CMA

CHEMICAL MANUFACTURERS ASSOCIATION

March 11, 1996

Association
CMA
Vinyl Chloride Panel

Dear Vinyl Chloride Health Committee Members:

The following items are enclosed:

1) February 9, 1996 letter to David Siegel regarding the reports submitted to the California Office of Environmental Health Hazard Assessment;

2) the Committee's comments on ATSDR's Toxicological Profile for vinyl chloride. These comments were prepared by Tom Downs of Patton Boggs, LLP, based on comments from PPG Industries, Inc., Dow Chemical Company, Occidental Chemical Corporation, and Vista Chemical Company; and,

3) the Committee's comments on ATSDR Medical Management Guidelines for vinyl chloride. These comments were prepared by Tom Downs based on comments from Dow Chemical Company and PPG Industries, Inc.

I will schedule a conference call in the near future to brief the Committee on the status of discussion with ENSR research proposal from Dr. Swenborg, the Memorandum of Understanding with ATSDR, EPA's Risk Assessment of vinyl chloride, and other issues.

I look forward to talking with you soon.

Sincerely,

Jon Burch for

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

Enclosure

MAR 13

SL 109921

1300 WILSON BOULEVARD, ARLINGTON, VA 22209 • TELEPHONE 703-741-5000 • FAX 703-741-6000

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A Public Commitment

February 9, 1996

David M. Siegel, Ph.D., Chief
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
601 North 7th Street, MS-241
P.O. Box 942732
Sacramento, CA 94234

Dear Dr. Siegel:

The CMA Vinyl Chloride Health Committee submits the following reports to aid the California Office of Environmental Health Hazard Assessment in its cancer risk assessment for vinyl chloride using pharmacokinetic and mechanistic:

(1) Common Chemicals Found at Superfund Sites, Office of Emergency and Remedial Response, U.S. EPA, 1994;

(2) Predicting Cancer Risk from Vinyl Chloride Exposure with a Physiologically - Based Pharmacokinetic Model, Reitz et al, Toxicology and Applied Pharmacology (In Press); and,

(3) Considering Pharmacokinetic and Mechanistic Information In Cancer Risk Assessments for Environmental Contaminants: Examples with Vinyl Chloride and Trichloroethylene, Clewell et al, Chemosphere, 1995.

The Committee looks forward to receiving the final "Addendum Health Risk Assessment of Ambient Fugitive Vinyl Chloride Emissions From the Class I Unit of the BBK Landfill, West Covina, California," when completed and released.

Thank you for your consideration of the enclosed information in preparing a final risk assessment addendum for vinyl chloride.

Please call me at 703-741-5637 if you have any questions or need additional information. My fax number is 703/741-6091.

Sincerely,

Has Shah

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

cc: Lillian Kelley (with enclosures)
Enclosure

SL 109922

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
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, VA 22209

Langley A. Spurlock
Vice President -- CHEMSTAR

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

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2550 M Street, N.W.
Washington, D.C. 20037

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 xposure/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."

Production, Import, Use, and Disposal

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.

Potential for Human Exposure

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.

CHEMICAL MANUFACTURERS ASSOCIATION

March 7, 1996

Ms. Jennifer Heise
Peer Review Coordinator
ERG
110 Hartwell Avenue
Lexington, MA 02173

Re: ATSDR Medical Management Guidelines for Vinyl Chloride

Dear Ms. Heise:

This letter transmits the Chemical Manufacturers Association (CMA) Vinyl Chloride Panel's comments on the Medical Management Guidelines for Vinyl Chloride under development by the Agency for Toxic Substances and Disease Registry (ATSDR). At the request of Scott Wright of ATSDR, CMA is submitting these comments directly to you.

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

Enclosure

cc: Scott Wright

SL 109935

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Comments of the
Chemical Manufacturers Association
Vinyl Chloride Panel Health Committee
on the Agency for Toxic Substances and Disease Registry's
Proposed Medical Guidelines for Vinyl Chloride

March 7, 1996

The Agency for Toxic Substances and Disease Registry (ATSDR) recently requested review and comment on proposed Medical Management Guidelines for Vinyl Chloride. The Chemical Manufacturers Association (CMA) Vinyl Chloride Pan l, which represents producers of vinyl chloride, is pleased to provide these comments.

