity is. In its Drinking Water Criteria Document for VDC, EPA stated:

> "Very little is known about the mechanism of toxicity of cis- and trans-1,2-DCE. However, there has been considerable work directed toward defining the mechanism of toxicity of 1,1-DCE. . . . [M]ost of the acute and long-term toxic effects observed, e.g., hepatotoxicity, renal toxicity, mutagenicity and carcinogenicity, are due probably to the formation of toxic metabolites."1/

As the Interpretive Review explains, data clearly demonstrate that VDC is metabolized much more rapidly by mic than by rats.2/ It has been shown that there are much higher levels of covalently bound VDC metabolites in both the liver and kidney of mice than in the same organs of rats.3/ The formation of substantially larger amounts of toxic metabolites in the mouse explains the greater toxicity of VDC to the mouse than to the rat.

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1/ U.S. Environmental Protection Agency, Drinking Water Criteria Document for Dichloroethylenes (1,1-Dichloroethylene, cis-1,2-Dichloroethylene, and trans-1,2-Dichloroethylene) (Draft), December 1984 ("EPA Criteria Document"), at VII-1.

2/ Jones, B.K. and D.E. Hathway, 1978.

3/ EPA Criteria Document at VII-4.

The EPA Criteria Document noted:

> "It is generally believed that reaction of these metabolites, i.e., 1,1-dichloroethylene oxide, chloroacetyl chloride and chloroacetic acid, with macromolecules leads to the observed toxic effects: hepatotoxicity, renal toxicity, mutagenicity, and carcinogenicity." Id. at VII-3 (emphasis added).

It also noted the many studies that have shown that mice are far more susceptible to both kidney and liver damage from VDC than are rats. Id. at VII-5.

The extensive bioassay data confirm the Agency's observation, quoted above, that the reaction of VDC metabolites is generally believed to be the cause of the observed toxic effects. Thus, no significant increase in tumors was shown in Maltoni's inhalation study with Sprague-Dawley rats, in his inhalation study with Chinese hamsters or in his gavage study with Sprague-Dawley rats. It was only in his inhalation study with Swiss mice exposed to the nearly lethal dose of 25ppm that an increase in adenocarcinomas was observed. No other studies were positive, including an inhalation study with Wistar rats, an inhalation study with Sprague-Dawley rats, an inhalation study with CD-1 mice, an inhalation study with CD rats, another inhalation study with Sprague-Dawley rats, an ingestion study with Sprague-Dawley rats, another inhalation study with CD mice, another inhalation study with

CD rats, a skin application study with Swiss mice,4/ a subcutaneous injection study with Swiss mice, a third inhalation study with Sprague-Dawley rats, a gavage study with Sprague-Dawley rats, a gavage study with Fischer 344 rats and a gavage study with B6C3F1 mice. See infra, pp. 29-30.

In view of the disparity between the mouse kidney adenocarcinomas and the results in seventeen other bioassays, there is now a widely held view in the scientific community regarding the mechanism of tumor formation in the mouse study. In addition to the references summarized in the Interpretive Review, EPA has summarized that view as follows:

> "It has been suggested that development of kidney adenocarcinomas in mice is due to the increased rate of biotransformation of 1,1-DCE in mice, which produces a higher level of reactive intermediates that can subsequently react with macromolecules,

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4/ EPA has cited the Van Duren skin application study suggesting that VDC acted as a tumor initiator. In view of the negative skin application carcinogenicity study by Van Duren, these data cannot be cited as suggestive of VDC's carcinogenicity. In fact, taken together, the studies demonstrate that VDC is not a carcinogen to mice by dermal exposure. The HAD stated:

> "The relevance of positive results in this tumor initiation study with regard to the assessment of human health effects is not clear, particularly since complete carcinogenic activity could not be demonstrated. Maximally tolerated doses, estimated from preliminary short-term tests, were used in the tests for carcinogenicity performed by Van Duren et al. (1979)" HAD at 10-124.

> e.g., DNA. A study has been made of the potential of 1,1-DCE to cause DNA alkylation, DNA repair and DNA replication in the liver and kidneys of mice and rats, and these results were compared with results obtained using the potent carcinogen dimethylnitrosamine. Tumorigenic doses of dimethylnitrosamine produced relatively little tissue damage but caused a high degree of DNA alkylation and DNA repair synthesis. In contrast, tumorigenic doses of 1,1-DCE resulted in massive tissue damage but induced minimal DNA alkylation or DNA repair synthesis. These data were interpreted as suggesting that tumors observed in mice exposed to 1,1-DCE arise primarily through effects of the chemical on nongenetic components of cells." EPA Criteria Document at VII-8.5/

When this extensive data base is used to estimate potential risks to man, it can be seen that the oncogenicity data have questionable applicability to man. The rate of oxidative metabolism for halogenated hydrocarbons such as VDC appears to be related to body surface area, rather than body mass. Thus metabolic activation would occur more slowly in man than in small laboratory animals. This observation is consistent with findings of Ritz, et al. (1980) and Jones and Hathway (1978), who demonstrated that the rat metabolizes less VDC than the mouse; Andersen, et al. (1980), who related the slower rate of metabolism of VDC in man versus the rat to the

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5/ EPA cites Maltoni, 1977; Hathway, 1977; Henschler and Bonse, 1977; and Reitz, 1980. See also, Anderson, M.E., et al., 1979.

rate of pulmonary uptake; and Walker (1978), who reported that significant metabolic dissimilarities exist between man and the mouse relative to the monoxygenases which catalyze the metabolism of VDC to the reactive species.

After summarizing the data showing interspecies differences in metabolic effects, the Agency noted in its Criteria Document:

> "Since the rate at which an inhaled chemical is presented to the liver is related to pulmonary uptake, it would be expected that the smaller breathing volume (liters/kg/hr) in man relative to the rat would produce a corresponding slower rate of metabolism of 1,1-DCE in man . . . and the formation of smaller amounts of toxic metabolite(s)." Criteria Document at VII-2-VII-3.6/

Thus, the capability now exists to evaluate the relevance to man of the positive Maltoni study and the other bioassays. EPA's own scientists have noted the significance of the metabolic ~~saturation~~ dissimilarities in the mouse ~~and the effect of~~ in comparisons with other species. In view of the existing data, VDC toxicity and the potential risk to man are well-characterized. VDC exposure is unlikely to result in adverse health effects in man through the [illegible] pathway.

