BEFORE THE
UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CHEMICAL MANUFACTURERS ASSOCIATION VINYLIDENE CHLORIDE PROGRAM PANEL COMMENTS ON PROPOSED TEST RULE FOR 1,1-DICHLOROETHYLENE (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

VDC does not fit the usual pattern of Interagency Testing Committee designated chemicals proposed for testing. The toxicological data base for VDC is unique in terms of the number and variety of toxicity studies. VDC has been the subject of eighteen long-term animal toxicity and/or oncogenicity studies, several acute and subchronic (less than 90 days) studies, pharmacokinetic and metabolism studies and mechanism of toxicity, including oncogenicity, studies. In the long-term toxicity and/or oncogenicity studies, five routes of exposure and several strains of mouse and rat and one strain of hamster have been used. Never before has the Agency proposed to require testing of a chemical with such an extensive data base.

VDC also does not fit the usual pattern of potential exposure for Section 4 test rules. The data regarding exposure to VDC that was available to the Agency through the Health Assessment Document1/ showed that there was very little potential for exposure from manufacturing and processing. More recently obtained data confirm the little potential for exposure to VDC.

1/ EPA Office of Health and Evironmental Assessment, Health Assessment Document for Vinylidene Chloride, August 1985 ("HAD").

In this instance the test rule was prompted by the decision of the Office of Air Quality Planning and Standards ("OAQPS") not to regulate VDC under the Clean Air Act. OAQPS 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, including a single positive bioassay in the Swiss mouse, 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; that the evidence of carcinogenicity is limited; and that, even if carcinogenicity were assumed, the possible human risks utilizing worst-case assumptions are insufficient to justify regulation.

EPA has now proposed 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 believes that the proposed testing is unnecessary and urges the Agency to reconsider for the following reasons:

-- There is a large body of existing data regarding oncogenic effects and

regarding pharmacokinetic and metabolic effects and their relationship to toxicity. Much of these data are now being submitted for the record.

-- The scientific community is now looking at the use of pharmacokinetics and metabolism data to improve carcinogenicity risk assessments. The Workshop on Pharmacokinetics in Risk Assessment, organized by the National Academy of Sciences, sponsored by EPA with added support from the National Institutes of Environmental Health Sciences and the American Industrial Health Council, held in Washington, D.C., on October 7 to 10, 1986, brought together scientists to discuss recent state-of-the-art approaches in this area.

-- When pharmacokinetics and metabolism data are considered under state-of-the-art risk assessment methods, the Agency should conclude that VDC poses

no carcinogenic risk to humans through manufacture or processing.

-- The CMA VDC Panel has conducted a survey of manufacturers and processors to improve EPA's exposure assessment. Data from the survey indicates that emissions are considerably lower than estimated under EPA's worst-case analysis. Manufacture and processing are unlikely to result in significant human exposure.

-- The record, as supplemented with the voluminous studies and articles being submitted by the CMA Panel, does not support the findings that the Agency must make before issuing a test rule under Section 4(a)(1)(A) of TSCA.

These comments are organized into three sections as follows:

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 long-term animal toxicity and/or carcinogenicity

studies on VDC. Substantial research has been conducted into the metabolic pathways and pharmacokinetic changes encountered in various species and strains exposed to VDC. There is a sound scientific basis for understanding the positive findings in the Swiss mouse. Toxicologists 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 the circumstances under which a reviewing 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. When all available data are included, the record fails to support the proposed findings under Section 4(a)(1)(A).

The record shows that exposures from the manufacture and processing of VDC do not present an unreasonable risk -- a conclusion supported by the Agency's decision that VDC should not be regulated under any section of the Clean Air Act even if carcinogenicity were assumed. The evidence of minimal exposure, the information regarding inter-species metabolic differences, the negative oncogenicity test data and the

negative epidemiology data demonstrate that EPA 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 toxicology and exposure information permits the reasonable determination or prediction of the risk to health from 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 another oncogenicity 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 toxicology and exposure 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 AN ONCOGENIC RISK TO HUMANS

The potential oncogenicity of VDC and relevant metabolic and pharmacokinetic differences among animal species have been studied extensively. Although one study produced positive results, a consensus has developed among scientists who have studied the matter regarding the mechanism by which the tumors were produced. The oncogenic response, or lack thereof in species studied correlates with the extent to which the species metabolizes VDC to its toxic metabolites. An increased production of toxic metabolites in the mouse causes an increase in several toxicity endpoints. The oncogenic response in the Swiss mouse correlates with a high level of toxicity. The absence of an oncogenic response in other species correlates with lower levels of toxicity, which in turn correlate with reduced production of toxic metabolites.

A. Toxicology Data Suggest that VDC Oncogenicity is Mediated through Recurrent Tissue Damage.

Animal bioassays with VDC have been uniformly negative, with the one noteworthy exception cited by the Agency. Tumors were produced in the kidneys of Swiss mice in the Maltoni inhalation study at concentrations of VDC that were

notably toxic and near the acutely lethal concentration.2/ The record contains evidence of the greater sensitivity of this strain of mouse to VDC and of the toxic effects of that sensitivity. The single positive oncogenicity study appears to be related to the significant tissue injury in male mice exposed to VDC.

Attached as Appendix A is a data review 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 draft 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

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2/ HAD, 1985. Maltoni, et al., 1977 reported a high degree of toxicity and mortality within one week at 200, 100 ppm and 50 ppm in the Swiss mouse (p. 10-91).

probably to the formation of toxic metabolites."3/

As the Interpretive Review explains, 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 (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.

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, 1978.

5/ EPA Criteria Document at VII-4.

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 25 ppm that an increase in kidney 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,6/ a

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6/ EPA has cited the Van Duuren skin application study suggesting that VDC acted as a tumor initiator. Results of a study for complete carcinogenic activity also conducted by Van Duuren were negative. The aforementioned tumor initiation study should not be cited as suggestive of VDC's carcinogenicity. EPA has concurred in this determination:

> "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

(Footnote continued)

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. 29-31.

In view of the disparity between the mouse kidney adenocarcinomas and the results in seventeen other long-term studies, 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, 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

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performed by Van Duuren et al. (1979)" HAD at 10-124.

on nongenetic components of cells." EPA Criteria Document at VII-8.7/

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

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)

7/ EPA cites Maltoni, 1977; Hathway, 1977; Henschler and Bonse, 1977; and Reitz, 1980.