CMA appreciates ATSDR's desire to develop medical management guidelines for various chemicals that read clearly and accurately from a scientific and medical standpoint and are useful reference documents. ATSDR's final product on vinyl chloride should prove helpful to emergency medical personnel and oth rs in need of a medical reference on this chemical. CMA's specific suggestions for refining medical management guidelines for vinyl chloride are presented below.

Page 1, Route of Exposure, Inhalation
The fifth sentence (beginning "Occupational exposures have resulted") should be revised to read as follows: "Occupational exposures well above the current threshold limit value (TLV®) have resulted in the occurrence of a syndrome consisting of acroosteolysis, scleroderma-like skin changes, and Raynaud's phenomenon."

The last sentence (beginning "Chronic exposures have led to cancer") should be revised to read as follows: "Chronic exposures (well above the current TLV®) have led to increased risk of cancer, particularly of angiosarcoma of the liver. Increased risks of cancer of the lung and brain have been reported but not substantiated."

Page 3, Health Effects, boxed text
The third sentence (beginning "Vinyl chloride has been shown") should be revised to read as follows: "Vinyl chloride has been shown to induce angiosarcoma of the liver in humans and in laboratory animals with chronic exposure."

The fourth sentence (beginning "Immunological effects") should be revised to read as follows: "Immunological effects and effects on reproduction have not been conclusively demonstrated in humans or animals."

Page 3, Acute Exposure, Cardiovascular
The last sentence (beginning "Chronic exposure to vinyl chloride") should be removed from the Acute Exposure section and placed under Chronic Exposure, on page 4. The sentence also should be revised to read as follows: "Chronic exposure to vinyl chloride (well above the current TLV®) can cause a syndrome consisting of acroosteolysis (dissolution of the bones of the terminal phalanges of the fingers, toes, and sacroiliac joints), Raynaud's phenomenon, and scleroderma-like skin changes."

Page 4, Chronic Exposure, Carcinogenicity
This paragraph should be revised to read as follows:

"The Environmental Protection Agency has classified vinyl chloride as a known human carcinogen. Vinyl chloride has been shown to induce cancer of the liver (angiosarcoma) in humans and laboratory animals when they are exposed for long durations above the current TLV®. There is inconsistent and inconclusive evidence suggesting that vinyl chloride exposure also may be associated with cancer of the lung, brain, and central nervous system."

Page 5, Reproductive and Developmental Effects
The first paragraph should be revised to read as follows:

"Occupational vinyl chloride exposure has been reported to result in decreased sexual performance both in men and women, although this theory has not been substantiated in controlled epidemiologic studies. In men, occupational exposure has been reported to be associated with decreased libido, impotence, and decreased testosterone production. In women, vinyl chloride exposure has been reported to result in decreased sexual function and elevated blood pressure and ed ma during pregnancy (i.e., pre-eclampsia). The reports of these findings largely have been based on individual random cases, and are not considered strongly suggestive of vinyl chloride's health effects. Animal studies have not conclusively d monstrated the presence or absence of vinyl chloride reproductive toxicity, but additional studies currently under way should clarify these issues."

Supplementary material
The information that follows should be added to the Chronic Exposure section or possibly to a new section entitled "Occupational Exposure":

- ANGIONEUROTIC DISORDERS IN THE HANDS AND FEET (RAYNAUD'S PHENOMENON)
  exposure criteria:
  minimum intensity of exposure:
  confirmed occupational exposure, assessed if possible by:
  - anamnesis and study of exposure conditions
  - and, if appropriate, atmospheric sampling

- ACRO-OSTEOLYSIS IN THE UNGUAL PHALANGES OF THE HANDS AND FEET
  May accompany angioneurotic disorders confirmed by X-ray (loss of substance from bones)
  exposure criteria:
  minimum intensity of exposure:
  confirmed occupational exposure, assessed if possible by:
  - anamnesis and study of exposure conditions
  - and, if appropriate, atmospheric sampling

- DISTAL SKIN DISORDERS
  Pseudosclerodermal syndrome with penetration of the skin, possibly accompanied by general symptoms (arthralgia, myalgia); follows on from angioneurotic disorders.

  exposure criteria:
  minimum intensity of exposure:
  confirmed occupational exposure, assessed if possible by:
  - anamnesis and study of exposure conditions
  - and, if appropriate, atmospheric sampling