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6/ EPA cited Anderson, M.E., et al., 1980.

B. Epidemiology Data Fail To Support a Finding That Manufacture or Processing May Present an Unreasonable Risk.

An epidemiology study of employees working in a VDC facility has documented no adverse health effects associated with VDC exposure. See Ott, M.G., et al., 1976.

EPA has indicated that the population studied "may be too small to evaluate oncogenic potential for a weak oncogen." 51 Fed. Reg. 28842. The Panel concedes that the study, while well conducted, may lack adequate statistical power to detect excesses of rare carcinomas. It should be noted, however, that the potential exposures observed in that occupational population (ranging up to 70 ppm) far exceeded exposures that would be present in the ambient environment.

C. Available Data Indicate That the Toxic Effects of VDC Bear No Similarity to the Effects of Vinyl Chloride.

EPA has suggested that the "structural relationship" between VDC and vinyl chloride is cause for concern. While it may be appropriate in some circumstances to consider structural relationships in the absence of toxicity data for one of the "related" substances, it is entirely inappropriate to give any weight to such relationships when actual test data demonstrate the toxicologic dissimilarities between the substances. Any structural similarity between VDC and vinyl chloride disappears when the toxicity data are considered.

As EPA has observed, exposure to other chlorinated hydrocarbons typically causes injury to the endoplasmic reticulum in the liver. VDC, on the other hand, causes nuclear changes, mitochondrial swelling and the rupture of outer mitochondrial membranes. EPA has said: "This indicates a basic difference in the mechanism of toxicity of 1,1-DCE." EPA Criteria Document at VII-4. After reviewing the oncogenicity data, EPA stated further: "In summary, the carcinogenic potential of 1,1-DCE has been shown to be quite different from that of vinyl chloride." Id. (Emphasis added.) In view of the extensive toxicity data, evidence of structural similarity to vinyl chloride has no bearing on VDC's potential for risk.

A review of the available toxicity data, as concisely summarized in the EPA Criteria Document and as submitted for the record in this rulemaking, reveals that VDC toxicity is well characterized and that the effects of metabolic saturation in the mouse are not indicative of a potential human risk.

## II. THE RULEMAKING RECORD FAILS TO SUPPORT THE FINDINGS REQUIRED TO SUSTAIN A SECTION 4(a)(1)(A) RULE

The test rule for VDC is being proposed pursuant to EPA's authority under Section 4(a)(1)(A) of TSCA. As the proposed rule notes, a test rule promulgated under Section 4(a)(1)(A) must be supported by three findings. First, the

Agency must find that the manufacture, distribution, processing, use or disposal of a substance "may present an unreasonable risk of injury to health or the environment." Second, the Agency must find that there are insufficient data and experience upon which the effects of manufacture, distribution, processing, use or disposal on health or the environment "can reasonably be determined or predicted." Finally, EPA must find that the proposed testing is necessary to develop such data. 15 U.S.C. § 2603(a)(1)(A). The panel submits that none of these findings can be sustained on the basis of the complete record now before the Agency.

### A. The Toxic Substances Control Act Requires that EPA Support its Test Rules with Substantial Evidence in the Rulemaking Record Taken as a Whole.

TSCA imposes a particularly heavy burden on the Agency to support its findings under Section 4(a)(1)(A) with substantial evidence. Under Section 19(c), TSCA specifically requires that a reviewing court "shall hold unlawful and set aside" a test rule under Section 4(a) "if the court finds that the rule is not supported by substantial evidence in the rulemaking record . . . taken as a whole." 15 U.S.C. § 2618(c)(1)(B). (Emphasis added.)

The legislative history of TSCA makes it clear that Congress intended that EPA satisfy a standard of justifying its rules that was considerably more stringent than the usual

"arbitrary and capricious" standard. In reporting the bill that was to become TSCA, the Conference Committee explained:

> "The conferees recognize that in rulemaking proceedings such as those contained in this bill, . . . the traditional standard for review is that of 'arbitrary and capricious'. However, the conferees have adopted the 'substantial evidence' test because they intend that the reviewing court focus on the rulemaking record to see if the Administrator's action is supported by that record."7/

As one of the sponsors of TSCA in the House, Congressman Eckhardt, explained during debate on the House Committee Report:

> "We have tried to avoid the evil . . . of creating a presumption of risk without any proof of it, the evil of making the defendant prove himself not guilty with respect to the chemical. We put the burden on the EPA to identify the danger in every respect." Legislative History at 548.

Moreover, by requiring that EPA's findings be supported by substantial evidence in the rulemaking record "taken as a whole," Congress called upon the Agency, and ultimately a reviewing court, to look to the entire record. The Agency cannot premise its findings on a discrete part of the record,

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7/ H.R. Con. Reg. No. 1679, 94th Cong., 2d Sess. 96, reprinted in House Committee on Interstate and Foreign Commerce, Legislative History of the Toxic Substance Control Act, December 1976 (hereinafter cited as "Legislative History") at 709.

while ignoring inconsistent data in other parts of the record. Similarly, a reviewing court cannot uphold a rule adopted under Section 4(a) unless the findings required by that section are supported by substantial evidence in the rulemaking record taken as a whole. A court will review the entire record and will have to determine whether the record taken as a whole provides the substantial evidence necessary to support the Agency's findings.

To substantiate its proposed test rule, therefore, the Agency may not limit its consideration to the few studies found in the record at the time the proposal was issued. The Panel is submitting for inclusion in the record the many ~~additional~~ studies that comprise the data base for VDC. The Panel urges EPA to review the entire data base before making any findings regarding Section 4.

### B. The Record Does Not Support the Finding that the Manufacture and Processing of VDC May Present an Unreasonable Risk of Oncogenic Effects, as Required by Section 4(a)(1)(A)(i).

#### 1. TSCA Requires Actual Evidence that Manufacture and Processing May Present an Unreasonable Risk.

While the statute clearly places the burden on EPA to demonstrate with substantial evidence that a substance may present an unreasonable risk, the Agency relies here on a presumption. EPA's approach to determining when the findings of Section 4(a)(1)(A) apply was originally set forth in the

first test rule (Proposed Test Rule for Chlorinated Benzenes, 45 Fed. 48524, 48529 (July 18, 1980)) and has been included by reference in the VDC proposal (51 Fed. Reg. at 28841).

