CHEMICAL MANUFACTURERS ASSOCIATION

February 20, 1996

Ms. Kim E. Jenkins
Division of Toxicology
Agency for Toxic Substances and Disease Registry
Mailstop E-29
1600 Clifton Road, N.E.
Atlanta, Georgia 30333

Re: ATSDR-102

Dear Ms. Jenkins:

The Chemical Manufacturers Association (CMA) Vinyl Chloride Panel represents producers of vinyl chloride. CMA appreciates this opportunity to assist the Agency for Toxic Substances and Disease Registry (ATSDR) in characterizing the toxicological effects associated with vinyl chloride by providing comments on the draft Toxicological Profile for Vinyl Chloride.

CMA wishes to acknowledge ATSDR's efforts in drafting a well researched and organized report on known toxicological effects associated with vinyl chloride. CMA has identified areas in the draft Profile that are in need of revision, and areas in which the discussion is incomplete. Specific suggestions for improving the draft are presented in the enclosed comments.

CMA believes that the development of this Toxicological Profile offers ATSDR an appropriate occasion to more fully consider the use of physiologically-based pharmacokinetic (PBPK) models to assess risk by routes other than inhalation. For example, the draft Profile states that certain oral toxicity data on vinyl chloride do not exist or have not been identified. In these areas of the report, as set forth in detail in the enclosed comments, the utility of available PBPK models in addressing data needs should be recognized. In this regard, a paper entitled "Predicting Cancer Risk from Vinyl Chloride Exposure with a Physiologically-Based Pharmacokinetic Model" (Reitz et al. 1995) is enclosed. This paper has been accepted for publication in volume 137 of the

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Journal of Toxicology and Applied Pharmacology. This new paper offers an approach similar to, but more selective than, that employed by Clewell et al. (1995), to which the draft Profile refers.

In identifying data needs, the final Toxicological Profile should make reference to the reproductive and developmental toxicity study to be conducted by CMA pursuant to a Memorandum of Understanding with ATSDR. Suggested references to this study are noted in the comments.

Please call me at (703) 741-5637 if you have questions or need additional information on the enclosed comments.

Very truly yours,

Has Shah

Hasmukh C. Shah, Ph.D.
Manager
Vinyl Chloride Panel

Enclosures

BEFORE THE AGENCY FOR TOXIC SUBSTANCES
AND DISEASE REGISTRY

DRAFT TOXICOLOGICAL PROFILE FOR VINYL CHLORIDE

Comments of the
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February 20, 1996

Comments of the
Chemical Manufacturers Association
on the Agency for Toxic Substances and Disease Registry's
Draft Toxicological Profile for Vinyl Chloride

Introduction

The Agency for Toxic Substances and Disease Registry (ATSDR) recently requested comment on a draft updated Toxicological Profile for Vinyl Chloride. The Chemical Manufacturers Association (CMA) Vinyl Chloride Panel, which represents producers of vinyl chloride, is pleased to provide these comments.

Public Health Statement

The Public Health Statement describes the health effects of vinyl chloride in a balanced, accurate way, and uses language that a person not trained in the sciences could understand. There are instances, however, where we believe that additional interpretation of the available data or identification of expected exposure levels is necessary. More specific changes needed to improve the Public Health Statement are set forth below.

Page 3, section 1.3, second to the last paragraph
CMA is not aware of any data indicating that workers who use polyvinyl chloride (PVC) to make objects such as pipe are exposed to PVC. Unless ATSDR can identify such data, this paragraph should be revised in one of two ways: (1) the number of workers reported in the second sentence to be using vinyl chloride (80,000) should be reduced to eliminate those who use PVC to make other products, and the sentence that follows shortened to end following "vinyl chloride and PVC"; or (2) a new sentence should be added at the end of the paragraph to the effect that "There is no evidence that people who use PVC to make other items are exposed to PVC or vinyl chloride in the workplace." This second alternative may be the best way to eliminate the uncertainty.

Page 5, section 1.5, third paragraph
The third sentence (beginning "Studies of women") should be revised as follows: "could not prove" should be changed to "did not show." This would be consistent with other statements in the draft Profile, including the succeeding two sentences ("Studies using pregnant animals show..."; "Animal studies also show..."), and it is more objective in tone.

Page 5, section 1.5, last paragraph
The second sentence (ending "...breathing it daily for several years") should be revised to read simply "breathing vinyl chloride." It is unhelpful to refer to a cancer risk based on a "daily" exposure rate (at what dosage level?) over an undefined period (i.e., how many is "several" years?).

