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Zeb G. Bell, Jr., Sc.D.
Director
Health Administration and Toxicology
Environment, Health & Safety Department

TO: R. Bruce Dickson

DATE: March 30, 1989

RE: CMA VDC Panel Comments on ATSDR

My comments on the VDC ATSDR are provided now since I will be on the West Coast when the panel decided to have the meeting or conference call.

There are several areas where I feel we need to emphasize or more clearly state our position:

1. The one positive mice study for renal adenocarcinoma was only in male mice and we should not let the readers of our comments establish in their mind that it might be in both sexes of mice (Maltoni study cited).

2. We need to discuss the reason for the industry standard being what it is presently due to the toxic effects and not because of any carcinogenic response when the data base is reviewed in its entirety.

3. While there may be some people who would not like to make comparisons between chemicals, I believe it makes scientific sense to show that VDC cannot be placed in the same class as vinyl chloride because there is no good rationale when you know the results of VCM animal studies and the association of human tumors with VCM as opposed to any human evidence for VDC. It is important to remind the Agency that the Permissible Exposure Limits for the two substances are essentially the same but for entirely different reasons. It simply doesn't make any sense to make VDC appear as a potential human carcinogen because of structural similarity between these compounds.

4. I believe the industry has demonstrated that it is responsible because of the actions it has taken to reduce, contain, and control exposures in the workplace and the community.

5. I have marked on the attached some of my suggested changes.

Sorry I cannot be present for the meeting, but if a conference call can be arranged, I can be reached at our Torrance, CA

facility, telephone number (213) 328-7260 from 4/3-7/89 and at our Chehalis plant in Washington state, telephone number (206) 748-9196.

Zeb G. Bell, Jr., Director
Health Administration & Toxicology

Attachment

cc J.A. Barter
C.P. Blahous
J. Norris, Dow Chemical
R.L. Romano

MAR [illegible]

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March 23, 1989

WRITER'S DIRECT DIAL NUMBER

OUR FILE NO.

MEMORANDUM TO THE CMA VDC PROGRAM PANEL

After discussions with Bob Romano, Jessie Norris and Zeb Bell, I have prepared the enclosed rough cut of comments from CMA to the ATSDR regarding the Tox Profile for VDC. Panel members should review carefully the Tox Profile, with particular attention on Chapter 5 (Potential Exposure) and Sections 2.2.1.8, 2.2.2.8, and 2.2.3.8 (the carcinogenicity sections). If there are particular statements made in the Tox Profile which members feel should be responded to directly, we should incorporate those comments in this draft.

The attached attempts to incorporate arguments that were made before EPA in the general discussion of carcinogenicity as a response to those sections of the Tox Profile which address cancer issues. The draft also addresses ATSDR's conclusory statement regarding the need for additional testing.

You will notice that the due date for comments is April 14, 1989. I suggest that the Panel plan either a meeting or a conference call during the week of April 3. It would also be helpful if Panel members would provide their comments to me by April 4. I will be out of town from March 24 through April 1.

R. Bruce Dickson

RBD/mbl
Attachment

SL 064964

BEFORE THE
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
AGENCY FOR TOXIC SUBSTANCESE
AND DISEASE REGISTRY
AND
THE ENVIRONMENTAL PROTECTION AGENCY
(DOCKET CONTROL # ATSDR - ___)

CHEMICAL MANUFACTURERS ASSOCIATION VINYLIDENE CHLORIDE PROGRAM PANEL COMMENTS ON DRAFT TOXICOLOGICAL PROFILE FOR 1,1-DICHLOROETHENE

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April 14, 1989

BEFORE THE
UNITED STATES DEPARTMENT OF HEALTH AND HUMAN SERVICES
AGENCY FOR TOXIC SUBSTANCESE
AND DISEASE REGISTRY
AND
THE ENVIRONMENTAL PROTECTION AGENCY
(DOCKET CONTROL # ATSDR - ___)

CHEMICAL MANUFACTURERS ASSOCIATION
VINYLIDENE CHLORIDE PROGRAM PANEL
COMMENTS ON
DRAFT TOXICOLOGICAL PROFILE FOR 1,1-DICHLOROETHENE

The Chemical Manufacturers Association ("CMA") Vinylidene Chloride Program Panel ("VDC Panel") submits these comments and responds to the ___ Fed. Reg. notice and the draft toxicological profile for 1,1-Dichloroethene ("Tox Profile"). 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.

