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)

Geraldine V. Cox, Ph.D.
Vice President
Technical Director
Chemical Manufacturers
Association

David E. Zoll, Esq.
Vice President
General Counsel
Chemical Manufacturers
Association

Robert R. Romano, Ph.D.
Manager
Vinylidene Chloride Program
Chemical Manufacturers
Association

Of Counsel:

R. Bruce Dickson
Michael A. Wiegard
Lori Schmidt-Praul
Paul, Hastings, Janofsky & Walker
1050 Connecticut Avenue, N.W.
Suite 1200
Washington, D.C. 20036

Chemical Manufacturers Association
2501 M Street, N.W.
Washington, D.C. 20037

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(OPTS-42082; 51 Fed. Reg. 28840
(August 12, 1986))

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 Task Force ("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 thoroughly studied in eighteen separate oncogenicity studies and in an abundance of acute and subchronic 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 r garding exposure to VDC, and what data exist show very low ambient concentration levels.

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 data 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 the comments describes the legal standard under which a test rule must be issued and circumstances

under which a revi wing court must overturn a test rule. Under the 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. The Agency may not select the few items from the record that tend to support its position, while ignoring the abundant data that do not support its position.

Part II reviews the record pertaining to the possible adverse health effects of VDC. When all available data are considered, the record fails to support the proposed finding under Section 4(a)(1)(A)(i) that the manufacture and processing of VDC may present an unreasonable risk. On the contrary, 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.

Part III of these comments reviews the sufficiency of the current data. 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. The only additional data that might be useful in evaluating the many existing bioassays and their relevance to health effects may be generated by a series of state-of-the-art short term studies.

In Part IV, the comments discuss EPA's contention that the proposed testing is necessary to develop data upon which the effects of manufacture or processing can be predicted. 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. In view of the total lack of data regarding human exposure, the Agency has conceded that it cannot regulate VDC under the Clean Air Act even if it is assumed to be a human carcinogen. The Agency cannot substantiate its proposed finding under Section 4(a)(1)(A)(iii) that the nineteenth oncogenicity study is necessary to develop data upon which the effects of VDC manufacture or processing can reasonably be determined or predicted. While certain short term studies might assist the Agency in interpreting the many existing bioassays, the DEM

studies that EPA has proposed cannot be considered "necessary."

Finally, Part V 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 herein, and as demonstrated in the health effects data being submitted herewith, the proposed rule is not supported by the record and should not be adopted.

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

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 r asonably 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).

In addition to the requirement that EPA justify a test rule with these three findings, TSCA imposes a particularly heavy burden on the Aqency to support these findings 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."1/

As one of the sponsors of TSCA in the House,

1/ 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.

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 discreet part of the record, 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 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.

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 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 any oncogenic risk to man.

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II. The Record Does Not Support the Finding that the Manufacture and Processing of VDC May Present an Unreasonable Risk of Oncogenic Effects.

A. 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.

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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.

B. 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 apparently combed the extensive data base for VDC and identified 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 enable the Agency reasonably to assess potential health effects.2/

1. The record is devoid of any 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

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2/ 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. In the interest of completing the record, the VDC Panel is submitting all available studies of VDC that may be relevant to an evaluation of potential health effects.

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> 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.

This caveat was apparently overlooked when the Agency issued the proposed test rule. Apart from the HAD, there is no information in the record regarding sources, emissions, ambient air concentrations or public exposure. Yet none of th information in the HAD regarding exposure was intended to support any conclusions regarding risks to public health. The rulemaking record therefore provides no support for the exposure element of the Agency's proposed finding that the manufacture and processing of VDC may present an unreasonable risk.

Even if the Agency were to include in the record all available data on VDC emissions, it could not demonstrate that manufacture or processing leads to significant human xposure. The 1983 report entitled "Occurrence of 1,1-Dichloroethylene in Drinking Water, Food and Air," Lethiewics, F., et al., JRB Associates, (the "Occurrence Document") demonstrates that the Agency has extremely little data suggesting human exposure. The Occurrence Document reveals that 99.7 percent of all surface water systems and 98 percent of all groundwater systems have no VDC or less than 0.2 ug/l.

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While certain quantities of VDC enter the atmosphere, the Occurrence Document notes that the "tropospheric lifetime is estimated to be less than 1 day." (Id. at 6.) Based upon very limited measurements, the Occurrence Document estimates that adult intake ranges from 0.0 ug/g/day in rural/remote areas to 0.0086 ug/kg/day in urban/suburban areas. Source dominated areas are said to show 4.6 ug/kg/day exposure to a maximum of 8.9 ug/kg/day. The data on which the source and maximum levels are based is extremely sketchy, however. [Discuss CMA's survey?]