- LIVER FIBROSIS WITH PORTAL HYPERTENSION
  Portal Hypertension syndrome fibrosis confirmed by endoscopy or histology or indirectly by echography.
  exposure criteria:
  minimum intensity of exposure:

confirmed occupational exposure, assessed if possible by:
- anamnesis and study of exposure conditions
- and, if appropriate, atmospheric sampling

◆ ANGIOSARCOMA
angiosarcoma, usually hepatic
exposure criteria:
minimum intensity of exposure:
confirmed occupational exposure, assessed if possible by:
- anamnesis and study of exposure conditions
- and, if appropriate, atmospheric sampling

Mobil

P. O. BOX 1038
PRINCETON, NEW JERSEY 08543-1038

CORPORATE MEDICAL DEPARTMENT

November 15, 1995

Ms. Kari Barrett
Chemical Manufacturers
Association
2501 M Street, NW
Washington, DC 20037

MEDICAL MANAGEMENT GUIDELINES

Dear Ms. ~~Barrett~~ Kari:

Enclosed are the 10 Medical Management Guidelines (MMGs) that we discussed. Your assistance in distributing these draft documents as widely as possible for review and comment is appreciated. I've also enclosed a "Charge to Reviewers" statement that may be of value as well.

Please call (609-737-6102) if we should discuss our distribution strategy further. We had briefly discussed preparing a form letter addressed to the safety and health representative at each CMA member company seeking individuals interested in reviewing one or more of the 10 draft documents.

I will need to receive all comments on these MMGs by December 15th.

Thanks for your help on this project.

Sincerely,

David C. Logan

David C. Logan, M.D.
Medical Director, Field Services
and Health Effects Programs

DCL695/fc
enclosures

cc: J. M. Cannella, M.D.

Vinyl Chloride (C_2H_3Cl)
CAS 75-01-4; UN 1086

Synonyms include chloroethene, chloroethylene, 1-chloroethylene, ethylene monochloride, monochloroethylene, VC, VCM, vinyl chloride monomer.

- **Persons exposed to vinyl chloride gas do not pose a risk of secondary contamination to personnel outside the Hot Zone. Persons whose clothing or skin is contaminated with liquid vinyl chloride or dust containing vinyl chloride can secondarily contaminate response personnel by direct contact or through off-gassing of vinyl chloride vapors.**
- **Vinyl chloride is a colorless, gas or liquid with a mild sweet odor. As a vapor, vinyl chloride is highly flammable at room temperature.**
- **Vinyl chloride is used in the production of plastics, in organic synthesis reactions, and historically as a chemical refrigerant. The primary route of exposure to vinyl chl ride is via inhalation which, at high levels, can cause central nervous system depression and death. Systemic effects can be caused from exposure by any route.**

Description

Vinyl chloride is a colorless vapor with a mild, sweet odor. At room temperature, vinyl chloride is highly flammable. If kept under high pressure, vinyl chloride can exist as a colorless liquid with a mild, sweet odor. Almost all vinyl chloride is anthropogenic. It is generally shipped as a liquefied compressed gas.

Routes of Exposure

Inhalation

Humans are primarily exposed to vinyl chloride by inhalation of the gaseous form. Breathing high levels of vinyl chloride (10,000 ppm for 5 minutes) can induce central nervous system depression, lightheadedness, nausea, and alterations of visual and auditory responses. At high air concentrations, death has been reported in humans (>10,000 ppm) and in animals (>100,000 ppm). Systemic effects of acute inhalation exposure include respiratory tract irritation, dysrhythmia, anorexia, nausea, and heartburn. Occupational exposures have resulted in an increased incidence f Raynaud's disease. Chronic exposures have led to cancer, particularly of the liver, lungs, brain, kidneys, and connective tissue.

Skin/Eye Contact

Vinyl chloride is a known skin irritant; contact with the liquid form of vinyl chloride may induce frostbite as it evaporates. Vinyl chloride is not well absorbed through the skin.

Ingestion

Ingestion is not a major route of exposure for vinyl chloride because of its high volatility (i.e., gas at room temperature) and its low solubility in water.

Sources/Uses

Vinyl chloride is widely employed in industry in the production of low-cost polymers, such as polyvinyl chloride (PVC). PVC is found in automotive parts and accessories, furniture, packaging materials, pipes, wall coverings, and wire coating. Vinyl chloride has been used as an extraction solvent for heat-sensitive materials and in the production of chloroacetaldhyde and trichloroethane. Historically, vinyl chloride has been used as a chemical refrigerant.