In announcing the policy it proposed to follow in Chlorinated Benzenes and in future rulemakings, EPA stated:

> "If there is substantial evidence that exposure to a chemical may lead to a serious health effect or increase in mortality and that people may be exposed to the chemical, EPA will presume that the activities in question (manufacturing, processing, using, transporting, disposing) 'may present an unreasonable risk' unless the rule is likely to result in a significant loss to society of the benefits of the substance. In the latter instance, if EPA's analysis shows that the costs of testing may cause manufacturers or processors to cease or severely restrict their commercial activities, EPA will weigh this potential adverse impact against the benefits of testing before presuming that the chemical may present an unreasonable risk. Whether this balancing is necessary will depend upon the economic impact of such rule." 45 Fed. Reg. 48529.

Under ~~EPA's~~ interpretation, all it must show to find an unreasonable risk is (a) "that exposure to a chemical may lead to a serious health effect or increase in mortality," and (b) "that people may be exposed to the chemical." It will then rely on a presumption to satisfy two requirements of the Act -- that the potential risk be unreasonable and that it be presented by the manufacture, distribution, processing, use or disposal of the substance.

EPA's "policy" is directly contrary to the Congressional intent, as expressed in the language of the statute and as explained by one of the sponsors of the bill upon passage. The Agency was not to rely on presumptions to support its findings. Instead, it was expected to prove that its rules were being adopted to address unreasonable risks. Congressman Broyhill discussed the limitations on EPA's authority to issue test rules during the House debate on the Conference Report:

> "The general standard for taking action under the legislation is that the substance may present an unreasonable risk. The conferees intend to limit the Administrator to taking action only against unreasonable risks because to do otherwise assumes that a risk-free society is attainable, an assumption that Congress does not make." (22 Cong. Rec. 11, 343 (Sept. 28, 1976).)

Congress expressly provided that only unreasonable risks may justify a test rule. EPA cannot ignore that requirement in applying its presumption policy.

Moreover, as the legislative history quoted above at 6 makes clear, Congress "tried to avoid the evil . . . of creating a presumption of risk without any proof of it. . . ." Legislative History at 548. While it is true that EPA need not prove that an unreasonable risk is actually presented, the use of the word "may" does not permit the Agency to rely upon speculation. In explaining what was meant

by the word "may" in the House version of TSCA, the House Report stated:

> "[T]he term 'may' . . . does not permit the Administrator to make a finding respecting probability of a risk on the basis of mere conjecture or speculation, i.e., it may or may not cause a risk." Legislative History at 425.

EPA may not rest its findings upon a potential for risk, speculation regarding exposure and a presumption that manufacturing or other activities are the cause. The law instead imposes upon the Agency the burden of establishing, on the basis of substantial evidence, that the manufacture or processing of VDC leads to exposure to the substance, that that exposure is not insignificant, and that that exposure may pose a risk that is unreasonable.

2. The Record Taken In Its Entirety Does Not Support EPA's Proposed Finding that the Manufacture and Processing of VDC May Present an Unreasonable Risk.

In addition to the Agency's long-standing "policy" presumption regarding Section 4(a) findings, quoted above, EPA bases its "may present" findings for VDC manufacture and processing on the following select elements drawn variously from portions of the record, from certain unspecified assumptions and from speculation regarding the relevance of structural similarity:

i. The population living within 5 miles of plants producing or processing VDC is estimated to be 3.6 million. The proposal implies that this population is exposed and therefore potentially at risk.

ii. A single inhalation study conducted by Maltoni, et al., was reported to have produced an increase in kidney adenocarcinomas in male mice exposed to 25 ppm VDC.

iii. A number of short-term studies were said to have generated evidence of mutagenicity and interaction with DNA.

iv. One study was cited as evidence that VDC acted as a tumor initiator.

v. EPA noted that VDC is structurally related to vinyl chloride.

The Agency has selected for inclusion in the record all items that could possibly support a call for more testing. By isolating these items, however, EPA has ignored the vast array

of data that do enable the Agency reasonably to assess potential health effects.8/

a. The record is devoid of data regarding human exposure.

The only exposure data cited by the Agency is drawn from the HAD (cited by EPA as "Ref. 1"). See 51 Fed. Reg. at 28841 (second column). It is ironic that the HAD is the sole source of data supporting the exposure element of EPA's findings, when the Document expressly states:

> "Any information regarding sources, emissions, ambient air concentrations, and public exposure has been included only to give the reader a preliminary indication of the potential presence of this substance in the ambient air. While the available information is presented as accurately as possible, it is acknowledged to be limited and dependent in many instances on assumption rather than specific data. This information is not intended, nor should it be used, to support any conclusions regarding risks to public health." HAD at iii and at 5-1; emphasis added.

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8/ The rulemaking record to date contains only the Maltoni studies, the NTP study and the Health Assessment Document for Vinylidene Chloride ("HAD"). The extensive remaining data base has apparently not been considered, except to the extent that it is summarized in the HAD. As noted above, the interest of completing the record, the VDC Panel is submitting additional studies of VDC that may be relevant to an evaluation of potential health effects.

The reasons for this severe caveat are clear -- the Agency's estimates of human exposure to VDC depend upon no fewer than four assumptions:

- an assumption regarding the sites at which VDC is;
- an assumption regarding releases of VDC from the manufacture and processing of VDC;
- an assumption regarding the atmospheric fate of VDC, in the face of conflicting data;
- an assumption regarding the time of transport from source to population areas.

The HAD states:

> "The estimation of the number of people exposed to vinylidene chloride would require knowledge of the chemical's transport characteristics. Theoretically, dispersion modelling could provide an estimate of vinylidene chloride concentrations at different distances from the plant sites; however, such data are not presently available." HAD at 7-6.

Accordingly, EPA has been unable to assess exposure.

In an effort to generate data which would provide a more reliable basis upon which to estimate exposure, CMA conducted a survey of manufacturers and processors of VDC. A confidential questionnaire was sent to each company identified in the HAD, as well as to customers of the manufacturers, seeking information regarding emissions from process vents,

storage tanks and fugitives. Estimates of populations residing within five miles of plants and distances from VDC process facilities to property boundaries and to the nearest residents were also obtained. Finally, the questionnaires asked about the availability of meteorologic data and of occupational monitoring data.

i. Number of VDC sites

The survey revealed that many of the companies listed in the 1976 HAD no longer use VDC. Of a total of 40 companies reported by EPA to be producing or using VDC, 5 companies indicated that they no longer used or produced VDC and 18 companies did not respond to the questionnaire. The manufacturers of VDC believe that most of the companies that did not respond do not presently use the chemical.

ii. Quantity of VDC released

The HAD estimated that emissions of VDC from these facilities amounted to 1,300,400 pounds per year. HAD at 5-12. If the CMA survey data are combined, less than 136,700 pounds per year were reported lost through process vents, fugitive emissions, storage tanks and loading/unloading areas. While it is possible that this figure would be somewhat larger if the survey had received a 100 percent response rate, actual emissions are probably quite close to this

figure. Because all of the major processors of VDC have responded, additional emissions are likely to be slight.

