CHEMICAL MANUFACTURERS ASSOCIATION

January 9, 1984

GERALDINE V. COX, Ph.D.
Vice President
Technical Director

Robert M. Bruce, Ph.D.
Environmental Criteria and
Assessment Office (MD-52)
U.S. Environmental Protection
Agency
Research Triangle Park, North Carolina 27711

Re: Health Assessment Document for Vinylidene Chloride
EPA 600/8-83-031A

Dear Dr. Bruce:

On October 31, 1983, the Environmental Protection Agency announced in the Federal Register the availability of an external review draft of its Health Assessment Document for Vinylidene Chloride (VDC). 48 Fed. Reg. 50153.

The Vinylidene Chloride Panel of the Chemical Manufacturers Association (CMA) represents all U.S. manufacturers of vinylidene chloride and a substantial portion of the industry, both domestic and foreign, which converts vinylidene chloride into other products. The accompanying materials are the initial comments of the Panel on the preliminary Draft Health Assessment Document for Vinylidene Chloride.

Following discussions on the topic with Agency staff, on December 12, 1983, CMA requested a 90-day extension of time in which to prepare and supply the Agency with its comments on the preliminary Draft. CMA was advised by Agency staff on December 29, 1983, that the request for an extension of time in which to file comments was denied.

The Panel is disappointed that, at this juncture, it can only provide these brief comments on the Agency's draft. Given the difficulty in developing a properly detailed response within the comment deadline, it is requested that the attached comments be considered an overview of the issues that the Panel intends to address in its presentation to the Science Advisory Board.

The preliminary Document is a substantial first effort. We agree with the tentative conclusions in the draft that: (1) certain data and information available at this stage of the Agency's review are limited. For example, we note a significant shortage of data in the areas covering sources, environmental levels, and human exposure; (2) only limited data suggests that VDC might be an animal carcinogen; and (3) the available evidence regarding the carcinogenicity of VDC, judged by International Agency for Research on Cancer criteria, is limited and insufficient to provide a firm conclusion on the carcinogenic potential of VDC in humans.

In the portion of the Document which addresses metabolism, mechanistic and related effects, the data are considerably more complete. Regretably, it is the failure of the Agency to use the information from this portion of the document in estimating potential risk to humans exposed to VDC which most troubles industry. The Agency has elected to ignore the preponderance of the data while making a quantitive carcinogenic risk estimation in man from admittedly limited (positive) data. Likewise, the ranking of vinylidene chloride as having carcinogenic potential similar to other substances recently addressed by the Agency is considerably overstated.

If you have any questions on the enclosed material, please feel free to call Dr. Has Shah of my staff at (202) 887-1192.

Thank you.

Sincerely,

Geraldine V. Cox

Geraldine V. Cox, Ph.D.
Vice President
Technical Director

cc: Joseph E. Hadley, Jr.
La Roe, Winn & Moerman

Enclosure

BEFORE THE U.S. ENVIRONMENTAL PROTECTION AGENCY

Docket No.
EPA 600/8-83-031 A

COMMENTS OF THE CMA VINYLIDENE CHLORIDE PROGRAM PANEL ON EPA'S DRAFT HEALTH ASSESSMENT DOCUMENT ON VINYLIDENE CHLORIDE

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

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

Hasmukh C. Shah, Ph.D.
Manager
Vinylidene Chloride Program
Chemical Manufacturers Association

Of Counsel:

Joseph E. Hadley
La Roe, Winn & Moerman
1120 G Street, N.W.
Washington, D.C. 20005

Chemical Manufacturers Association
2501 M Street, N.W.
Washington, D.C. 20037
(202) 887-1100

January 6, 1984

General Comments on Biologic Effects Sections

Although the preliminary Draft Health Assessment Document on Vinylidene Chloride is a rather substantial first effort at producing a Health Assessment Document on this substance, we agree with the draft, albeit tentative, Health Assessment Document conclusions that (1) certain data and information available at this stage of the Agency's review are limited; for example, we note a significant shortage of data in the areas covering sources, environmental levels, and human exposure; (2) of the substantial data on the chronic effects of VDC there is meager evidence to suggest that VDC may be an animal carcinogen; and (3) measured by criteria established by the International Agency for Research on Cancer (IARC), the evidence on VDC is limited and insufficient to provide a firm conclusion regarding the carcinogenic potential of the chemical for humans.