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-3.8/

Thus, the capability now exists to evaluate the relevance to man of the positive Maltoni study and the other bioassays. EPA's scientists have noted the significance of the metabolic dissimilarities in the mouse in comparison 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 manufacture or processing of the chemical.

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 or carcinogenic 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 agrees that the study, while well conducted, may lack adequate statistical power to detect excesses of rare carcinomas. It should be

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

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 toxicological dissimilarities between the substances. Any significance placed on structural similarity between VDC and vinyl chloride is negated when the toxicity data for the two substances 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 risk.

D. Even EPA's Worst-Case Assumptions Fail to Demonstrate a Significant Risk.

EPA determined in its Notice of Decision not to regulate VDC under the Clean Air Act that, if VDC were assumed to be carcinogenic as a part of a worst-case scenario using the single positive mouse study, the possible cancer risks are small. The aggregate upper-limit value risk was calculated by the Agency to be 0.07 cases per year. (50 Fed. Reg. 32632, 32633.)9/

EPA stated:

> "[E]ven if VDC were assumed to be carcinogenic, the magnitude of the public health cancer risk is low. Using the unit risk number provided by EPA's Carcinogen Assessment Group (CAG) and preliminary emission estimates, EPA estimates the cancer risk to the most exposed individuals to be 8.3×10^{-4} and the aggregate risk to be 0.07 cases per year. Thus, the EPA has

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9/ EPA has described its "aggregate risk" estimate as follows:

> "...[T]he cumulative cancer cases per year that would result from exposure to all sources in the analysis is estimated. This measure is the aggregate risk estimate." 50 Fed. Reg. 32632.

> concluded that the available evidence does not support specific regulation of VDC as a carcinogen under any section of the Clean Air Act at this time."

Thus even if the proposed study is conducted and confirms the Maltoni Swiss mouse results, the resulting data are unlikely to alter the Agency's "worst-case" risk assessment. The upper bound risk level estimated by the Carcinogen Assessment Group was insufficient to support regulation under the Clean Air Act, even assuming that VDC is carcinogenic. A second study is unlikely to alter that analysis. Indeed, the lower emissions levels described below suggest that the level of risk under an assumption of carcinogenicity would be even lower.

The Panel submits that any risk that a new study might identify would also be insignificant. Therefore, an additional bioassay is unnecessary.

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."10/

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, while ignoring inconsistent data in other parts of the record. Similarly, a reviewing court cannot uphold a rule

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10/ 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.

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 other 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 this interpretation, a finding of unreasonable risk results from the determination (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." EPA will then rely on a presumption to satisfy the requirement of the Act -- that the potential risk be presented by the manufacture, distribution, processing, use or disposal of the substance and that it be unreasonable.

However, TSCA was not intended to authorize test rules based solely upon presumptions regarding exposure or the need for testing. The legislative history of TSCA clearly provided that EPA was expected to prove that its rules were being adopted to address unreasonable risks. Congressman Broyhill noted 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.

The law 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 the level and extent of exposure is not insignificant, and that the level and extent of 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.11/

11/ The rulemaking record to date contains only the Maltoni studies, the NTP study and the 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 are relevant to an evaluation of potential health effects.

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). However, in the HAD, the Agency concludes:

> "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.

The reasons for the HAD's 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 manufactured or processed;
- an assumption regarding releases from 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 the HAD. However, if the HAD is not used, there is a total lack of data in the record to support EPA's conclusions regarding 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 and storage tanks, and fugitive emissions. 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 manufacturers and processors

The survey revealed that many of the companies listed in the 1976 HAD no longer use VDC. Of a total of 41 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. All major processors did submit responses, and 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 1,300,400 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 responding. 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 of release 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.

Based on the previously available emissions estimates, the Agency concluded that levels of public exposure to VDC were low (50 Fed. Reg. at 32634). The recently obtained emissions data support that conclusion, suggesting emissions

an order of magnitude lower than estimated by EPA. These additionally collected data may improve the Agency's exposure assessment, and are unlikely to change the conclusion that public exposures are low. In order for a test rule to be appropriate, the Agency must demonstrate that exposures are significant.

b. The extensive data base regarding the effects of VDC exposure demonstrates that VDC manufacture or processing does not pose a health risk to humans.

The extensive toxicological 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 not pose a health risk to humans from manufacture or processing. As demonstrated in Part I of these comments, 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 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 toxicity and/or 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 additional 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 to provide the data necessary to enable the Agency to make a reasonable assessment of human risk.

Even if exposure to VDC is assumed, the extensive existing data base is sufficient to make a reasonable prediction of health effects. 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 long-term animal toxicity and/or oncogenicity 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 large body 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 long-term animal toxicity and/or oncogenicity studies, 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 Duuren, et al., 1979.

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

(14) Inhalation study with Sprague-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 now 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. Saturable metabolism and the acute toxicity of 1,1-dichlorothylene, Toxicol. Appl. Pharmacol. 47:385-393, 1979.

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

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

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

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

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

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

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

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

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

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

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

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

(14) Henck, J.W., J.F. Quast, L.W. Rampy and J.M. Norris. A comparison of four mouse strains exposed to subchronically inhaled vinylidene chloride (VDC), Report of The Dow Chemical Company, 1980.

(15) Hong, C.B., J.M. Winston, L.P. Thornberg, C.C. Lee and J.S. Woods. 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, 1981.

(16) Humiston, C.G., J.F. Quast, C.E. Wade, J. Ballard, J.E. Beyer and R.W. Lisowe. 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, 1978.

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

(18) Jaeger, R.J., L.G. Shoner and L.J. Coffman. 1,1-Dichloroethylene hepatotoxicity: Proposed mechanism of action of distribution and binding of ^{14}C radioactivity following inhalation exposure in rats, Environ. Health Perspect. 21:113-119, 1977.

(19) Jones, B.K. and D.E. Hathaway. The Biological fate of vinylidene chloride in rats, Chem.-Biol. Interactions 20:27-41, 1978.

(20) Jones, B.K. and D.E. Hathway. Differences in metabolism of vinylidene chloride between mice and rats, Br. J. Cancer 37:411-417, 1978.

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

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

(23) 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.