Page 8, section 1.7
The following new paragraph should be added after the first paragraph:

"Physiologically-based pharmacokinetic (PBPK) models capable of describing the metabolism of vinyl chloride in animals and humans have been developed and validated by Reitz and Clewell, among others. Predictions of cancer risks using such a PBPK model generally are more reliable than methods which rely on default assumptions in lieu of pharmacokinetic data."

Health Effects

Page 52
Before the last paragraph, insert the following new paragraphs:

"At least one analysis of cancer epidemiology exposed weaknesses in the data supporting any causal link between vinyl chloride exposure and brain cancer. See Doll (1988).

"Reference also should be made to the article on Diagnostic Bias in Occupational Epidemiologic Studies: An Example Based on the Vinyl Chloride Literature (Wong et. al. 1993)."

Page 56, Section 2.2.2.1 Death, second paragraph
The first sentence states that no studies of acute and intermediate duration by the oral route have been conducted. The table on page 118, however, indicates that there are published studies of intermediate duration by the oral route. Presumably, the statement on page 56 requires reconsideration.

Page 65, section 2.3 Toxicokinetics
The first sentence of section 2.3, beginning on page 65, should be removed or rewritten. A fair number of toxicokinetic inhalation studies have been conducted using animals. PBPK modeling, particularly as developed by Reitz et al., and enclosed with these comments, should be recognized at this point. Vinyl chloride is volatile and exposure occurs largely by inhalation.

Page 66, section 2.3 Toxicokinetics, first full paragraph
The second sentence (Beginning "Animal studies indicate") should be modified. Vinyl chloride largely is eliminated via the lungs after inhalation. Smaller amounts are metabolized and eliminated in urine or react with tissue. The distribution of the metabolites appears to be well covered in this paragraph.

Page 66, section 2.3 Toxicokinetics, last paragraph
Remove "After inhalation exposure" from the first sentence. Vinyl chloride is metabolized by P-450 enzymes. The route of administration appears only to be important in identifying the route used in the study conducted by Sabadie et al. (1980). The metabolic pathway Figure 2-3 could be introduced at this point.

Page 67, section 2.3 Toxicokinetics, second paragraph
This paragraph should be removed and relocated to page 66, following the first full paragraph, to provide for a more logical progression of the text.

Page 67, section 2.3.1.1. Inhalation Exposure, first paragraph
Raabe studied the retention of a number of chlorinated solvents in human volunteers (students) using low concentrations (Raabe 1988). According to these studies, 40% of the inhaled solvents were retained by the body tissues. Retention appears to be a function of metabolism, solubility in body fluids and binding to macromolecules. An exposure period of six hours may not be long enough to equilibrate body tissues with inhaled vinyl chloride at low exposure concentrations.

Page 69, section 2.3.1.3 Dermal Exposure, second paragraph
This section should note the size of the area of exposed skin in the rhesus money studies.

Page 69, section 2.3.2 Distribution
The partition coefficients, referred to in the second sentence, were obtained for use in PBPK models. A statement to this effect should be added to the paragraph. A reference to the vial equilibration methods also should be included.

Page 72, section 2.3.3.1 Inhalation Exposure, first paragraph
In the first sentence, add a reference or references to gas uptake experiments.

Page 72, section 2.3.3.1 Inhalation Exposure, second paragraph
This paragraph should discuss incubation time, substrate concentration (vinyl chloride in water phase) and milligrams of protein or nmoles of P-450 (S-9 fraction) used in reaction.

Page 72, section 2.3.3.1 Inhalation Exposure, third paragraph
Figure 2-3 (referred to in the second sentence) should be reviewed carefully for accuracy. According to the pathway, vinyl chloride is metabolized to an alcohol in the first step. The product should be an aldehyde. The glutathione metabolite is hydrolyzed to yield the cysteine conjugate(s). It is unclear if there is any evidence for the dipeptide conjugate. Loss of glutamic acid and glycine should be indicated in the pathway.

Page 74, section 2.3.3.1 Inhalation Exposure, first paragraph (continued)
Metabolic pathways in the current PBPK models need to be updated to reflect the formation of aldehydes, acids and their conjugates.