In any event, the total emissions are about a factor of 10 lower than the 1,300,000 pounds per year estimated in the HAD.

iii. Population

EPA had estimated that a total of 3,573,395 people lived within five miles of producing or processing plants. HAD at 7-7. The CMA survey revealed a total of only 673,965 living within five miles of facilities surveyed. This figure is lower than EPA estimate by a factor of 5.

iv. Transport

The HAD noted that dispersion modelling could theoretically provide an estimate of VDC concentrations at certain distances from the plant sites, but that such data were not presently available. The CMA survey attempted to generate data that could be used in such modelling and to determine the availability of additional necessary information.

The distance from the source of release to the property boundary reported in the survey ranged from 100 feet to 5,900 feet. The distance from the source to the nearest resident ranged from 260 feet to 6,600 feet. The

survey also revealed that meteorologic data and occupational monitoring data are available for nearly all sites surveyed.

In view of the brief atmospheric half-life of VDC, the limited quantities released and the distances to the nearest residents, it is unlikely than an improvement in the Agency's exposure assessment will demonstrate significant exposure to VDC. Without significant exposure, a test rule is inappropriate.

b. The extensive data base regarding the effects of VDC exposure demonstrates that VDC would pose no oncogenic risk to humans even if there were significant exposure.

The abundant toxicity data regarding the potential effects of VDC and regarding the inter-species differences demonstrate, not only that the Agency has not met its burden, but that VDC would pose no oncogenic risk to humans even if there were significant human exposure. As demonstrated in Part I of these comments, the toxicity data cited by the Agency in support of the proposed rule have been taken out of context from the over-all data base. The limited data that tend to support the proposed findings have been highlighted in the proposal, while the extensive body of data that do not support the proposal have been summarily dismissed. This extremely selective review of the data base must be rejected in favor of a comprehensive assessment.

When that review is completed, the Agency should reach the following conclusions:

- The potential for VDC to cause tumors has been subjected to extremely close scrutiny, with studies in several species, with several routes of exposure and at widely varying dose levels.
- The potential mutagenicity of VDC has also been studied in several test systems.
- Metabolic differences among test animal species, that are directly relevant to the differences in oncogenic effects seen in studies, have been well-documented.
- While improvement in the data base for VDC is possible, as it is with any chemical, the existing data do permit a reasonable determination or prediction of the effects of VDC manufacture and processing on human health.
- The data demonstrate that VDC is not likely to pose an oncogenic risk to man.

### C. EPA Has Not Demonstrated that the Record Contains Insufficient Data upon which the Effects of Manufacture or Processing Can Reasonably Be Determined or Predicted, as Required by Section 4(a)(1)(A)(ii).

#### 1. Testing May Be Required Only if a Reasonable Determination or Prediction of Risk Cannot Presently Be Made.

The law clearly prohibits the Agency from promulgating a test rule when the existing data provide a sufficient basis for making a reasonable determination or prediction of the effects of manufacture or processing on human health. The Agency may not issue a test rule merely to refine or perfect the data base for a chemical. Moreover, the fact that addi-

tional research will improve the Agency's efforts at risk assessment is not sufficient to justify a rule. The Agency must find under Section 4(a)(1)(A)(ii) that it cannot presently make a reasonable determination or prediction of health effects.

TSCA was intended to enable the Agency to require that data be generated when little is known about a chemical. The testing provision of Section 4 was intended -- not to fill an abstract curiosity about substances or to be certain that every conceivable data gap is filled -- but to provide only the data necessary to enable the Agency to make a reasonable assessment of human risk.

The sufficiency of existing data depends upon two factors -- evidence of human exposure and the comprehensiveness of the data base. If there is little evidence of human exposure, then very little data will be needed for a reasonable prediction of health effects. Similarly, if there is a large toxicity data base in existence, then a reasonable prediction of health effects can be made without additional testing.

Even if exposure to VDC is assumed, the massive existing data base is sufficient to make such a prediction. As summarized in EPA's Criteria Document and as a review of this record demonstrates, the potential health effects of VDC

exposure can reasonably be determined or predicted without additional oncogenicity testing.

2. The Record Contains Sufficient Data to Enable The Agency Reasonably to Determine or Predict the Effects of Manufacture or Processing.

Never before has the Agency proposed a test rule to require oncogenicity testing for a chemical which has already been subjected to eighteen ~~oncogenicity~~ long term chronic toxicity and/or oncog... studies and extensive pharmacokinetics, metabolism, distribution and excretion studies. The Panel submits that the proposed finding required by Section 4(a)(1)(A)(ii) cannot be made in view of the record now before the Agency.

EPA has very briefly and generally stated its objections to seventeen of the studies, including the one positive study. Apart from its general recitation of objections in the proposal and suggested improvements noted in the HAD, however, EPA has not explained its reasons for ~~rejecting~~ the totality of data on this chemical. Without an explanation of the specific flaws found in each study, the Panel cannot effectively comment on this proposed finding.

a. The existing data base is extensive.

The record contains the following 17 bioassays, each of which produced negative results:

(1) Inhalation study with Sprague-Dawley rats
Negative results were reported by Maltoni, C., et al., 1985.

(2) Inhalation study with Chinese hamsters
Negative results were reported by Maltoni, C., et al., 1985.

(3) Gavage study with Sprague-Dawley rats
Negative results were reported by Maltoni, C., et al., 1985.

(4) Inhalation study with Wistar rats
Negative results were reported by Viola and Caputo, 1977.

(5) Inhalation study with Sprague-Dawley rats
Negative results were reported by Viola and Caputo, 1977.

(6) Inhalation study with CD-1 mice
Negative results were reported by Lee, et al., 1978.

(7) Inhalation study with CD rats
Negative results were reported by Lee, et al., 1978.

(8) Inhalation study with Sprague-Dawley rats
Negative results were reported by McKenna, et al., 1982.