In the portion of the Document which addresses metabolism, mechanistic, and related effects, the data are considerably more complete. Perversely, it is the failure of the Agency to use the information from this portion of the document in estimation of potential risk to humans exposed to VDC which most troubles industry. Unfortunately the Agency has elected to ignore the preponderance of the data and has, instead, made the quantum leap from admittedly limited (positive) data to a quantitative carcinogenic risk estimation in man and estimated VDC's rank among chemical carcinogens.

There have been a total of 18 studies performed on VDC and these involved 4 rat strains, 4 mouse strains, and one hamster strain. These studies have employed all exposure routes, namely, dermal, subcutaneous, oral and inhalation. Of these studies, all but one reach negative conclusions. Specifically:

Species	Exposure Route	Findings	Reference
Sprague-Dawley rat	Inhalation	Negative	Maltoni et al., 1980, 1977
Chinese hamster	Inhalation	Negative	Maltoni et al., 1980, 1977
Sprague-Dawley rat	Gavage	Negative	Maltoni et al., 1980, 1977
Wistar rat	Inhalation	Negative	Viola and Caputo, 1977
Sprague-Dawley rat	Inhalation	Negative	Viola and Caputo, 1977
CD-1 mouse	Inhalation	Negative	Lee et al., 1977, 1978
CD rat	Inhalation	Negative	Lee et al., 1977, 1978
Sprague-Dawley rat	Inhalation	Negative	McKenna et al, 1982
Sprague-Dawley rat	Inhalation	Negative	Quast et al., 1983
Fischer 344 rat	Gavage	Negative	NCI/NTP, 1981
B6C3F1 mouse	Gavage	Negative	NCI/NTP, 1982
CD-1 mouse	Inhalation	Negative	Hong et al., 1981

Species	Exposure Route	Findings	Peference
CD rat	Inhalation	Negative	Hong et al., 19[illegible]
Ha:ICR Swiss mouse	Dermal Initiation/ Promotion	No malignant tumors	Van Duuren et al. 1980
Ha:ICR Swiss mouse	Subcutaneous Injection	Negative	Van Duuren et al. 1980
Sprague-Dawley rat	Inhalation	No brain tumors (only tissue histologically examined)	Maltoni et al., 1982
Sprague-Dawley rat	Gavage	No brain tumors (only tissue histologically examined)	Maltoni et al., 1982
3 strains	unknown	Negative	Maltoni (cited in ICAIR, 1981)

The only information which might contradict the above-listed data is drawn from a preliminary report on a study conducted by Maltoni in Italy. In that preliminary report the male Swiss mouse is said to have shown a positive reaction to vinylidene chloride at a level of 25 ppm but not at 10 ppm. Subsequently, Maltoni reported that he had been unable to replicate the tumorigenic finding in three other strains of mice.

The CMA Vinylidene Chloride Panel stresses the need for EPA to acknowledge the extensive research on VDC which has elucidated the mechanism of toxic action in animals, including the tumorigenicity in the Swiss mouse. Further, the Agency must use such

data in reaching conclusions as to the significance for man. Thus the Panel tends to agree with EPA's final Guidelines for Performing Regulatory Impact Analyses required under Executive Order 12291. Regarding carcinogens, the Guidelines state (EPA, 1984):

> A determination of the likelihood that a substance is a human carcinogen should be based on a weight-of-evidence judgment. All available information from human epidemiological studies and from animal studies should be evaluated, along with evidence from short-term tests, studies of comparative metabolism, structure-activity analysis and other relevant toxicological and biological analysis. The evaluation should consider the number and kind of tumorigenic responses and their statistical significance, as well as the quality of the available studies. Properly evaluated animal data may be used to predict human responses. (emphasis added)

In addition, EPA's ranking of vinylidene chloride as having a carcinogenic potential similar to other substances recently addressed by the Agency is considerably overstated for reasons delineated below.