(24) Liebler, D.C., M.J. Meredith and F.P. Guengerich. Formation of glutathione conjugates by reactive metabolites of vinylidene chloride in microsomes and isolated hepatocytes, Cancer Research 45:186-193, 1985.

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

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(27) 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.

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

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

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

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

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

(33) McKenna, M.J., J.A. Zempel, E.O. Madrid and P.J. Gehring. The pharmacokinetics of [$^{1-14}$C] vinylidene chloride in rats following inhalation exposure, Toxicol. Appl. Pharmacol. 45:599-610, 1978.

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

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

(36) Rampy, J.W., J.F. Quast, C.G. Humiston, M.F. Balmer and B.A. Schwetz. 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, 1977.

(37) Ray, P.L. and L. Moore. 1,1-Dichloroethylene inhibition of liver microsomal calcium pump in vitro, Arch. of Biochem. Biophys. 218:26-30, 1982.

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

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

(40) 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.

(41) Reitz, R.H., P.G. Watanabe, M.J. McKenna, J.F. Quast, and P.J. Gehring. 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, 1980.

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

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

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

(45) Watanabe, P.G., R.H. Reitz, A.M. Schumann, M.J. McKenna, J.F. Quast and P.J. Gehring. Implications of the mechanisms of tumorigenicity for risk assessment, In: The Scientific Basis of Toxicity Assessment (H. Witschi, ed), 69-89, Elsevier/ North-Holland Biomedical Press, 1980.

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 the specific flaws it sees in any of the other 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 long-term toxicity and/or oncogenicity 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 species 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 (published as Quast, et al., 1986); and Quast, et al., 1983. The HAD 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 extensive data base on comparative pharmacokinetics and metabolism of VDC and the mechanism of action data indicate that the mouse is uniquely sensitive to the effects of VDC. 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 CMA 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 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 indicate that a MTD was achieved under the criteria set forth in the position paper. See, Harris, J.E., et al., Position Paper on Maximum Tolerated Dose in Oncogenicity Studies, 1986 at p.5.

This study represents the longest inhalation exposure duration (18 months) used in a laboratory investigation on toxicity and oncogenicity of VDC to date. No oncogenic response was noted in this study, in spite of what amounted to a lifetime exposure for the Sprague-Dawley rat.

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 for either species. The doses were 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. 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, 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 CD-1 mouse strains. 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 the Swiss mouse.

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 more chemically-reactive compounds (primarily 1,1-dichloroethylene oxide). These reactive substances

probably produce toxicity through reaction with biological macromolecules.

Furthermore, glutathione plays a key role in modulating the reactivity and resulting toxicity 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 or minimal (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 Has Not Demonstrated 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 informa-

tion," 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 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. This finding cannot be made 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. 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, the record does not support 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-dichloroethylene'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. The CMA exposure survey demonstrated that release of VDC from manufacturing and pro-

cessing is extremely limited and the potential for exposure small. As these comments demonstrate, the extensive existing data base is sufficient to make such a reasonable determination of the potential risks of manufacturing and processing.

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 HAD and in the EPA Criteria Document, an extensive data base on pharmacokinetics and metabolism already exists for VDC. The only purpose for additional work on pharmacokinetics and metabolism would be to gain a more precise expression for the quantitative relationship between administered and internal dose of the reactive metabolite in various species. The Panel believes such additional information is not necessary to assess potential human effects from exposure as low as ambient environmental levels resulting from the manufacture or processing of VDC. If more precise quantitative relationships were required, the experi-

mental work would require significant deviation from the proposed DEM studies.

C. The Desire for Another 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.

The Panel believes that the differential response seen in the Maltoni Swiss Mouse study, which can be explained by the experimental exposure levels for that strain of mouse and the production of high levels of toxic metabolites as a result of more extensive metabolism of VDC by mice relative to other species, 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 without another bioassay. Further oncogenicity testing will provide little, if any, additional perspective on human health effects at very low exposure levels and should, therefore, not be required.

D. Another Epidemiology Study Would Be Unlikely to Improve Upon the Existing Epidemiology Data Base.

The Agency asks whether an epidemiology study should be required in lieu of a 2-year animal bioassay. In light of the Agency's concern 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. The existing study conducted by Ott, et al., despite power limitations, represents the best study to be conducted on occupational exposure to VDC, given the magnitude of the exposure and size of the cohort. It seems unlikely, in view of the small number of producers of VDC and the similarly small number of processors, that a suitably sized cohort could be identified which would improve upon the existing epidemiology data base for VDC. In addition, VDC is frequently processed in conjunction with vinyl chloride monomer. The potential for this exposure could pose as a confounder in the interpretation of the results, as would personal risk factors known to be associated with human cancer such as cigarette smoking and alcohol consumption. It seems unlikely that the Agency could satisfy its requirements for a well-conducted epidemiology study for this compound.

E. The Panel Cannot Comment Effectively on Possible Protocol Modifications Because of Inadequate Notice.

The Agency requests comments on several possible protocol modifications.

As already stated, the Panel believes that the testing program proposed is not necessary. Nevertheless, the Panel recognizes that, under the procedures being used by EPA in Section 4 single-phase rulemaking, this is the only opportunity that the Panel will have to comment on the guidelines proposed for testing VDC. The Panel urges EPA to consider the following brief comments, should the Agency proceed with the testing as proposed.

The guidelines intended for use in the proposed DEM study in the present rulemaking were initially proposed in a rule proposed for testing cumene. 50 Fed. Reg. 46104. Neither the cumene rule nor the guideline has yet been published in final form. Therefore, the Panel has no way of knowing the extent to which the initial proposed procedures will be modified in response to the comments of interested parties. Further, the changes proposed in the present rulemaking are not definitive enough to allow a fully informed comment. As a matter of good scientific policy, EPA should either finalize the guidelines proposed in the cumene rule and simultaneously propose changes for the guideline to be used with VDC, or, alternatively, propose a specific VDC guide-

line. Either of these procedures would provide a fair opportunity for review and comment.

Similar considerations apply to the oncogenicity testing guideline proposed with changes in the present rule. EPA proposed to change this guideline in 1986, (51 Fed. Reg. 1572), but has not published a final guideline. (Dow commented on this guideline in March 1986. A copy of the Dow comments is included in these comments as Appendix B.) Thus EPA is proposing changes to a guideline before those who must respond have had an opportunity to review the Agency response to comments on the prior proposal. In order to allow meaningful comment on this guideline, EPA should first finalize the oncogenicity testing guideline, and then repropose the changes specific to the proposed VDC testing.