(9) Ingestion study with Sprague-Dawley rats
Negative results were reported by Quast, et al., 1983.

(10) Inhalation study with CD mice
Negative results were reported by Hong, et al., 1981.

(11) Inhalation study with CD rats
Negative results were reported by Hong, et al., 1981.

(12) Skin application study with Ha:ICR Swiss mice
Negative results were reported by Van Duren, et al., 1979.

(13) Subcutaneous injection study with Ha: ICR Swiss mice
Negative results were reported by Van Duren, et al., 1979.

(14) Inhalation study with Spraque-Dawley rats
Negative results were reported by Maltoni, et al., 1982.

(15) Gavage study with Spraque-Dawley rats
Negative results were reported by Maltoni, et al., 1982.

(16) Gavage study with Fischer 344 rats
Negative results were reported by NTP, 1982.

(17) Gavage study with B6C3F1 mice
Negative results were reported by NTP, 1982.

As noted above, the only study that produced a positive result was the inhalation study in which Swiss mice were exposed for 12 months to 25 ppm VDC and held until spontaneous death reported by Maltoni, et al., 1985.

In addition, the record contains the following studies relevant to metabolic, distribution, excretion and toxicity values among several species of laboratory animals:

(1) Andersen, M.E., J.E. French, M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1979a. Saturable metabolism of the acute toxicity of 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 47:385-393.

(2) Andersen, M.E., M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1979b. The use of inhalation techniques to assess the kinetic constants of 1,1-dichloroethylene metabolism. Toxicol. Appl. Pharmacol. 47:395-409.

(3) Andersen, M.E., M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1980a. Determination of the kinetic constants for metabolism of inhaled toxicants in vivo using gas uptake measurements. Toxicol. Appl. Pharmacol. 54:100-116.

(4) Andersen, M.E., O.E. Thomas, M.L. Gorgas, R.A. Jones and L.J. Jenkins, Jr. 1980b. The significance of multiple detoxification pathways for reactive metabolites in the toxicity of 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 52:422-432.

(5) Balmer, M.F., L.W. Rampy and J.F. Quast. 1976. 90-Day repeated inhalation toxicity study of vinylidene chloride in rats. Report of The Dow Chemical Company.

(6) Bonse, G., T. Urban, R. Montessano and L. Tomatis. 1975. Chemical reactivity, metabolic oxirane formation and biological activity of chlorinated ethylenes in the isolated perfused rat liver preparation. Biochem. Pharmacol. 24:1829-1834.

(7) Boyland, E., and L.F. Chasseaud. 1969. The role of glutathione and glutathione S-transferases in mercapturic acid biosynthesis. Adv. Enzymol. 32:173-219.

(8) Costa A.K., and K.M. Ivanetich. 1982. The 1,2-dichloroethylenes: Their metabolism by hepatic cytochrome P-450 in vitro. Biochem. Pharmacol. 31:2093-2102.

(9) Dallas, C.E., F.W. Weir, S. Feldman, L. Putcha and J.V. Bruckner. 1983. The uptake and distribution of 1,1-dichloroethylene in rats during inhalation exposure. Toxicol. Appl. Pharmacol. 68:140-151.

(10) Filser, J.G., and H.M. Bolt. 1979. Pharmacokinetics of halogenated ethylenes in rats. Arch. Toxicol. 42:123-136.

(11) Gage, J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. Brit. J. Industr. Med. 27:1-18.

(12) Hathway, D.E. 1977. Comparative mammalian metabolism of vinyl chloride and vinylidene chloride in relation to oncogenic potential. Environ. Health. Perspect. 21:55-59.

(13) Hayakawa, T., R.A. Lemahieu and S. Udenfriend. 1974. Studies on glutatione-S-arene oxidase transferase - a sensitive assay and partial purification of the enzyme from sheep liver. Arch. Biochem. Biophys. 162:223-230.

(14) Henck, J.W., J.F. Quast, L.W. Rampy and J.M. Norris. 1980. 10-Day toxicity study on inhaled vinylidene chloride in four strains of laboratory mice. Report of The Dow Chemical Company.

(15) Hong, C.B., J.M. Winston, L.P. Thornberg, C.C. Lee and J.S. Woods. 1981. Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: Tumor incidence and mortality subsequent to exposure. J. Toxicol. Environ. Health 7:909-924.

(16) Humiston, C.G., J.F. Quast, C.E. Wade, J. Ballard, J.E. Beyer and R.W. Lisowe. 1978. Results of a two-year toxicity and oncogenicity study with vinylidene chloride incorporated in the drinking water of rats. Report of The Dow Chemical Company.

(17) Jaeger, R.J., R.B. Conolly and S.D. Murphy. 1974. Effect of 18 hour fast and glutathione depletion of 1,1-dichlorethylene-induced hepatotoxicity and lethality in rats. Exp. Mol. Pathol. 20:187-198.

(18) Jaeger, R.J., L.G. Shoner and L.J. Coffman. 1977a. 1,1-Dichloroethylene hepatotoxicity: Proposed mechanism of action of distribution and binding of $^{14}C$ radioactivity following inhalation exposure in rats. Environ. Health Perspect. 21:113.

(19) Jones, B.K., et al., The Biological Fate of Vinylidene Chloride in Rats, Chemical Biological Interactions, 20:27-41, 1978.

(20) Jones, B.K., et al., Differences in Metabolism of Vinylidene Chloride Between Mice and Rats, Br. J. Cancer, 37:411, 1978.

(21) Jones, B.K., and D.E. Hathway. 1978a. Differences in metabolism of vinylidene chloride between mice and rats. Br. J. Cancer 37:411.

(22) Lee, C.C., J.C. Bhandari, J.M. Winston, W.B. House, P.J. Peters, R.L. Dixon and J.S. Woods. 1977. Inhalation toxicity of vinyl chloride and vinylidene chloride. Environ. Health. Perspect. 21:25-32.

(23) Lee, C.C., J.C. Bhandari, J.M. Winston, W.B. House, R.L. Dixon and J.S. Woods. 1978. Carcinogenicity of vinyl chloride and vinylidene chloride. J. Toxicol. Environ. Health 4(1):15-30.

(24) Liebler, D.C. and F.P. Guengerich. 1983. Olefin oxidation by cytochrome P-450: Evidence for group migration in catalytic intermediates formed with vinylidene chloride and trans-1-phenyl-1-butene. Biochemistry 22:5482-5489.