EPA concluded on page 10-1 of the Document that the available pharmacokinetic data on VDC sufficiently characterize the disposition and metabolism in experimental animals including the effects of age, sex, route, species and fasting. The Panel takes the position that although actual pharmacokinetic/metabolism data on VDC have not been developed in humans, the potential biological effects in man versus the rat and mouse are predictable on a comparative physiologic and metabolic basis. Specifically understood are

the species relationships regarding: (1) the toxicity of VDC and its correlation with metabolism; (2) the metabolism; (3) the biomolecular events; and (4) the potential for expression of a tumorigenic response. The species relationships relevant to the understanding of possible carcinogenicity of VDC for humans include:

1. Toxicity

   mouse > rat > man

2. Metabolism

   mouse > rat > man

3. Biomolecular events (DNA damage in target organ)

   mouse > rat

4. Tumorigenic potential

   mouse > rat (no tumors) > man.

An interpretive review of the pertinent data, prepared for EPA's Criteria and Standards Division, Office of Drinking Water by ICAIR Systems Division, Life Systems, Inc., Cleveland, Ohio, dated October 1981 (hereafter referred to as the ICAIR document), is consistent with the views of the Panel. Pertinent statements in the aforementioned document (pages 85-91) are:

> . . . . there has been considerable work directed toward defining the mechanism of toxicity of 1,1-DCE. . . . Most of the acute and long-term toxic effects observed, e.g., hepatotoxicity, renal toxicity, mutagenicity and carcinogenicity, are probably due to the formation of toxic metabolites. It has been suggested that the acute toxicity of 1,1-DCE can be correlated to the amount of

metabolite formed. For short-term inhalation exposures, mortality occurred in rats after the formation of 25-30 mg of metabolites/kg (Andersen et al., 1979(b)). Additionally, it has been shown that mice metabolize 1,1-DCE more rapidly than rats. There is a corresponding higher mortality resulting from a given dose with mice than with rats, presumably due to the formation of a greater amount of toxic metabolite (Short et al., 1977(a); Maltoni, 1977; Jones and Hathway, 1978(b)).

The biotransformation of 1,1-DCE has been demonstrated to be a saturable process that follows Michaelis-Menten Kinetics. At low doses, below the metabolic saturation point, the majority of an administered dose is biotransformed to water soluble products which are excreted via the kidney. However, when large doses of 1,1-DCE are administered by any route and metabolism is saturated, large amounts of unmetabolised 1,1-DCE are excreted via the lungs. . . . There is also a tremendous difference in the toxic effects caused by continual exposures to 1,1-DCE compared to those caused by repeated intermittent exposures. Whereas adverse reactions including increased lethality were observed in several species following continual exposures to 1,1-DCE concentrations as low as 5 ppm, no toxic effects were observed following exposure for 8 hr/day, 5 days/week for six weeks to 100 ppm (Prendergast et al., 1967). With the intermittent exposure regimen, there was probably rapid elimination of unmetabolized 1,1-DCE between exposures, as well as opportunity for glutathione levels in organs to return to normal. Similarly, at high exposure concentrations, the acute inhalation toxicity was related to the duration of the exposure, i.e., the total amount of toxic metabolite formed when metabolism was proceeding at V_{MAX}, rather than to the ambient concentration (Andersen et al., 1979(a)). At low concentrations, it has been suggested that the rate of metabolism of 1,1-DCE is limited by the blood flow to the liver. Since the rate at which an inhaled chemical is presented to the liver is related to pulmonary uptake, it would be expected that the smaller breathing volume (liters/kg/hr) in man relative to the rat would produce a corresponding slower rate of metabolism of 1,1-DCE in man (Andersen et al., 1980(a)) and the formation of smaller amounts of toxic metabolite.

The metabolism of 1,1-DCE is generally hypothesized to proceed via oxidation of the parent compound by microsomal enzymes of the mixed function oxidase system (MFOS) to produce 1,1-dichloroethylene oxide. This compound can subsequently follow one of several pathways: reaction with glutathione to produce a water soluble metabolite which undergoes renal excretion, presumably a detoxification mechanism; reaction with macromolecules to produce covalently bound metabolites; or rearrangement to form chloroacetyl chloride. This latter compound can either react with macromolecules or under hydrolysis to form chloroacetic acid, which reacts with glutathione to form a series of water soluble metabolites . . . . It is generally believed that reaction of these metabolites, i , 1,1-dichlorethylene oxide, chloroacetyl c ride, and chloroacetic acid, with macromolecules leads to the observed toxic effects: hepatotoxicity, renal toxicity, mutagenicity, and carcinogenicity.