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 strain of 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. Indeed, new information generated by CMA shows that release of VDC from manufacture and processing is substantially less than EPA had previously estimated.

- 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 well-documented differences in metabolism and pharmacokinetics. Existing data demonstrate that man is substantially less sensitive to VDC than the mouse.

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

- The proposed testing is not necessary to enable EPA 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.

While the record is entirely adequate for risk assessment purposes and does not justify a test rule, there are steps the Agency can take to improve the data base.

- EPA should consider improving its exposure assessment, using updated information.

- EPA should also use state-of-the-art pharmacokinetics and metabolism approaches to refine its risk assessment of VDC.

These steps should enable the Agency better to use the extensive existing data to assess human risk. They should also enable the Agency to conclude, as the Panel has, that the proposed test rule is not warranted.

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Appendix A

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

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ABSTRACT

An interpretive review of the animal toxicologic and related data on vinylidene chloride (VDC) is presented. The appropriateness of extrapolating findings from the various laboratory animal species to man and the overall implications of the animal data for man are discussed. Pharmacokinetic/metabolism and biomolecular events in rodents exposed to VDC clearly demonstrate the inherent species differences which contribute to differences in target organ toxicity and in a species/strain-specific and sex-related tumorigenic response. The target organ toxicity in the rodent species is related to the capacity to biotransform VDC to reactive species with the mouse having a far greater capacity than the rat. The tumorigenic response to VDC appears to be mediated via a non-genetic mechanism, namely, recurrent tissue damage. Man, by virtue of having a slower rate of oxidative metabolism than either rodent species, is likely to be less sensitive to the toxic effects of VDC than the rat and significantly less sensitive than the mouse. Exposure to VDC concentrations not causing cytotoxicity would be unlikely to result in adverse health effects in man.

1. INTRODUCTION

The results of several long-term inhalation and ingestion studies on VDC (Rampy et al., 1977; Humiston et al., 1978; McKenna et al., 1980; Maltoni et al., 1977, 1980; Viola and Caputo, 1977) have shown that the mouse is more sensitive than the rat or the hamster to toxic effects of VDC; mice exposed to 25 ppm showed liver and marked kidney changes whereas 25 ppm exposure of hamsters was a no-toxic effect concentration and 75 ppm exposure of rats caused only minimal, reversible liver changes. Furthermore, only following lifetime exposure of mice to vapor concentrations that were markedly toxic and near the acutely lethal level (Maltoni et al., 1977, 1980) was a tumorigenic response observed. Various shorter term studies have demonstrated significant differences between the rat and mouse in the expression of frank toxicity. The objective of this interpretive review is to present biological evidence that is relevant to the assessment of safety of man exposed to VDC at permissible levels in the workplace, or to trace quantities that may exist in the ambient environment.

2. ANIMAL TOXICOLOGICAL AND RELATED DATA

A. The Mouse is More Sensitive to the Toxic Effects of Vinylidene Chloride Than the Rat or the Hamster.

A direct comparison study to delineate the differences between male CD rats and male CD-1 mice following exposure to various vapor

concentrations of VDC up to 60 ppm, 23 hours/day, was conducted by Short et al., 1977. After 2 days of exposure to 60 ppm VDC, mortality differences between the species were dramatic, 80% mortality in the mice and 0% in the rats. VDC was observed to produce a greater effect as measured by elevated serum enzymes, in the liver of the mice than in the rats. A dose-related increase in both serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT) occurred in mice exposed to VDC for one day. The serum enzymes in the rats were also increased, however, the increase, which was evident after the 2nd day of exposure to 60 ppm, was not nearly as large as that observed in the mice (Table 1).

TABLE 1

Effect of Vinylidene Chloride Exposure on Serum Enzymes in Male Rats and Mice

Days Exposure	Serum Enzyme	VDC - (ppm) Rats[a] 0	Rats[a] 60	Mice[b] 0	Mice[b] 60
1	SGOT	66±10	74±6	56±8	1946±271
	SGPT	28± 2	44±7	32±6	3043±209
2	SGOT	63± 4	264±33	82±30	751±150
	SGPT	34± 4	198±29	38±4	1112±226
3	SGOT	81± 4	238±47	64±14	no sur-
	SGPT	34± 6	122±29	29±2	vivors

[a]Control and 60 ppm n = 5.

[b]Control n = 4 or 5; 60 ppm day 1 n = 4, day 2 n = 2.

Adapted from Short et al., 1977

The toxicity to the liver of the mice and rats as revealed by the elevation of serum enzymes, was confirmed by histopathologic observations. Examination of kidney tissue of the CD-1 mice showed the kidney also to be a target organ with all the mice exposed to 15, 30 or 60 ppm VDC having severe tubular necrosis after 1 or 2 days of exposure; no kidney toxicity was observed in the rats at 60 ppm.

Longer-term exposure of Sprague-Dawley, CD and Alderley Park rats to VDC via inhalation or ingestion likewise revealed the liver to be the target organ in this species. Specifically, the results of a 90-day toxicity inhalation study and a two-year toxicity and oncogenicity study of Sprague-Dawley rats to 25 or 75 ppm VDC, 6 hours/day, 5 days/week, showed a minimal exposure-related effect characterized as a midzonal hepatocellular fatty change. This change ~~occurred~~ was observed after 30 and 90 days in the 90-day study and after 3, 6 and 12 months in the 2-year study (Balmer et al., 1976; McKenna et al., 1980). The non-progressive liver change in the rats was readily reversible on cessation of the exposure after 18 months in the 2-year study (McKenna et al., 1980). No toxicologically significant exposure-related changes were observed in serum enzymes values in either study.

Lee et al., 1977 reported that the liver of CD rats exposed to 55 ppm VDC, 6 hours/day, 5 days/week for periods up to 12 months, showed marked or severe focal, disseminated vacuolization indicative of fatty change. No persistent change was found in serum enzyme values. Gage, 1970 reported that Wistar-derived Alderley Park rats

exposed to 500 ppm VDC, 6 hours/day, 5 days/week for 4 weeks showed liver cell degenerative changes whereas at 200 ppm no liver toxicity was observed. Serum enzymes determinations were not made in this study.