2. 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. 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 little 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.

A thorough review of the data reveals that the potential toxicity of VDC is well characterized. The response seen in the Maltoni Swiss mouse study can be understood as an effect of certain metabolic characteristics of the laboratory species studied -- characteristics that are not found in other species that have been studied and that are not present in humans.

a. Toxicology data suggests 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 n gative, with the one noteworthy exception cited by the Agency. It was only when mice were exposed for two years in the Maltoni 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 the mouse to VDC and of the mechanism whereby that sensitivity is expressed. The only positive oncogenicity in existence appears to be directly related to the well-documented saturation of the metabolic pathways in the mouse.

As EPA itself recognized in its Drinking Water Criteria Document for VDC,

> "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."3/

Data clearly demonstrate that VDC is metabolized much more rapidly by mice than by rats.4/ 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.5/ 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.

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.

3/ 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.

4/ Jones, B.K. and D.E. Hathway, "Differences in metabolism of vinylidene chloride between mice and rats," Br. Jour. Cancer 17:411 (1978).

5/ EPA Criteria Document at VII-4.

Studies have shown that mice are far more susceptible to both kidney and liver damage from VDC than are rats. Id. at VII-5.

Even the mutagenicity data show that the toxic effect is directly related to the presence of microsomal enzymes from the liver, kidney and lung of mice and rats.6/

The extensive bioassay data confirm the Agency's observation, quoted above, that the reaction of VDC metabolites is generally believed to cause 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 adenocarcenomas was observed. All other studies were negative, 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, a subcutaneous injection study with Swiss mice, a third inhalation study with Sprague-Dawley rats, a gavage study with Sprague-Dawley rats,

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6/ Jones, B.K. and D.E. Hathway, "Tissue-mediated mutagenicity of vinylidene chloride in Salmonella typhimurium TA1535," Cancer Lett. 5:1-6 (1978).

a gavage study with Fischer 344 rats and a gavage study with B6C3F1 mice. See infra, pp. 25-27.

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. 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, 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-8.7/

7/ EPA cites Maltoni, 1977; Hathway, 1977; Henschler and Bonse, 1977; and Reitz, 1980. [Use full cites.] See also, Anderson, M.E., et al., Saturable Metabolism and the Acute Toxicity of 1,1-Dichloroethylene, Toxicology and Applied Pharmacology, 47:385-393, 1979.

When this extensive data base is used to estimate potential risks to man, it can be seen that the oncogenicity data have no applicability to man. 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 metabolishm of 1,1-DCE in man . . . and the formation of smaller amounts of toxic metabolite(s)." Criteria Document at VII-2-VII-3.8/

In view of the extremely low levels of exposure, extrapolation from the available data demonstrates that VDC is most unlikely to pose any oncogenic risk to man. [Discuss tumor initiator data.]

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., A Health Study of

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8/ EPA cited Anderson, M.E., et al., "Determination of the kinetic constants for metabolism of inhaled toxicants in vivo using gas uptake measurements," Toxicol. Appl. Pharmacol. 51:100-116 (1980).

Employees Exposed to Vinylidene Chloride, Journal of Occupational Medicine, 18:735-738, 1976, Appendix ___.

EPA has indicated that the population studied "may be too small to evaluate oncogenic potential for a weak oncogen." 51 Fed. Reg. 28842.

[Further comments?]

c. Available data indicate that the toxic effects of VDC bear no similarity to the effects of vinyl chloride.

The final argument advanced by the Agency to suggest that VDC may pose an unreasonable risk is premised on the "structural relationship" between VDC and vinyl chloride. While on an elementary level EPA may be correct in suggesting a structural similarity between VDC and vinyl chloride, the similarity 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. "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. In view of the extensive

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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, reveals that there is no substantial justification for the conclusion that VDC manufacture and processing may present an unreasonable risk.

III. EPA Has Not Demonstrated that the Record Contains Insufficient Data upon which the Effects of Manufacture or Processing Can Reasonably Be Determined or Predicted.

A. 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 expand the data base for a chemical or in an effort to generate a positive test response. Moreover, the fact that additional research will improve the Agency's efforts at risk assessment is not sufficient to justify a rule. The Agency must find 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 depend 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 xposure can reasonably be determined or predicted.

B. 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 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 each of the existing studies. Without an explanation of the specific flaws found in each study, the Panel cannot effectively comment on this proposed finding.