The extent of hepatotoxicity of 1,1-DCE appears to be related to the rate of formation of toxic metabolites relative to the rate of detoxification of these materials. Glutathione conjugation is apparently a crucial detoxification mechanism since increased susceptibility to liver damage has been demonstrated when hepatic glutathione concentration is decreased by any of several methods: fasting; pretreatment with certain chemicals, e.g., diethyl maleate; pretreatment with thyroxine; or normal diurnal variation. Conversely, thyroidectomy, which increases hepatic glutathione concentration, decreases hepatotoxicity. It has been shown that there is an increase in 1,1-DCE metabolites covalently bound to liver macromolecules, when the glutathione levels are decreased.

It has been demonstrated that a greater percentage of any orally administered dose is metabolized in mice than in rats. This has been attributed to greater activity of the cytochrome P-450 system in mice relative to rats which would lead to the formation of a larger amount of 1,1-dichlorethylene oxide and its rearrangement product, chloroacetyl chloride, in mice (Jones and Hathway, 1978(b)). This difference in metabolism is reflected in a change in the ratio of the metabolites formed. Additionally, the administration of 1,1-DCE has a much more toxic effect on

mice (oral LD_{50}:200 mg/kg) than on rats (oral LD_{50}: 1500 mg/kg). One possible explanation for this difference is that 1,1-DCE and its metabolites are equally toxic to mice and rats, but the difference in the LD_{50}represents the relative ability of the two species to metabolize 1,1-DCE to the active metabolites. It has also been shown that there are much higher levels of covalently bound 1,1-DCE metabolites in both liver and kidney in mice than in rats.

Continuing with the pertinent statements from the ICAIR document:

. . . . For 1,1-DCE, aspects of the reported carcinogenicity appear conflicting and indicate sex, species and strain specificity. In mice, the most pronounced increases in tumor incidence caused by 1,1-DCE were kidney adenocarcinoma and mammary gland adenocarcinoma in Swiss mice. However, kidney adenocarcinomas were observed almost exclusively in male Swiss mice, and neither tumor type was observed in four other strains of mice. . . .

It has been suggested that development of kidney adenocarcionmas 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 (Maltoni, 1977; Hathway, 1977; Henschler and Bonse, 1977). 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 (Reitz et al., 1980). Tumorigenic doses of dimethylnitrosamine produced relatively little tissue damage but caused a high degree of DNA alkylation and DNA repair synthesis. In contrast, tumorigenic doses of 1,1-DCE resulted in massive tissue damage but induced minimal DNA alkylation or DNA repair synthesis. These data were interpreted as suggesting that tumors observed in mice exposed to 1,1-DCE arise primarily through effects of the chemical on non-genetic components of cells.

For many xenobictics, 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 laboratory rodents. This observation is consistent with: (1) the findings of Reitz et al., 1980 and Jones and Hathway, 1978(b), who demonstrated that the rat metabolizes less VDC than the mouse; (2) Andersen et al., 1980(a) who related the slower rate of metabolism of VDC in man versus the rat to the rate of pulmonary uptake; and (3) 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 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 but not in DNA repair. Thus the probable mechanism of the tumor formation was shown to be non-genetic. 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.

The preponderance of the evidence, therefore, indicates that the exposure of man to concentrations which do not produce cytotoxic effects would be unlikely to produce a tumorigenic response. Furthermore, metabolic differences seen in the rodents and man make it unlikely that organ injury would result from exposure of man to the current ACGIH TLV of 10 ppm. The extremely low ambient levels which might exist in the vicinity of VDC manufacturing or user plants present virtually no hazard.

In vitro 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, 1978(b), reported that Salmonella Typhimurium, strains TA1535 and TA100, exposed to VDC gave a weakly mutagenic response in the presence of S-9 mixture from Aroclor 1254-induced tissues. In rats, only liver preparation from Aroclor-induced animals gave a positive, but weak, bacterial mutagenic response. VDC was also shown to be weakly positive in Salmonella Typhimurium mediated by liver S-9 mixture from a human subject who had been on long-term phenoarbitone medication, but no bacterial mutagenic response was observed in the same test systems mediated by liver S-9 mixture from a normal human subject or from normal marmosets.