A 90-day toxicity study incorporating VDC in the drinking water of Sprague-Dawley rats at concentrations of 60, 100 or 200 ppm (equivalent average doses 6, 10 or 19 mg VDC/kg body weight/day for male rats and 8, 13 or 26 mg/kg/day for female rats) showed minimal hepatocellular fatty changes in rats ingesting 200 ppm VDC. The changes were not progressive in nature as demonstrated by the results of the 2-year toxicity and oncogenicity drinking water study conducted at the same concentrations (Humiston et al., 1978). The group of male rats ingesting 200 ppm VDC over a 2-year period showed, in addition to minimal hepatocellular changes, an increased incidence of periportal hepatocellular hypertrophy. The female rats at all dose levels showed minimal hepatocellular fatty change and periportal hepatocellular hypertrophy.

Species differences were likewise observed relative to the maximum dose tolerated by rats and mice in inhalation studies conducted. Specifically, histopathologic examination of animals on these studies established that 25 ppm in the mouse and 200 ppm in the Sprague-Dawley rat exceeded the maximum tolerated dose. Long-term studies on rats, Sprague-Dawley and Wistar, revealing that the highest level of inhaled VDC tolerated by rats was less than 200 ppm

were reported by Maltoni et al., 1977, 1980; Viola and Caputo, 1977. After only two sequential daily exposures of 4 hour duration to 200 ppm, VDC produced strong toxic effects, namely, fatty degeneration in the liver and early necrotic changes of renal tubuli in the Sprague-Dawley rat (Maltoni et al., 1977, 1980). The highest "bearable" level for prolonged exposure was 150 ppm. Likewise, Viola and Caputo, 1977, reported that the high exposure level in their original study on Wistar rats was lowered from 200 ppm to 100 ppm in the 6th month to avoid toxic reactions from occurring during the remainder of the 12-month study. A second study by these investigators was conducted on the Sprague-Dawley rat at 100 ppm and 75 ppm VDC; the pathologic findings in this study have not been reported.

A study on Swiss mice revealed high mortality and severe toxic effects as a result of exposure, 4 hours/day, to VDC vapor concentrations of 200 or 100 ppm for 2 days, and of 50 ppm for 4 days, and the mice exposed to 25 ppm reportedly showed severe toxic effects in kidneys and liver (Maltoni et al., 1977, 1980; Maltoni, 1977a). Based on the severity of the histopathological changes, 25 ppm was a concentration that exceeded the currently acceptable maximum tolerated dose for mice on a long-term study.

B. The Response Observed in Swiss Mice is Species/Strain-, Sex- and Dose-Related.

The response in the kidney of Swiss mice is apparently unique to that strain and is associated with the degree of toxicity expressed in the target organ. Strain specific toxicity data reported from two comparison studies revealed exposure-related signs of toxicity including mortality, lowered mean body weights, increased liver and kidney weights and increased serum glutamic pyruvic transaminase with significant differences existing between the sexes (Maltoni, 1977a; Henck et al., 1980). Maltoni, 1977a reported a sex-related difference in mortality in the various strains exposed to 200 ppm VDC, 4 hours/day for 2 consecutive days. Mortality among the male mice, and particularly the Balb/c and Swiss male mice was greater than that of the females:

TABLE 2

Mortality in Various Strains of Mice Exposed to 200 ppm Vinylidene Chloride

Mouse Strain	Mortality Rate	
	Male	Female
Balb/c	24/30	0/30
Swiss	51/60	0/60
C_3H	17/30	11/30
$C_{57}Bl_6$	7/30	0/30

The major histopathologic changes in these strains of mice reportedly occurred in the kidneys and liver with the Swiss male mice showing a marked effect.

A comparison study has been conducted on four strains of mice, Ha(ICR), $B_6C_3F_1$, CD-1 and CF-W, a strain of Swiss-Webster derived mice believed to be genetically comparable to Maltoni's Swiss mouse (Henck et al., 1980). The mice were exposed to 55, 100 or 200 ppm VDC for 6 hours/day, 5 consecutive days/week for a total of 10 exposures. No-exposure related mortality was observed among the mice exposed to 55 or 100 ppm. At 200 ppm male Ha(ICR), CD-1 and CF-W mice had higher mortality rates than the females of the respective strains, but no sex-related differences in mortality was observed in the $B_6C_3F_1$ mice (Table 3).

TABLE 3

Mortality in Various Strains of Mice Exposed to 200 ppm Vinylidene Chloride

Mouse Strain	Mortality Rate	
	Male	Female
Ha(ICR)	6/10	4/10
$B_6C_3F_1$	10/10	10/10
CD-1	10/10	0/10
CF-W	10/10	1/10

Gross and histopathologic examination of these strains of mice showed that the male mice at all exposure levels had a marked degree of nephrotoxicity with renal failure which accounted for the mortality. Renal toxicity was insignificant in all female mice when

compared to the male mice of the same strain. The cause of death in the Ha(ICR) and $B_6C_3F_1$ female mice was reportedly associated with acute hepatotoxicity.

The greater sensitivity of the Swiss mouse, and particularly the male mouse, to the toxic effects of VDC has been correlated with a tumorigenic response after repeated exposure to a concentration of 25 ppm. This concentration, which was near the lethal concentration (50 ppm) for the Swiss mice, produced marked changes in the kidneys of the mice. Exposure to 10 ppm, a concentration producing significantly less toxicity, did not result in a tumorigenic response.

No tumorigenic response was observed in a third species, the Chinese hamster, following inhalation exposure of 25 ppm VDC, 4 hours/day, 4 days/week for 1 year and held for 1 year post-exposure period before termination (Maltoni et al., 1977, 1980). No tumorigenic response was observed in Sprague-Dawley rats following exposure to 25 or 75 ppm VDC, 6 hours/day, 5 days/week for 18 months and held for observation for an additional 6 months (McKenna et al., 1982). Likewise no statistically significant increase in tumorigenic response was observed in CD rats exposed to 55 ppm, 6 hours/day, 5 days/week for 12 months or after 10 months of exposure followed by up to 12 month observation (Lee et al., 1978; Hong et al., 1981). No tumorigenic response was observed following oral administration via gavage of VDC in bioassays with the rat or the mouse (NCI, 1980;

Maltoni et al., 1977, 1980). NCI, 1982 reported that no tumorigenic response had been observed in a 2-year study in Fischer 344 rats, at dose levels, 1 or 5 mg/kg/day, nor in $B_6C_3F_1$ mice given 2 or 10 mg/kg daily. Maltoni et al., 1977, 1980 reported no tumorigenic response in Sprague-Dawley rats administered via gavage 20, 10 or 5 mg/kg/day and 0.5 mg/kg/day for 4 or 5 days/week for 1 year and held for 1 year post-exposure period before termination. Humiston et al., 1978 reported no tumorigenic response in Sprague-Dawley rats maintained on drinking water containing up to 200 ppm VDC and providing doses as high as 26 mg/kg/day.