Standards and Guidelines

OSHA permissible exposure limit (PEL) = 1 ppm (averaged over an 8-hour work shift)

OSHA short term exposure limit (STEL) = 5 ppm (15-minute exposure)

NIOSH immediately dangerous to life or health (IDLH) = not determined

Physical Properties

Description: Colorless gas with faint, sweet odor; colorless liquid with faint, sweet odor; odor threshold 300–500 ppm

Warning properties: faint, sweet odor

Molecular weight = 62.5

Boiling point = 7.88° F (-13.4° C)

Freezing point = -244.84° F (-153.8° C)

Vapor pressure = 2530 mm Hg at 68° F (20° C)

Vapor density = 2.16 (air = 1)

Water solubility = 0.01% at 77° F (25° C)

Flammability = flammable gas

Flammability range is 3.6–33% (concentration in air)

Incompatibilities

Vinyl chloride reacts with copper, oxidizers, aluminum, peroxides, iron, and steel. It polymerizes in the presence of light. An unstable polyperoxide is formed in vinyl chloride through oxidation by atmospheric oxygen in the presence of contaminates. Long-term storage under these conditions may result in increased concentrations of polyperoxides, leading to violent chemical reactions and explosions.

Health Effects

- **The primary route of exposure to vinyl chloride in humans is inhalation; the central nervous system is the primary target of acute vinyl chloride toxicity. Breathing high levels of vinyl chloride (10,000 ppm for 5 minutes) can induce central nervous system depression, lightheadedness, nausea, and alterations of visual and auditory responses. Exacerbation of pre-existing asthmatic conditions can also occur. Vinyl chloride has been shown to induce liver cancer in humans and in laboratory animals with chronic exposure. Immunological effects and effects on reproductive function may also occur.**
- **Ingestion is not a major route of exposure for vinyl chloride. The potential for toxic effects from contaminated water exposure is unlikely due to vinyl chloride's low solubility in water. Dermal exposure to vinyl chloride occurs by contact with either the gas or liquid forms. Absorption through the skin of either phase of vinyl chloride is considered negligible when compared to the respiratory route.**

Acute Exposure

Central Nervous System

The central nervous system is the primary target organ of vinyl chloride toxicity. The symptoms most commonly reported in acute exposure are those related to the anesthetic properties of vinyl chloride, including dizziness, ataxia, fatigue, drowsiness, headache, and loss of consciousness. Symptoms of acute exposure resolve quickly when the victim is removed from the source of exposure. The threshold for central nervous system symptoms is approximately 8,000 ppm. Humans exposed to 8,000–25,000 ppm vinyl chloride for 3 minutes reported dizziness, disorientation, a burning sensations in the feet, and headache upon recovery. Alterations of visual and auditory responses have also been reported.

Cardiovascular

Dysrhythmia is a possible effect of acute vinyl chloride exposure. The threshold for cardiac dysrhythmia, however, is not known. It is likely that vinyl chloride lowers the myocardial threshold to the dysrhythmogenic effects of catecholamines and may predispose t ventricular fibrillation. In animals, exposure has led to ECG abnormalities, including ventricular ectopy, heart block and T-wave inversions.

Chronic exposure to vinyl chloride can cause a syndrome of acroosteolysis (dissolution of the bones of the terminal phalanges of the fingers, toes, and sacroiliac joints), Raynaud's disease, and scleroderma-like skin changes.

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Respiratory Little inf rmation about the acute inhalation effects of vinyl chloride in humans is available. Vinyl chl ride inhalation results in a sense of breathlessness and mild respiratory tract irritation. Wheezing and chemical bronchitis are potential pulmonary consequences of vinyl chloride exposure. Asthma may be provoked in those who are prone to broncho-constriction secondary to respiratory irritants. In laboratory animals, acute exposures to high concentrations (>100,000 ppm) of vinyl chloride cause respiratory inflammation, respiratory depression, pulmonary congestion, edema, hemorrhages, and death.

Hematologic Limited evidence in humans believed to have been exposed to high concentrations of vinyl chloride vapor demonstrated that the blood failed to clot, and may be related to the presence of thrombocytopenia. Hematologic effects due to vinyl chloride are very limited.