In addition, exposure of V79 Chinese hamster cells to VDC atmospheres in the presence of supernatant from rat or mouse liver or in the absence of metabolic activating enzymes gave no indication of mutations (Drevon and Kuroki, 1979) (see p. 10-75 of

preliminary Draft Health Assessment Document for Vinylidene Chloride, October 1983). Cytogenetic studies conducted in bone marrow cells of rats exposed to VDC vapor concentrations of 25 or 75 ppm for 6 months showed no chromosomal aberrations (Rampy et al., 1977).

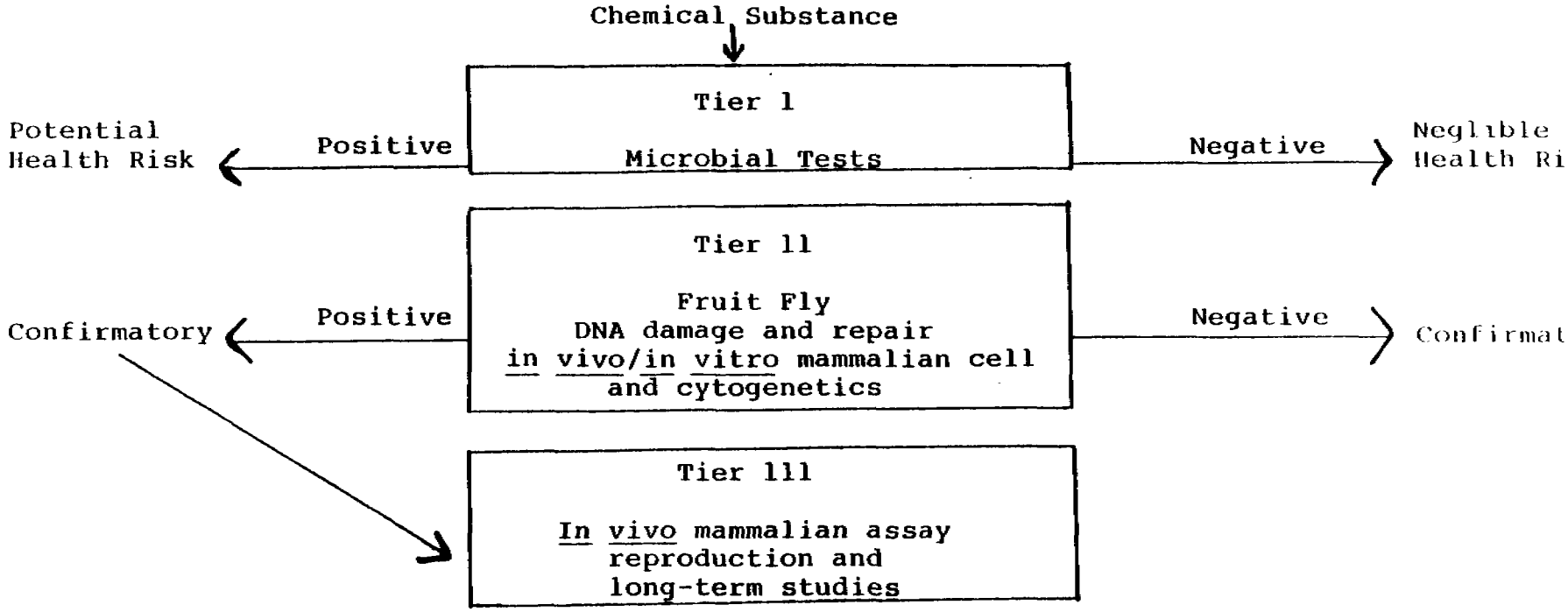
The Panel believes the interpretation of the available mutagenicity data should be made in a manner consistent with the tier system approach for mutagenicity testing of chemicals, as is diagrammed in Figure 1. The above-referenced data demonstrate that VDC does exhibit low activity in Tier I assays (microbial tests); however, Tier II/III assays (in vitro mammalian cell and cytogenetic studies, the three-generation reproduction study, as well as 17 of the 18 long-term toxicity and/or oncogenicity studies), suggest that this material lacks mutagenic/carcinogenic potential in higher organisms, including man.