C. The Toxicity and Tumorigenicity in Mice Correlates With the Greater Capacity of the Mouse to Metabolize Vinylidene Chloride.

In an attempt to understand the differences between the mouse and the rat, studies were designed to characterize the pharmacokinetics and metabolism in various strains of both rodent species. A comparison of the overall fate of inhaled or ingested VDC in rats and mice showed that the major differences were quantitative rather than qualitative. The most conspicuous difference was in the greater amount of the parent compound excreted via the pulmonary system by the rat as compared to the mouse following an oral dose of 50 mg/kg (Jones and Hathway, 1978a). Twenty-eight percent (28%) of the administered dose of VDC was excreted unchanged via the lungs of

Wistar derived Alderley Park rats whereas in the Alderley Park mice only 6% of the administered dose was thus excreted. McKenna et al., 1978 reported that Sprague-Dawley rats administered the same dose, 50 mg/kg, excreted 19% of the administered dose as unchanged VDC via the pulmonary system.

A major quantitative difference in the metabolism of VDC between the rat and mouse was in the considerably greater amount of N-acetyl-S-cysteinyl acetyl derivative formed by the mouse (Jones and Hathway, 1978a).

The quantitative differences in the metabolism of VDC between the species are attributable to a combination of physiological and biochemical factors. The initial step in the metabolic pathway for VDC (Figure 1) in mammals appears to be the epoxidation of VDC catalyzed by microsomal monooxygenases with further biotransformation, via two pathways, one to chloroacetic acid via rearrangement of the metabolite (I) 1,1-dichloroethylene oxide to (II) chloroacetyl chloride and (III) monochloroacetic acid, and the other ultimately to the glutathione conjugate, N-acetyl-S-cysteinyl acetyl derivative, (IV) N-acetyl-S-(carboxymethyl) cysteine, catalyzed by glutathione-S-transferases which are thought to have a physiological role in initiating the detoxification of potential alkylating agents (Boyland and Chasseaud, 1969). Specific epoxide-hydrating pathways appear to be of minimal significance in the metabolism of VDC to reactive species (Andersen et al., 1980). Since the mouse possesses high monooxygenase activity relative to the rat (Oesch et al., 1977;

Oesch, 1973), a greater proportion of VDC administered to the mouse is metabolized to the reactive metabolite, 1,1-dichloroethylene oxide. The relative proportions of the N-acetyl-S-cysteinyl acetyl derivative arising through the reaction of 1,1-dichloroethylene oxide with glutathione, in the mice and rats parallel with activities of liver glutathione-S-epoxide transferase in these species (Hayakawa et al., 1974). Since the mouse, however, excretes greater than expected amounts of the N-acetyl-S-cysteinyl acetyl derivative, it would appear that the greater production is due to the higher cytochrome P-450 activity which is found in the organs of the mouse (Litterst et al., 1975). This observation (Jones and Hathway, 1978a) is consistent with results of a pharmacokinetic comparison study reported by McKenna et al., 1977, 1979, in that not only was metabolism of VDC greater in the Ha(ICR) mouse than in Sprague-Dawley rat exposed to 10 ppm VDC for 6 hours, but the production of the reactive metabolites in the target tissues for VDC-induced toxicity was markedly greater in the mouse. The fact that the enhanced production of reactive VDC metabolite in the mouse tissue could not be solely attributed to the increased metabolism of VDC over that of the rat was indicated on normalization of the binding data for differences in metabolism. Thus the ratios of covalently bound ^{14}C-activity/gram of protein in the liver and particularly in the kidney of the mouse to the total VDC metabolized by the mouse were increased relative to ratios determined for the rat. The data obtained from this comparison study are summarized below:

TABLE 4

Vinylidene Chloride Metabolism and Covalently Bound ^{14}C-Activity in Male Sprague-Dawley Rats and Ha(ICR) Mice (10 ppm, 6 Hour Exposure)

Animal Species (Strain)	A Metabolized VDC (mg/Eq/kg)	Tissue	B Covalent Binding (ug Eq ^{14}C-VDC/g Protein)	Ratio B/A
Rat (Sprague-Dawley)	2.84±0.26	Liver	5.28±0.14	1.86
		Kidney	13.14±1.25	4.63
Mouse (Ha(ICR))	5.27±0.74	Liver	22.29±3.77	4.23
		Kidney	79.55±19.11	15.09

All values are x ± S.E.; n = 4.

Adapted from McKenna et al., 1979

McKenna et al., 1977, 1979 furthermore reported that the time course for the disappearance of covalently bound ^{14}C-activity from the liver and kidney of Sprague-Dawley rats and the liver of CD-1 mice exposed to 5 ppm or 100 ppm was consistent with those observed for normal protein turnover in rodent tissues, $t_{1/2}$ 51-65 hours (Omura et al., 1967). However, the time course for covalently bound ^{14}C-activity in mouse kidney was exposure-concentration dependent. At a concentration of 100 ppm the ^{14}C-activity was persistent ($t_{1/2}$ >500 hours), whereas at 5 ppm the time course was consistent with normal turnover time. The observed enhanced production in the mouse of covalently bound ^{14}C-activity in the liver (22.29 vs. 5.28 ug Eq ^{14}C-VDC/g protein) and particularly in the kidney (79.55 vs. 13.14 ug Eq ^{14}C-VDC/g protein) and the dose-dependent time course for disappearance of the ^{14}C-activity from the kidney correlate with the

reported greater susceptibility of the mouse relative to the rat to the toxic effects of VDC in these target organs and the tumorigenic response in the kidneys of Swiss mice following exposure to concentrations producing marked toxicity.