Gastrointestinal Acute vinyl chloride inhalation exposure may cause anorexia. Other symptoms may include nausea, heartburn, and abdominal distention. The threshold for these effects has not been established in humans. Because of the low solubility of vinyl chloride in water, there is little likelihood of acute toxic effects from ingestion. There are no studies of ingestion of liquid vinyl chloride in humans.

Dermal Acute exposure to vinyl chloride gas may have an irritant effect on the skin. Exposure to escaping compressed gas or liquid vinyl chloride results in a frostbite effect on exposed skin. Absorption of vinyl chloride through the skin is negligible compared to respiratory absorption.

Ocular Corneal and conjunctival burns result from exposure to vinyl chloride gas or liquid.

Potential Sequelae Symptoms of acute inhalation exposure to vinyl chloride resolve quickly when the victim is removed from the source of exposure. Asthma may be provoked in persons with prior history of asthma.

Chronic Exposure

Carcinogenicity The Environmental Protection Agency (EPA) has classified vinyl chloride as a carcinogen. Vinyl chloride has been shown to induce cancer in humans and in laboratory animals when they are exposed for chronic durations. Vinyl chloride has been documented to induce cancers of the liver (angiosarcoma), brain and central nervous system, respiratory tract, and lymphatic/hematopoietic system (leukemia and lymphomas, particularly in women).

Reproductive and Developmental Effects

Vinyl chloride has been shown to decrease sexual performance in both men and women. In men, chronic occupational exposure to vinyl chloride has been associated with decreased libido, impotence, and decreased testosterone production. In women, vinyl chloride exposure also induced a decrease in sexual function, in addition to an increased incidence and severity of elevated blood pressure and edema during pregnancy (i.e., eclampsia). These studies were often complicated by co-exposure to other chemicals, but are considered to be strongly suggestive of vinyl chloride toxicity. Animals studies have demonstrated decreased male fertility after exposure to vinyl chloride.

Human studies evaluating the fetotoxicity and teratogenicity in humans exposed to vinyl chloride are inconclusive. Several animal studies have shown that vinyl chloride induced developmental effects, such as decreased litter size and fetal weight, and delayed ossification when pregnant animals inhaled <500 ppm vinyl chloride. Lower inhaled vinyl chloride concentrations (<14 ppm) resulted in decreased maternal erythrocyte counts, with fetal hemorrhages apparent in rats.

Prehospital Management

- **Victims exposed only to vinyl chloride gas do not pose a risk of contamination to rescuers. Victims or their clothing contaminated with liquid vinyl chloride may secondarily contaminate rescue personnel by direct contact or off-gassing.**
- **Protective equipment includes respiratory and skin protection. A self-contained breathing apparatus or full-face supplied-air respiratory, and eye protection are necessary protection against gas exposure. Protective clothing is necessary when contact with liquid vinyl chloride is expected.**
- **The central nervous system is the primary target organ system. Vinyl chloride also irritates the respiratory mucosa.**
- **There is no specific antidote or specific treatment for vinyl chloride toxicity. Medical treatments are limited to supportive therapy.**

Hot Zone

Rescuers should be trained and appropriately equipped with personal protective equipment and/or clothing before entering the Hot Zone. Vinyl chloride presents both gaseous and liquid contact exposure dangers. If appropriate protective equipment is not available and/or the rescuers have not been trained in its use, call for assistance from a local or regional HAZMAT team or other properly equipped response organization.

Rescuer Protection

Vinyl chloride gas is readily absorbed by inhalation, is a mild respiratory tract irritant, and may exacerbate pre-existing asthmatic conditions. Contact with escaping compressed gas or the liquid phase of vinyl chloride results in frostbite of contacted body surfaces. Vinyl chloride is not well absorbed through the skin.

Respiratory protection can be provided by self-contained breathing apparatus or full-face supplied air. Eye protection against gas exposure is also necessary. Particle filter masks are not effective.

Skin protection is not generally required when only vapor is expected. When contact with liquid is anticipated, protective clothing is recommended to prevent skin irritation or injury.

Immediate Care

In cases of suspected trauma, quickly stabilize the cervical spine. Ensure a patent airway in the unconscious victim while supporting breathing and circulation. The most important aspect of initial care is to safely remove the victim to an area of fresh air.

Victim Removal

If victims can walk, lead them out of the Hot Zone to the Decontamination Zone. Victims who are unable to walk may be removed on backboards or gurneys. If these are not available, carefully carry or drag victims to safety.