ATSDR has compiled a comprehensive body of data regarding VDC. However, as is to be expected, given the limited time available and the comprehensive nature of the

document, the draft profile contains several statements that are inaccurate or could otherwise mislead a reader as to the nature of and weight to be given certain types of data. CMA is submitting these comments in an effort to aid ATSDR in issuing a more accurate profile on VDC.

[Comments are necessary on the discussion in Chapter 5 of the potential for human exposure, if the Panel feels that that discussion is inaccurate.]

These comments are principally directed to those sections of the Tox Profile which concern cancer (Sections 2.2.1.8, 2.2.2.8, and 2.2.3.8). The comments also address toxicokinetics (Section 2.6). [Specific objections to statements made in the document should be set forth here.]

Following a discussion of inhalation, oral and dermal carcinogenicity, the Tox Profile states that:

> "Data from animal studies on the chronic toxicity and carcinogenicity of DCE are sparse, and limited in their usefulness because of experimental design flaws. The data presented do not sufficiently characterize the carcinogenic or chronic toxic effects of DCE. However, the available information does suggested that DCE is carcinogenic in animals. Additional information on the chronic

> toxicity and carcinogenicity of DCE from well-conducted animal bioassays and human epidemiological studies using various routes of exposure would be useful in predicting the likelihood that such effects occur in humans." (Tox Profile at 73)

CMA believes that sufficient oncogenicity studies and studies regarding relevant metabolic and pharmacokinetic differences among animal species exist and that the likelihood of carcinogenic effects occuring in humans can be predicted on the basis of existing data.

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.

Animal bioassays with VDC have been uniformly negative, with one noteworthy exception. The suggestion in the Tox Profile that the Maltoni rat inhalation study provided "some evidence" of carcinogenicity represents a serious mischaracterization of the results of that study. (Tox Profile at 32). The Tox Profile accurately points out the serious flaws in the Maltoni rat study (at 33). In view of those flaws, the document should not characterize the study as producing "evidence of a carcinogenic effect associated with DCE exposure."

Tumors were produced in the kidneys of Swiss mice in the Maltoni inhalation study. However, as the Tox Profile notes, these effects were accompanied by severe toxic effects. Indeed, they were seen at concentrations of VDC that were notably toxic and near the acutely lethal concentration. 1/ There exists considerable evidence of the

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1/ 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).

and then only reported in ♂ mice - tumors found but not in ♀ mice

greater sensitivity of this strain of mouse to VDC. This 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 probably to the formation of toxic metabolites." 2/

As the Interpretive Review explains, data clearly demonstrate that VDC is metabolized much more rapidly by mice than by rats.3/ 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.4/ The formation of substantially large 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).

2/ 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). [Obtain final]

3/ Jones, B.K. and D.E. Hathaway, 1978.

4/ EPA Criteria Document at VII-4.

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

The extensive bioassay data confirm EPA'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, [cite] an inhalation study with Sprague-Dawley rats, [cite] an inhalation study with CD-1 mice, [cite] an inhalation study with CD rats, [cite] another inhalation study with Sprague-Dawley rats, [cite] an ingestion study with Sprague-Dawley rats, [cite] another inhalation study with CD mice, [cite] another inhalation study with CD rats, a skin

application study with Swiss mice,5/ a subcutaneous injection study with Swiss mice, [cite] a third inhalation study with Sprague-Dawley rats, [cite] a gavage study with Sprague-Dawley rats, [cite] a gavage study with Fischer 344 rats [cite] and a gavage study with B6C3F1 mice [cite]. 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

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5/ [cite] The Tox Profile cites the Van Duuren skin application study suggesting that VDC acted as a tumor indicator. 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 performed by Van Duuren et al. (1979)" HAD at 10-124.

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 or nongenetic components of cells." EPA Criteria Document at VII-8.6/

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

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

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) 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-3.7/

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

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 at 2.5 ppm is unlikely to result in adverse health effects in man through the manufacture or processing of the chemical.

[Panel members will need to address specifically those statements contained in the Tox Profile which suggest that there are more than a single positive bioassay for VDC, as well as those comments which note flaws in existing studies -- flaws the Panel wishes to dispute -- and those which claim that all studies are inconclusive.]

Bruce - We need to discuss the relative toxic effects of VDC and the present limits (PEL) - ACGIH and compare them with VCM. The PEL for VCM is 1.0 ppm and an appropriate level for VDC would be 5.0 or 2.5 ppm because of the protective aspects of its greater toxicity not specifically carcinogenicity - We need to find the common sense, ultimate goal and not be bound to call VDC an animal carcinogen much less a probable human carcinogen. There is absolutely no suggestion that it is a carcinogen to humans. Fib

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