The transformation of the 1,1-dichloroethylene oxide to chloroacetic acid, via the second pathway, is a potentially saturable process (Hathway, 1977). Therefore since the availability of both 1,1-dichloroethylene oxide and its rearrangement product, chloroacetyl chloride is greater in the mouse than in the rat due to increased cytochrome P-450 activity in the mouse, the potential of these reactive species to bind with macromolecules is likewise greater. Thus saturation of the chloroacetic acid process is likely to be more significant in the mouse than in the rat (Jones and Hathway, 1978a).

D. The Mechanism of Action for the Vinylidene Chloride-Induced Tumors in the Mouse appears to be Non-Genetic.

The potential of VDC to cause DNA alkylation, DNA repair, and/or DNA replication with associated tissue damage in the rodent target organs has been researched in male Sprague-Dawley rats and male CD-1 mice exposed to 10 ppm and 50 ppm for 6 hours (Reitz et al., 1980).

Overall alkylation of DNA by VDC was minimal in both kidney and liver of the rat and mice following exposure to 50 ppm or 10 ppm and DNA repair, measured directly in the mice, showed a very small but

significant increase only in the kidneys of mice exposed to 50 ppm VDC (Table 5).

Failure to demonstrate significant genetic effects at the tumorigenic doses of VDC in mice suggests that the tumors in the kidneys of mice were unlikely to be mediated by direct genetic interaction.

There are a variety of indirect processes which can influence the tumor incidence during an animal bioassay. One such process is the production of recurrent cytotoxicity with concurrent cell death and subsequent cellular regeneration (Reitz et al., 1980a; Watanabe et al., 1980). This process is frequently encountered in animal biossays were maximally "tolerated" doses of chemical are administered in order to increase the chances of detecting a carcinogenic response.

During chronic administration of cytotoxic doses, DNA replication is stimulated in the affected tissues. Since there is a tiny, but still finite chance for error in each replication system, the net effect may be to increase the spontaneous mutation rate and ultimately affect the tumorigenic process.

Another consequence of increasing cell division is that the relative rates of DNA repair and DNA replication are altered. This may be very important because there is evidence that the existing DNA has been copied during replication. Consequently, repair becomes less

effective in protecting cells from the consequences of genetic damage after cellular replication. It appears that this type of cytotoxicity occurs in mice exposed to vinylidene chloride at near acutely-lethal vapor concentrations. eg., 25 ppm.

TABLE 5

DNA Alkylation and DNA Repair in Tissue of Mice and Rats Exposed to Vinylidene Chloride; Ratio of Treated Animals to Controls

Species/Exposure/ Tissue	Alkylations/ Nucleotide ($\times 10^6$)	DNA Repair Ratio[a] (Observed/Expected[b] ± 95% Confidence Limits)
Mouse - 50 ppm		
Kidney	30	1.38±0.090*
Liver	6.1	1.16±0.363
- 10 ppm		
Kidney	11	1.16±0.255
Liver	0.94	0.764±0.222
Rat - 10 ppm		
Kidney	2.0	N.A.
Liver	0.87	N.A.

[a]Repair ratio of 1.0 indicates little or no repair is present; any increase above 1.0 is taken as indication that prior DNA damage has occurred.

[b]Observed hydroxy urea-resistant TdR incorporation to expected using control data.

*Ratio significantly greater than 1.0 ($p<0.05$, t-test).
N.A. - not available.

Adapted from Reitz et al., 1980b.

Reitz et al., 1980b reported dose-related tissue damage and increased DNA replication (Table 6) in the kidneys of mice. Effects comparable to those observed in the mouse kidney were not observed in the liver of either species or in the kidneys of the rats.

TABLE 6

DNA Synthesis in Tissues of Vinylidene Chloride Exposed to Rats and/or Mice

	VDC Concentration - ppm		
	Mouse		Rat
	10	50	10
DNA Synthesis[a]			
Kidney	7.72*	24.7*	2.20*
Liver	1.20	2.45	0.88

[a]DNA synthesis was estimated by determining specific radioactivity of DNA following (^{3}H) thymidine ((^{3}H)TdR) injection. (^{3}H)TdR was injected 48 hours after the treatment suspected of causing cytotoxicity. A positive response is indicated by an increased rate of incorporation of (^{3}H)TdR into DNA relative to a control group, resulting in a ratio greater than 1.0.

*Radio significantly greater than 1.0 ($p<0.05$, t-test).

Adapted from Reitz et al., 1980b.

The tissue damage in the kidneys of mice exposed to 50 ppm VDC for 6 hours determined directly after cessation of exposure at various times up to 192 hours thereafter showed toxic nephrosis immediately after exposure, progressive nephrosis at 8 and 24 hours, and regeneration after 96 hours. At the 10 ppm concentration slight dilation and swelling were observed immediately after exposure with nephrosis evident after 96 hours post-exposure.

3. IN-VITRO MUTAGENICITY TESTS

In-vitro comparison mutagenicity tests conducted on VDC using tissue extracts from rats and mice have given results consistent with species differences observed in in-vivo studies. Jones and Hathway, 1978b reported that Salmonella typhimurium strain TA1535 and TA100 exposed to VDC gave a weakly mutagenic response in the presence of S-9 mixture from normal mouse liver or kidney and a strongly mutagenic response in presence of S-9 mixture from Aroclor 1254-induced mice. In rats liver preparation from Aroclor-induced animals, gave a positive, but weak, bacterial mutagenic response, while preparations from normal animals were inactive. VDC was also shown to be weakly positive in Salmonella typhimurium strain TA 1535 and TA100 mediated by liver S-9 mixture from a human subject who had been on long-term phenobarbitone medication, but no bacterial mutagenic response was observed in the same test systems mediation by liver S-9 mixture from a normal human subject or from normal marmosets.

4. SIGNIFICANCE FOR MAN

The pharmacokinetic/metabolism and biomolecular data on VDC exposed rats and mice clearly indicate that inherent species differences contributed to the observed differences in target organ toxicity, and in the tumorigenic response in the kidney of the mice following exposure to concentrations in excess of a maximum tolerated dose

(associated with significant organ toxity) for a long-term study. The capacity to metabolize VDC to the reactive metabolites correlated with the sensitivity to the toxic effects of VDC observed in these species. The mouse which has a greater capacity to metabolize VDC than does the rat, is more sensitive to VDC-caused tissue injury and tumorigenicity.