Page 78, section 2.3.4.4 Other Routes of Exposure, second paragraph
In the intravenous study the dose was small (0.25 mg/kg), while the dose rate was large, giving rise to a high percentage of unchanged vinyl chloride in exhaled air. Differences in the amount of vinyl chloride exhaled largely can be explained by examining the dose rate resulting from the different routes of exposure/administration.

Page 80, Summary of PBPK/PD Models, first paragraph
The last sentence should be revised to indicate that the PBPK model was used to obtain the internal dose of chloroethylene oxide (actual carcinogen) while the multistage model was used to estimate probability of cancer. These are separate models. A PBPK/PD model is not available for vinyl chloride.

Page 84, Table 2-5
The information on this table appears to be incorrect. Vmax is the P-450 value for the formation of chloroethylene oxide from vinyl chloride. This should be given in umoles/hr/kg. If this is correct, then Kfc is not the first order rate for the formation of the epoxide (chloroethylene oxide).

Page 85, section 2.3, end of first paragraph (continued)
A reference should be added here to Reitz et al. (1995), which is included with these comments.

Page 85, section 2.4.1 Pharmacokinetic Mechanisms, first paragraph
The last two sentences do not adequately summarize all the pharmacokinetic data presented on the preceding pages regarding elimination via the lung. These sentences either should be deleted or appropriately expanded.

Page 86, section 2.4.2 Mechanisms of Toxicity, third full paragraph
This paragraph needs to be revised and developed further. The mechanism for angiosarcomas and hepatotoxicity has not been well studied, contrary to the statement in the third sentence. No one knows why vinyl chloride produces angiosarcomas while other epoxides do not. References to appropriate studies are needed here. The structures of these adducts should be given in a Figure. Furthermore, no reference is made to repair mechanisms.

Page 86, section 2.4.2 Mechanisms of Toxicity, last paragraph (unfinished)
At the beginning of the paragraph, add the following new sentence: "There also is evidence of the metagenicity of 2-chloroacetaldeleyde in cultured human cells (Matsuda, T., et al. 1995)."

Page 87, section 2.4.3 Animal to Human Extrapolations, second paragraph
This paragraph should disclose the exposure concentrations used in the primate study.

Page 87, section 2.4.3 Animal to Human Extrapolations, third paragraph
This paragraph should discuss whether alpha 2u globulin was involved in male rats.

Page 88, section 2.5 Relevance to Public Health, first full paragraph
This paragraph needs to be expanded, and references should be included. Vinyl chloride currently used for food containers contains little if any detectable (free) vinyl chloride (see discussion on page 3). In the case of PVC water pipe, the vinyl chloride residues come from the glue used to cement the joints. The glue is composed of solvent and PVC.

Page 88, section 2.5 Relevance to Public Health, second full paragraph
Dispersion models currently are used to model vinyl chloride releases from point sources. Some discussion is needed to describe their use in modeling activities involving vinyl chloride.

Page 89, section 2.5 Relevance to Public Health, first full paragraph
This paragraph should describe histopathological changes, with references.

Page 89, section 2.5 Relevance to Public Health, second full paragraph
References should be added to this paragraph. The discussion also should indicate whether the changes are permanent.

Page 89, section 2.5 Relevance to Public Health, last paragraph
References should be added to this paragraph.

Page 90, Inhalation MRLs
The discussion under the two bullet paragraphs should reflect the fact that the acute-duration (gestation) and intermediate-duration inhalation MRLs are lower by a factor of 10 than they need to be to protect humans. CMA will be conducting a two-generation inhalation reproduction study in rats in 1996. Dose levels will be 0, 10, 100 and 1000 ppm.

The chronic-duration oral MRL also appears to be too low by at least a factor of 10. According to Dr. James Swenburg of the University of North Carolina, natural products produce DNA adducts identical to the VCM-DNA adducts. A glycosylase present in tissues is capable of removing these adducts.

Page 103, first full paragraph
The sixth sentence ("Because the epidemiological") should be revised to read as follows: "Epidemiological data have been used to calculate cancer potency factors for inhalation."

At the end of this paragraph, discussion of PBPK modeling and risk assessment should be included. The differences and similarities between Reitz, Clewell (and possibly other PBPK reports) should be explained. It also should be noted that the Reitz paper gives risk estimates based on human data.

Page 103, paragraph beginning at bottom of page
This discussion should indicate whether PBPK models were used to estimate the amount of chloroethylene oxide formed in tissues, and whether internal dose was used to estimate risk using the linearized multistage model.