Potency Indexing

A comparison using only one criterion for carcinogenic potency must have drawbacks. While a potency ranking might be useful to obtain regulatory perspective, the Panel stresses that the use of the slope in the linear risk extrapolation model to compare relative potencies assumes several points that have not been substantiated. It assumes that: (1) the linear risk extrapolation is valid; (2) all studies are of equal scientific validity; (3) the data from all animal species are equally extrapolatable to man; (4) all tumor types have equal significance; (5)

FIGURE 1

TIER TESTING APPROACH FOR MUTAGENICITY TESTING



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all compounds induce cancer by a mechanism that can be described by a linear model; and (6) all negative cancer study results are irrelevant.

Furthermore, the Panel is concerned with EPA's comparison of relative potencies and the compounding of uncertainty by a failure to explain the substantive variations between the various drafts and final Health Assessment Documents. The slope and potency of vinylidene chloride (1,1-dichloroethylene in the potency table) changed by an order of magnitude between the May 1983 Final Acrylonitrile Document and the October 1983 Vinylidene Chloride draft Document. While EPA does note that changes may be made in potency calculations as new data become available, the Agency has not identified the basis of the substantial change in this case. The draft Document neither explains why the recalculation was made nor identifies the new data underlying it. EPA should publicly justify the utility of a priority list that changes without apparent explanation or notice.

The deceptive simplicity of EPA's table of relative potencies is further underscored by its ranking of vinylidene chloride as being more potent than proven human carcinogens. The Panel suggests that a comparison of the scientific bases for assessment of relative potency would not support the rankings. In the case of vinylidene chloride, EPA's draft Document has taken very limited data and made VDC to appear a more potent carcinogen than well-established human carcinogens.

To alleviate the uncertainties associated with EPA's comparison of carcinogenic potencies, the Agency should reevaluate the entire ranking methodology and, perhaps, the objective need for such a ranking in the first place.

Production Data/Exposure Information

It should also be pointed out that in the Document preliminary data on VDC production and ambient exposure levels of VDC resulting from production losses to the atmosphere are so dated as to be no longer applicable.

For example, at one of the three production facilities, current VDC capacity is less than half the amount stated in Chapter 5. The source data underlying this statement of capacity date from 1976-1978. In the interim, conditions have changed considerably.

Similarly, the related information on ambient VDC levels contained in Chapter 7 needs updating. The data presented are not considered current based on our knowledge of the analytical techniques employed, changes in manufacturing conditions, and/or increased levels of control.

It is most strongly suggested that additional, more current and accurate data, which industry plans to submit, be substituted for the old data cited in the preliminary Draft. To be a useful regulatory tool, the final Document must include up-to-date, accurate data.

CONCLUSION

Taking a preponderance of the evidence approach, there is no evidence of VDC's carcinogenicity in the studies reported in the preliminary Draft Health Assessment Document. Only a preliminary report, which cannot be duplicated, contradicts the main body of data.

Since evidence of carcinogenicity is lacking, the preliminary Draft Health Assessment Document is unwarranted in assuming carcinogenicity for VDC. In that light, the inclusion of vinylidene chloride in a potency listing for carcinogens and the conduct of a carcinogenicity risk assessment for man become untenable. The assumptions made regarding carcinogenicity are not reinforced by a review of metabolic, pharmacokinetic, mutagenic or related data. Furthermore, there is no evidence of human carcinogenicity associated with vinylidene chloride.

Additionally, the data on vinylidene chloride production and ambient exposure levels which result from production losses to the atmosphere are out-of-date and must be brought current.

Without support for the assumptions made in the preliminary Draft, the conclusions must be regarded as incorrect based on the data presented. The data reviewed demonstrate an unequivocally negative finding on carcinogenicity and this is the only conclusion that the data allow.

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*/ All other references in these comments are included in the draft Health Assessment Document for Vinylidene Chloride.

The Panel believes modification of the ~~doc.~~ r.a. chapter will not solve the problem ē the doc., however, if the SAB should find that there may be merit in the agency's response (intentions, it is the Panel position that it be developed + placed on agenda for future public review ~~& re-reviewed before closure~~ separate because it is a conceptual item. [The Panel does not know the substance of the agency's proposed changes.]

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