(25) Liebler, D.C., M.J. Meredith and F.P. Guengerich. 1984. Reactive metabolites of vinylidene chloride: Characterization of covalent adducts formed with proteins and glutathione in microsomes and isolated hepatocytes. Cancer Res., In Press.

(26) Litterst, C.L., E.G. Mimnaugh, R.L. Reagan and T.E. Gram. 1975. Comparison of in vitro drug metabolism by lung, liver, and kidney of several common laboratory species. Drug Metab. Disposition 3(4):259-265.

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

(28) Maltoni, C., G. Cotti, L. Morisi, and P. Chieco. 1977. Carcinogenicity bioassays of vinylidene chloride. Research plan and early results. La Medicina del Lavoro 68(4): 241-262.

(29) Maltoni, C., G. Cotti, L. Morisi and P. Chieco. 1980. Toxicity and carcinogenicity bioassays of vinylidene chloride. II. Chronic toxicity and carcinogenicity. Report of the Institute of Oncology & Tumor Center, Bologna, Italy.

(30) McKenna, M.J., P.G. Watanabe and P.J. Gehring. 1977. Pharmacokinetics of vinylidene chloride in the rat. Environ. Health. Perspect. 21:99-105.

(31) McKenna, M.J., J.A. Zempel, E.O. Madrid, W.H. Braun, and P.J. Gehring. 1978. Metabolism and pharmacokinetic profile of vinylidene chloride in rats following oral administration. Toxicol. Appl. Pharmacol. 45:821-835.

(32) McKenna, M.J., J.A. Zempel and P.J. Gehring. 1979. A comparison of the pharmacokinetics of inhaled vinylidene chloride in rats and mice. Report of The Dow Chemical Company.

(33) McKenna, M.J., J.F. Quast, H.O. Yakel, M.F. Balmer and L.W. Rampy. 1980. Vinylidene chloride: a chronic inhalation toxicity and oncogenicity study in rats. Report of The Dow Chemical Company.

(34) McKenna, M.J., J.A. Zempel, E.O. Madrid and P.J. Gehring. 1978a. The pharmacokinetics of [$^{14}$C] vinylidene chloride in rats following inhalation exposure. Toxicol. Appl. Pharmacol. 45:599-610.

(35) Oesch, F. 1973. Mammalian epoxide hydrase: inducible enzymes catalyzing the inactivation of carcinogenic and cytotoxic metabolites derived from aromatic and olefinic compounds. Xenobiotica 3:305-340.

(36) Oesch, F., D. Raphael, H. Schwind, and H.R. Glatt. 1977. Species differences in activating and inactivating enzymes related to the control of mutagenic metaolites. Arch Toxicol. 39:97-108.

(37) Rampy, J.W., J.F. Quast, C.G. Humiston, M.F. Balmer and B.A. Schwetz. 1977. Interim results of two-year toxicological studies in rats of vinylidene chloride incorporated in the drinking

water or administered by repeated inhalation. Environ. Health. Perspect. 21:33-43.

(38) Ray, Prabhati, et al., 1,1-Dichloroethylene Inhibition of Liver Microsomal Calcium Pump in Vitro, Archives of Biochemistry and Biophysics, 218:26-30, 1982.

(39) Reichert, D., H.W. Werner and D. Henschler. 1978. Role of liver glutathione in 1,1-dichloroethylene metabolism and hepatotoxicity in intact rats and isolated perfused rat liver. Arch. Toxicol. 41:169-178.

(40) Reichert, D., H.W. Werner, M. Metzler and D. Henschler. 1979. Molecular mechanism of 1,1-dichloroethylene toxicity: excreted metabolites reveal different pathways of reactive intermediates. Arch. Toxicol. 42:159-169.

(41) Reichert, D., and H.W. Werner. 1978. Disposition and metabolism of ($^{14}$C) 1,1-dichloroethylene after single oral administration in rats (Abstract). Naunyn-Schmiedeberg's Arch. Pharmacol. 302(Suppl), R-22.

(42) Reitz, R.H., P.G. Watanabe, M.J. McKenna, J.F. Quast, and P.J. Gehring. 1980a. Effects of vinylidene chloride on DNA synthesis and DNA repair in the rat and mouse: A comparative study with dimethylnitrosamine. Toxicol. Appl. Pharmacol. 52:357-370.

(43) Short, R.D., J.M. Winston, J.L. Minor, C.B. Hong, J. Seifter and C.C. Lee. 1977. Toxicity of vinylidene chloride in mice and rats and its alteration by various treatments. J. Toxicol. Environ. Health. 3:913-921.

(44) Viola, P.L. and A. Caputo. 1977. Carcinogenicity studies on vinylidene chloride. Environ. Health. Perspect. 21:45-47.

(45) Walker, C.H. 1978. Species differences in microsomal monooxygenase activity and their relationship to biological half-lives. Drug Metab. Rev. 7(2):295-323.

(46) Watanabe, P.G., R.H. Reitz, A.M. Schumann, M.J. McKenna, J.F. Quast and P.J. Gehring. 1980. Implications of the mechanisms of tumorigenicity for risk assessment. In: The Scientific Basis of Toxicity Assessment (H. Witschi, ed). Elsevier/North-Holland Biomedical Press, Amsterdam, The Netherlands.

b. EPA's objections are vague and non-specific.

In its proposed rule, the Agency has not addressed the adequacy of existing metabolism, distribution, excretion or toxicity data. It has only commented on the adequacy of the bioassay data, noting:

> "The remaining 17 animal bioassays provide no evidence of oncogenicity. All but one of these studies had significant flaws in design.
>
> * * *
>
> "The negative findings in these studies may be partially explained by study characteristics such as dosing regimens of less than two years duration; less than a maximally tolerated dose; differences in routes of administration; and testing at a single dose level. These limitations individually or in combination reduce the sensitivity of detecting a positive response." 51 Fed. Reg. 28841, column 3, citing the HAD.

While the Agency stated that the NTP gavage studies did have "an adequate protocol to demonstrate a chemical's lack of oncogenic potential," it suggested that these studies "may not have achieved a sufficiently high dose." Apart from the NTP studies, the Agency has not identified any specific flaws in any specific studies.

c. The existing studies can be used to make a reasonable determination or prediction of health effects.