Page 103, last line on page
Deoxycytidine is misspelled. The structure of these adducts should be given in a Figure.

Page 104, section 2.6 Biomarkers of Exposure and Effect
Hemoglobin adducts should be included in this discussion.

Pages 119-120, Acute-Duration Exposure
In the last sentence on page 119, continuing on page 120, the draft Profile indicates that acute inhalation studies examining the threshold for cardiac irregularities would be helpful. Following a recent re-evaluation of the data, however, ATSDR (in a letter to CMA dated November 8, 1995) stated that there is no need to conduct additional inhalation studies of acute duration. This section of the draft Profile should be adjusted accordingly.

Pages 120-121, Intermediate-Duration Exposure
This discussion states that acute and intermediate duration studies should be performed using the oral route of exposure in order to examine developmental, neurological, and systemic effects. This suggests that research would be useful in determining whether any effects would occur when vinyl chloride-contaminated ground water or food products are consumed. There is little evidence in the draft Profile, however, to suggest that this route of exposure is relevant to human health. On page 3, the draft Profile states that most drinking water supplies do not contain vinyl chloride, and the extent of well contamination is unknown. The draft Profile also states on page 3 that because the amount of vinyl chloride used in food packaging is strictly regulated, the amount of vinyl chloride present in packaged food is "essentially zero." Thus, the proper focus of data gathering should be to gain a better understanding of the potential for exposure through the oral route. If there is no potential for exposure by this route, there will be no justification for these toxicological studies.

Page 123, Genotoxicity (continuation from page 122)
At the end of the sentence beginning on the fourth line ("there are also data") insert the following: "; and recent data suggest that chloroacetaldehyde is responsible for the direct action on the DNA. (Matsuda et al. 1995)."

Page 123, Reproductive Toxicity
In the middle of the paragraph (sentence beginning "A two-generation reproduction study in animals would be helpful"), reference should be made to the two-generation reproductive effects study to be conducted by CMA under a Memorandum of Understanding with ATSDR.

After the last sentence in this paragraph, the following new sentence should be added: "The PBPK model would be appropriate for assessing reproductive toxicity resulting from oral exposure to vinyl chloride."

Page 124, Developmental Toxicity
It should be noted here that a developmental toxicity study will be conducted by CMA in conjunction with the two-generation rat reproductive effects study mentioned above.

After the last sentence in this paragraph, the following new sentence should be inserted: "The PBPK model would be an appropriate tool in such risk assessment."

<u>Production, Import, Use, and Disposal</u>

Page 137, section 4.1 Production, second paragraph
On the fifth line down, substitute "West Lake" for "Lake Charles," Louisiana.

Page 138, Table 4-1
The list of facilities that manufacture or process vinyl chloride should be updated. Occidental Chemical Company does not manufacture vinyl chloride at Deer Park. Occidental no longer owns a plant at Addis, LA. The plant was sold to Borden. Vinyl chloride is made by Occidental at Pasadena and at Ingleside, Texas.

<u>Potential for Human Exposure</u>

Page 145, section 5.2.1 Air
In the fourth sentence, TRI data should be updated. There are more recent TRI data on releases than 1992.

Page 155, section 5.6 Populations with Potentially High Exposures
The title of this section should be changed to "Populations with Potential Exposures." Use of the term "high" may suggest that particular populations are experiencing adverse effects from vinyl chloride.

References

Matsuda, T., et al. 1995. Molecular analysis of mutations induced by 2-chloroacetaldehyde: The ultimate carcinogenic form of vinyl chloride, in human cells using shuttle vectors. Carcinogenesis (Oxford), 16 (10).

Raabe, OG. 1988. Retention and metabolism.of toxics: Inhalation uptake of xenobiotic vapors by people. Cal. Air Resources Board contract A5-155-33.

*Reitz, RH, Gargas, ML, Andersen, ME, Provan, WM, Green, TL. 1995. Predicting Cancer Risk from Vinyl Chloride Exposure with a Physiologically-Based Pharmacokinetic Model. Toxicol Appl Pharm. 137:___ (forthcoming).

*Shah, HC. 1993. Diagnosic Bias in Occupational Epidemiologic Studies. Am J Indus Med. 24:249-250.

*Wong, O, Whorton, MD. 1993. Diagnostic Bias in Occupational Epidemiologic Studies: An Example Based on the Vinyl Chloride Literature. Am J Indus Med. 24:251-256.

*A copy of these sources is provided.