For many xenobiotics, including the halogenated hydrocarbons, the rate of oxidative metabolism appears to be roughly related to the body surface area (Weiss et al., 1977; Schmidt-Nielsen, 1970; Pinkel, 1958). Thus in man, the total amount of reactive species formed by the metabolism of VDC would be less than that formed by the laboratory rodents. This observation is consistent with the findings of Reitz et al., 1980 and Jones and Hathway, 1978a, who demonstrated that the rat metabolizes less VDC than the mouse and Walker, 1978 who reported significant metabolic dissimilarities exist between man and the mouse relative to the monooxygenases which catalyze the metabolism of VDC to the reactive species.

The correlation between metabolism and toxicity was confirmed at the macromolecular level. At concentrations causing degenerative/regenerative changes in the kidneys of mice, there was significant binding of the reactive species to cellular macromolecules, and a significant increase in DNA replication, with little effect upon DNA repair. Thus the probable mechanism of the tumor formation was shown to be primarily non-genetic.

The results of the mechanism studies indicate that the exposure of man to concentrations which do not produce cytotoxic effects would be unlikely to produce a tumorigenic response. Furthermore, the metabolic differences seen in the rodents and man make it unlikely that organ injury would result from exposure of man to the concentration reported in the ambient environment or in the workplace. The lack of adverse health effects reported by Ott et al., 1976 in a health survey study of 138 employees exposed to up to 70 ppm VDC is supportive of the finding that man is less susceptible to VDC than the rat and far less than the mouse.

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Appendix B

Comments of

The Dow Chemical Company

on

EPAs Revision of

Toxic Substances Control Act (TSCA)

Test Guidelines

(Docket #OPTS-42079)

51 Federal Register 1522

March 20, 1986

SL 068301

V. CHRONIC EXPOSURE

40 CFR 798.3300 Oncogenicity

40 CFR 798.3300 (b)(5)

Proposed: "It is necessary that the duration of oncogenicity tests comprise the majority of the normal life span of the strain of animals to be used. This time period shall not be less than 24 months for rats and 18 months for mice, and ordinarily not longer than 30 months for rats and 24 months for mice." 50 Fed Reg 39419.

Comment: In general Dow agrees with the use of these exposure durations for oncogenicity studies in rodents; however, EPA should permit some flexibility regarding this matter. Considering the cost and resources required on overall effort necessary to conduct a rodent oncogenicity study, EPA should not adopt a guideline that could result in the invalidation of an otherwise acceptable oncogenicity study simply because its exposure duration did not meet an absolute requirement of 24 months.

Recommendation: The Guidelines as published in 1985 should not be changed.

40 CFR 798.3300 (b)(6)(i)(A)

Proposed: "The animals shall receive the test substance in their diet, dissolved in drinking water or given by gavage or capsule for a period of at least 24 months for rats and 18 months for mice." 50 Fed Reg 39419.

Comment: Dow agrees with the route of exposure specified in this section. However, the Guidelines should be modified to indicate that the test animals should receive the test substance for the duration of the observation (exposure) rather than specifying an exact time period. This would avoid the invalidation of an otherwise acceptable study in rats, for example, if the study ended at 23 instead of 24 months due to excessive mortality in any group, including controls, simply because it failed to meet the 24-month exposure requirement.

Recommendation: The Guidelines should not require fixed time periods for exposure but should simply indicate that dosing should occur for the duration of the study.

40 CFR 798.3300 (b)(7)(i)

Proposed: "Each animal shall be handled and its physical condition appraised at least once each day." 50 Fed Reg 39419.

Comment: Dow agrees with this proposal although our current protocols specify that test animals be observed twice daily.

However, it is not necessary that the animal be handled in order to detect overt signs of toxicity or assess its overall health status.

Recommendation: The Guidelines should be changed to read, 'The physical condition of each animal shall be appraised at least once each day.'

40 CFR 798.3300 (b)(8)(i)-(ii)

Proposed: 'The rate of air flow shall be monitored continuously and recorded at intervals of at least once every 30 minutes. During each exposure period the actual concentrations of the test substance shall be held as constant as practicable...' 50 Fed Reg 39419.

Comment: The requirement to record chamber air flow every 30 minutes is unwarranted and excessive. The actual chamber concentration of the test material should be determined analytically as frequently as possible during an inhalation exposure and not by calculation from air flow. Analytical determination of chamber concentration every 30 minutes is about the best that can be expected during a typical study involving three exposure groups and a control group; this results in approximately 12 measurements per chamber per 6-hour exposure period. Any appreciable changes in air flow are readily apparent by concomitant changes in the chamber concentration. The chamber analyses indicate that the actual chamber concentration is substantially different from the intended target concentration, the air flow should be rechecked and any deviation from the intended air flow should be recorded at the time an adjustment is made. However, inhalation chamber concentrations should not routinely be controlled by changing the air flow rate since this would result in different air flows in the various chambers in a given study. Rather the air flow rate should be held constant, and the chamber concentration should be adjusted by changing the rate of chemical delivery to the chamber. Hence, it is only necessary to set and record the chamber air flows at the beginning of each exposure period under these operational circumstances.

Recommendation: The rate of air flow should only be recorded at the beginning of the exposure period.

40 CFR 798.3300 (b)(9)

Proposed: 'At 12 months, 18 months and at sacrifice, a blood smear shall be obtained from all animals. A different blood count shall be performed on blood smears from those animals...differential blood counts shall be performed for the next lower group(s)...' 50 Fed Reg 39419-39420.

Comment: For most oncogenicity studies the need for interim (and terminal) blood smears is not cost-effective and is negated by the

conduct of extensive histopathologic examination of an extensive list of tissues which gives much more definitive diagnostic data.

Recommendation: Delete the mandatory requirement for obtaining interim or terminal blood smears of all animals.

40 CFR 798.3300 (e)(3)

Proposed: The proposed changes would require all the specific information listed in this paragraph to be part of the test report. 50 Fed Reg 39420.

Comment: Dow disagrees with the changes proposed in this paragraph. The proposed requirements are excessive and provide no means of handling exceptions based upon the type of study conducted. Although many of the required data are relevant to a well-conducted study, it seems clear that each and every specific element of information is not relevant to each study.

Recommendation: Delete the proposed changes.