The Panel submits that the objections posed by the Agency to the seventeen negative bioassays are insufficient to demonstrate that this enormous data base cannot enable EPA to make a reasonable determination or prediction of health effects. Moreover, the existing data regarding metabolic and pharmacokinetic differences and regarding the mechanism of toxicity in the mouse provide a reasonable basis to predict that humans are unlikely to exhibit health effects comparable to the mouse.

i. The CMA-sponsored studies were well-designed and well-conducted.

Two studies were performed for the CMA VDC Panel to assess the effects of VDC inhalation and ingestion in drinking water on Spraque-Dawley rats. McKenna, et al., 1982 and Quast, et al., 1983. The Health Assessment Document suggested that higher exposure levels in both studies might have "provided a broader evaluation for carcinogenicity." HAD at 10-113; see also HAD at 10-116. Apart from these comments and the general comments recited in the proposal, EPA has not given any reason why these studies do not enable the Agency to make a reasonable prediction of health effects.

The Panel submits that these studies were well designed and conducted and along with the NTP bioassay and the comparative pharmacokinetics, metabolism and mechanism of action studies, can provide a reasonable basis for an Agency assessment of potential risk.

The Panel submits that the extensive data base on comparative pharmacokinetics and metabolism of VDC and the mechanism of action data indicate that the rat is the more appropriate animal species to use as a model for man. The Panel believes that the long-term inhalation and drinking water studies using Sprague-Dawley rats (Quast et al., 1983, McKenna et al., 1982) are appropriate for the purpose of assessing the risk for man. The exposure period of the inhalation study was 18 months, with a final sacrifice at 24 months. The normal life-span of the Sprague-Dawley rat is considerably shorter than the Fischer 344 rat used by the NTP. In fact, the exposure period of the Sprague-Dawley rat in the inhalation study, 18 months, covered a comparable portion of the animals' life-span comparable to the portion of the Fischer 344 rat life span covered by the 2-year exposures. The historical survival data on Sprague-Dawley rats at the laboratory in which the long-term inhalation and drinking water studies were conducted were, for males, 40-81% at 18 months and 6-24% at 24 months. The survival of male and female Fischer 344 rats was 75% at 24 months. On the basis of

the exposure time, the inhalation study on the Sprague-Dawley rat is believed to be appropriate for assessing the potential risk to man from exposure to VDC.

The dose levels for the long-term inhalation study using Sprague-Dawley rats, 25 and 75 ppm, were sufficiently lower than the concentrations, 125 and 200 ppm, which caused hepatocellular necrosis after 30 days exposure in the female Sprague-Dawley rat (Quast, 1976), so as not to compromise the interpretation of the study outcome. In both the inhalation and drinking water exposure regimens using the Sprague-Dawley rat, the criteria for maximum tolerated dose accepted in the EPA position paper on MTD were satisfied. The presence of vacuolization and fatty infiltration of hepatocytes are conditions that would be appropriate under the position paper. See, Harris, J.E., et al., Position Paper on Maximum Tolerated Dose in Oncogenicity Studies, 1986 at p.5.

ii. The NTP studies were conducted at concentrations selected according to EPA criteria.

The Agency concedes the adequacy of the NTP studies, but suggests that the bioassays may not have utilized a sufficiently high dose. The dose was questioned because of the lack of an effect on weight gain or survival in the high dose population.

The Panel sumbits that the NTP studies were conducted with an appropriately high dose, based upon the findings in the subchronic phase of the studies and in accordance with the Agency's criteria. The dose levels were based upon levels which had produced body weight changes and histopathologic observations. Moreover, the highest dose selected in the NTP studies were comparable to the mg/kg dose used in the Maltoni Swiss mouse study. The NTP studies, along with the Quast, et al., 1983 study, can be used for risk assessment purposes.

iii. Other studies also provide valuable data.

The Agency dismisses the contributions that the extensive data base can make to the weight of evidence present on the toxicity and oncogenicity of VDC, stating merely that the existing studies are inadequate. On the contrary, inhalation studies by Lee et al (1978) and Hong et.al (1981) provide evidence of differences in species and strain sensitivity to the effects of VDC exposure. In these inhalation studies using CD-1 mice, exposures to 55 ppm VDC for 6 hours/day, 5 days/week for 12 months and 6 months, respectively, demonstrated no statistically significant differences in tumor occurrence between the exposed and control animals in the [illegible]. The exposure duration in the Lee et al. study was equivalent to that in the Maltoni study, while the dose was more than twice

the dose that Maltoni, et al. found as producing significant tissue injury and kidney adenocarcinomas in a different mouse strain.

Additional data can be derived from the McKenna, et al, 1982 (published as Quast, et al. 1986) inhalation study in Sprague-Dawley rats. This study represents the longest inhalation exposure duration (18 months) used in a laboratory investigation on toxicity and oncogenicity of VDC to date. Concentrations of 25 to 75 ppm were effect levels for target organ toxicity in the liver of the exposed animals, yet no oncogenic response was noted in this study, in spite of what amounted to a lifetime exposure for the Sprague-Dawley rat.

iv. Metabolism and pharmacokinetic data provide a good framework to evaluate the mouse data for possible relevance to humans.

The Panel submits that, given the extensive data on the pharmacokinetics and metabolism of VDC, the potential biological effects in man versus the rat and mouse are predictable on a comparative physiologic and metabolic basis. Accordingly, EPA should conclude that a reasonable prediction of human health effects can be made on the basis of existing data. A large number of distribution, excretion, metabolism and oncogenicity studies have already been conducted, and the results of these studies have been summarized by the Agency in the Health Assessment Document and the Drinking Water Criteria Document. See discussion above.

As noted in Part I, it appears that the toxicity of VDC is directly related to the metabolic conversion of the parent chemical into a more chemically-reactive compound (such as 1,1-dichloroethylene oxide). These reactive substances probably produce toxicity through reaction with biological macromolecules.

Furthermore, it appears that endogenous scavengers, such as hepatic glutathione, play a key role in modulating the reactivity of VDC. During prolonged inhalation exposures, the relative rates of metabolic activation and resynthesis of glutathione may determine whether toxicity will occur.

Finally, the occurrence of renal tumors in the Swiss mice was accompanied by significant cytotoxicity in the kidney. When cytotoxicity was absent (at lower doses or in other species), oncogenicity was not observed. Consequently, it appears likely that induction of cytotoxicity is associated with an increase in the incidence of tumors.

The extensive data available from pharmacokinetic and metabolism studies provide a framework by which to understand the species and strain differences observed in the large chronic data base. Similarly, these data may be used to better understand the relevance of the mouse tumor data to man.