1. The existing data base is extensive.

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

- Inhalation study with Sprague-Dawley rats - Negative results were reported by Maltoni [cite].
- Inhalation study with Chinese hamsters - Negative results were reported by Maltoni [cite].
- Gavage study with Sprague-Dawley rats - Negative results were reported by Maltoni [cite].
- Inhalation study with Wistar rats - Negative results were reported by Viola and Caputo [Cite].
- Inhalation study with Sprague-Dawley rats - Negative results were reported by Viola and Caputo [cite].

- Inhalation study with CD-1 mice - Negative results were reported by Lee, et al., 1978 [cite].

- Inhalation study with CD rats - Negative results were reported by Lee, et al., 1978 [cite].

- Inhalation study with Sprague-Dawley rats - Negative results were reported by McKenna, et al., 1982 [cite].

- Ingestion study with Sprague-Dawley rats - Negative results were reported by Quast, et al., 1983 [cite].

- Inhalation study with CD mice - Negative results were reported by Hong, et al., 1981 [cite].

- Inhalation study with CD rats - Negative results were reported by Hong, et al., 1981 [cite].

- Skin application study with Ha:ICR Swiss mice - Negative results were reported by Van Duuren, et al., 1979 [cite].

* note typo in other paragraph

- Subcutaneous injection study with Ha: ICR Swiss mice - Negative results were reported by Van Duuren, et al., 1979 [cite].

- Inhalation study with Spraque-Dawley rats - Negative results were reported by Maltoni, et al., 1982 [cite].

- Gavage study with Spraque-Dawley rats - Negative results were reported by Maltoni, et al., 1982 [cite].

- Gavage study with Fischer 344 rats - Negative results were reported by NTP, 1982 [cite].

- Gavage study with B6C3F1 mice - Negative results were reported by NTP, 1982 [cite].

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As noted above, the only study that produced a positive result was the inhalation study with Swiss mice reported by Maltoni, et al., 1985 [cite].

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

[Insert list of studies; include copies for record.]

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

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.
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> * * *
>
> "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.

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

The VDC Panel submits that the objections posed by the Agency to the seventeen negative studies 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.

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

Two studies were performed for the CMA VDC Panel to assess the effects of inhalation and ingestion in drinking water on Spraque-Dawley rats. McKenna, et al., 1982 [cite] and Quast, et al., 1983 [cite]. 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

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not enable the Agency to make a reasonable prediction of health effects.

The Panel submits that these studies were well designed and conducted and can provide a reasonable basis for an Agency assessment of potential risk. [Insert defense of dose levels, of exposure period and of usefulness for risk assessment.]

b. The NTP studies were well-designed and well-conducted.

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. First, the dose was comparable to the dose used in the Maltoni Swiss mouse study. Second, the effects seen in the subchronic phase of the studies justify the dose selected.

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[Toxicology input needed to justify dose. Refer to EPA Position Paper on MTD.]

c. Other ~~bioassays~~ studies also provide valuable data.

[Insert general defense of other studies, particularly the mouse inhalation studies.]

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

[Insert]

e. Additional studies may improve EPA's ability to evaluate the significance of the existing oncogenicity data for human risk assessment.

[Insert]

IV. EPA Cannot Demonstrate that the Proposed Testing Is Necessary to Develop Data Reasonably to Determine or Predict the Effects of Manufacture or Processing.

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.

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 heatlh. 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 data base is so extensive, it already permits a reasonable determination or prediction of the effects of exposure or processing. Only limited additional data are needed to expand the current metabolism/pharmacokinetic data base so that the bioassays can be fully understood.

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

V. Responses to Issues for Comment

The first four 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.

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. And 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.

Additional studies can be designed using current state-of-the-art methods to evaluate the validity of extrapolation from mouse, rat and hamster to man. [Expand]

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 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 a fifth 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. At most, the data base might be expanded with pharmacokinetic/ metabolism data to assess differences among species.

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D. Epidemiology Study.

[What comments are suggested?]

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.

The Panel believes that the data clearly show the mouse to be the most sensitive to VDC. The mechanism whereby greater effects are seen in the mouse than in the rat has been discussed in detail above.

[Comments on Swiss mouse?]

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.

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- 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.

- 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 now.

- At most, the Agency should consider state-of-the-art short term studies designed to assess further the validity of extrapolation from the existing bioassays to man.

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

Respectfully submitted,

Geraldine V. Cox, Ph.D.
Vice President
Technical Director
Chemical Manufacturers
Association

Of counsel:

David F. Zoll
Vice President and
General Counsel
Ch mical Manufacturers
Association

R. Bruce Dickson
Michael A. Wiegard
Lori J. Schmidt-Praul
Paul, Hastings, Janofsky & Walker
1050 Connecticut Avenue, N.W.
Washington, D.C. 20036

Counsel to the Chemical Manufacturers Association
Vinylidene Chloride Program Panel

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