D. EPA Cannot Demonstrate that the Proposed Testing Is Necessary to Develop Data Reasonably to Determine or Predict the Effects of Manufacture or Processing, as Required by Section 4(a)(1)(A)(iii).

EPA bases the finding required by Section 4 (a)(1)(A)(iii) on a determination of whether the proposed testing "would be capable of developing the necessary information," which the Agency interprets to mean "information . . . to reasonably determine or predict the effects of human exposure to the chemical." 51 Fed. Reg. 28841, column 2 (emphasis added).

TSCA imposes a slightly different requirement than is suggested under the Agency's interpretation. The law requires the Agency to find that the proposed testing is necessary to develop information reasonably to determine or predict the effects of manufacture or processing on human health. If, because of a lack of data showing that manufacture or processing leads to human exposure, the resulting toxicity data will not significantly improve the Agency's ability to assess the health effects of manufacture or processing, this finding cannot be made. As noted in these comments, EPA has cited no reliable data showing that manufacture or processing leads to significant human exposure. For that reason, the proposed testing cannot be said to be necessary to enable the Agency to predict or determine the effects of manufacture or processing. Similarly, because the existing oncogenicity,

metabolic and pharmacokinetic data base is so extensive, it already permits a reasonable determination or prediction of the effects of manufacture or processing.

For these reasons, EPA cannot make the findings required by Section 4(a)(1)(A)(iii) regarding the need for another oncogenicity study.

## III. Responses to Issues for Comment

The first two parts of these comments address several of the issues raised at 51 Fed. Reg. 28844. For the convenience of the Agency, the Panel has summarized relevant comments as they pertain to the six issues set forth in the proposal. However, these answers should be read in the context of the comments as a whole.

### A. Existing Oncogenicity Studies Are Adequate.

The form of the Agency's first question reveals a basic misunderstanding of the findings required under Section 4. EPA asks:

> "Are the existing studies of 1,1-diechloroethylene's oncogenic potential adequate to assess the risks of exposure to this substance?"

TSCA only permits the Agency to require testing which is necessary to develop sufficient data upon which the effects of manufacture or processing (or distribution, use or disposal)

"can reasonably be determined or predicted." EPA cannot assume that manufacture or processing leads to exposure. It cannot require testing if the current data base is sufficient to make a reasonable determination or prediction of the effects of manufacture or processing.

As these comments demonstrate, the extensive existing data base is sufficient to make such a reasonable determination.

B. The DEM studies proposed by EPA are inappropriate.

The Agency has proposed that distribution, excretion, and metabolism studies be conducted "because of the differences in the protocol and outcome between the negative in the NTP gavage and the positive in the Maltoni inhalation studies." The results of these studies are to be used by the Agency for decision-making and to aid in the design of the oncogenicity bioassay.

As described in the Health Assessment Document and in the Drinking Water Criteria Document, an extensive data base on pharmacokinetics and metabolism already exists for VDC. The Agency has already decided that the oncogenicity testing will be conducted in the "Swiss" mouse "because of its demonstrated sensitivity," and that the route of exposure will be inhalation. There is little utility in the described DEM studies, in view of the requirements outlined by the Agency.

A model could be designed using current state-of-the-art methods to evaluate the extrapolation from mouse, rat, and hamster to man without the proposed DEM studies. In order to reasonably determine or predict the effects of human health associated with VDC exposure, a physiologically-based pharmacokinetic model could be developed to 1) predict the rates of metabolic activation of VDC after administration by inhalation, oral, and dermal routes; 2) predict the rates of metabolic activation in different species, based on in vivo and in vitro data; 3) describe quantitatively the interplay between the reactive intermediate(s), glutathione, and biological macromolecules, incorporating endogenous rates of resynthesis of glutathione after depletion; and 4) evaluate the level of cytotoxicity associated with specific exposures to VDC.

C. The Desire for the Nineteenth Bioassay Cannot Be Justified by Differential Responses in Existing Studies.

The Agency states that it is basing the need for a further oncogenicity bioassay in mice on the differential response that can be seen in bioassays depending on the route of exposure.

The Panel believes that the differential response seen in the Maltoni Swiss Mouse study, which can be explained by the high exposure levels for that strain of mouse and the production of high levels of toxic metabolites, provides no

justification for the test requirement. TSCA does not permit EPA to use a test rule to further refine an already extensive data base, on the assumption that another mouse inhalation study may be positive. There are adequate data to enable the Agency to make a reasonable assessment of potential health effects. Further oncogenicity testing is not authorized under TSCA.

D. Epidemiology Study.

The Agency asks whether an epidemiology study should be required in lieu of a 2-year animal bioassay. In light of the Agency's assessment that VDC may act as a "weak oncogen", a large cohort with sufficient latency and level of exposure would have to be identified in order to satisfy the requirements for sufficient statistical power to detect a health effect which could be attributed to VDC exposure. It seems unlikely, given the small number of producers of VDC and the similarly small number of processors, that a suitably sized cohort could be identified at this time. In addition, VDC is frequently processed in conjunction with VDC monomer. The potential for this exposure would pose as a potential confounder in the interpretation of the results, as would personal risk factors such as cigarette smoking and alcohol consumption. It seems unlikely that the Agency could satisfy

its own requirements for a well-conducted epidemiology study for this compound.

E. Possible Protocol Modifications

The Agency requests comments on several possible protocol modifications.

[What comments are suggested?]

F. The Proposed Second Species Should be Rejected.

EPA asks whether two species should be tested, or whether data sufficiently show the mouse to be the most sensitive. As noted above, the Swiss mouse is clearly the most sensitive species.

CONCLUSION

For the reasons set forth in these comments, the VDC Panel submits that the record does not support the proposed testing.

- The record contains no data showing that manufacture or processing of VDC leads to significant human exposure.

- The record contains abundant data showing that VDC is not oncogenic when tested in several species and with several routes of exposure.

- The limited positive data in the mouse can be explained by differences in metabolism and pharmacokinetics that are well documented. Existing data demonstrate that man is substantially less sensitive than the mouse.

- Potential health effects have been thoroughly studied, and the Agency can reasonably predict that VDC does not present a potential risk to humans.

- The Agency cannot find that the proposed testing is necessary to enable it to make a reasonable prediction of the effects of manufacture or processing, since such a prediction can be made on the basis of the existing data.

The Panel urges EPA to review the entire record and to conclude that its proposed test rule is not warranted.

Dated: January 15, 1987