Decontamination Zone

Patients exposed only to vinyl chloride gas who have no skin or eye irritation do not need decontamination. They may be transferred immediately to the Support Zone. Others require selective decontamination (see *Basic Decontamination* below).

Rescuer Protection

Victims exposed only to vinyl chloride gas do not retain or release this chemical in toxic quantities. Rescuers should be protected against direct contact when caring for victims who may be contaminated with liquid vinyl chloride or vinyl chloride-containing dust.

Immediate Care

The majority of victims exposed to vinyl chloride will recover quickly after being removed to fresh air. In victims more seriously affected, evaluate and support the airway, breathing, and circulation. Intubate the trachea in cases of respiratory compromise. If the patient's condition precludes intubation, surgically create an airway. Administer supplemental oxygen as required. Assist ventilation with a bag-valve-mask device, if necessary.

Basic Decontamination

Irrigate exposed eyes with plain water or saline for 3–5 minutes. Remove contact lenses if present.

Flush exposed skin and hair with plain water for 2–3 minutes (preferably under a shower), then wash with mild soap, rinsing thoroughly with water.

Induction of vomiting is not recommended.

Contaminated clothing should be bagged for cleaning or disposal.

As soon as basic contamination is complete, those victims who have not fully recovered should be transported to the Support Zone.

Support Zone

Victims who have undergone decontamination or have been exposed only to gas pose no serious risks of secondary contamination of rescuers. In such cases, Support Zone personnel require no specialized protective gear.

ABC Reminders

Quickly ensure a patent airway. Administer supplemental oxygen as required. Assist ventilation with a bag-valve-mask device if necessary. Establish intravenous access in patients with respiratory symptoms or findings suggesting asthma or stridor.

Report to the base station and the receiving medical facility the condition of the patient, any treatment given, and the estimated duration of transport.

Additional Decontamination

In the presence of continued skin or eye irritation, further decontamination may be indicated (see *Basic Decontamination* above).

Advanced Treatment

Intubate the trachea in cases of respiratory compromise. Respiratory clinical monitoring should be especially useful for patients with a past history of asthma or wheezing. Cardiac monitoring sh uld be initiated before administering bronchodilator therapy. Bronchodilator therapy should be considered and initiated promptly if deemed clinically appropriate. Patients who are comatose, seizing, or hypotensive, should be treated according to ACLS protocols.

Transport to Medical Facility

Report to the base station and the receiving medical facility the condition of the patient, any treatment given, and the estimated duration of transport.

Multi-Casualty Triage

Patients who do not recover fully after being removed from the source of exposure should be transported to a medical facility for evaluation.

Asymptomatic patients may be discharged from the scene, after recording their names, addresses, and telephone numbers. If available, a brief individual description of their own exposure proximity and other "dose" information should also be obtained.

Patients with prior asthma history should be warned about this potential sequela, or clinically evaluated for bronchodilator therapy. These patients should be advised to rest and to seek medical care promptly if symptoms develop or recur (see the reverse side of the *Vinyl Chloride Patient Information Sheet*).

Emergency Department Management

- **Patients do not pose a serious contamination risk to others.**
- **The central nervous system is the primary target organ system. Vinyl chloride also irritates the respiratory mucosa.**
- **Treatment consists of supportive measures and monitoring for complications. Patients exposed to escaping compressed vinyl chloride gas and/or liquid vinyl chloride may have areas of frostbite requiring medical attention. Potential pulmonary consequences can include asthma, wheezing, and chemical bronchitis, potentially requiring bronchodilator use.**

Decontamination Area

Previously decontaminated patients and those who were exposed only to vinyl chloride gas who have no eye or skin irritation do not need further decontamination. They may be transferred directly to the Critical Care Area. Others may require further decontamination.

ABC Reminders

Evaluate and support the airway, breathing, and circulation. Intubate the trachea in cases of respiratory compromise. If the patient's condition precludes intubation, surgically create an airway. Establish intravenous access in seriously symptomatic patients if it has not been done previously.

Basic Decontamination

No additional decontamination is necessary as vinyl chloride would no longer be present as a liquid or gas.

Critical Care Area

ABC Reminders

Patients who are comatose, seizing, hypotensive, or experiencing cardiac dysrhythmias should be treated in the conventional manner.

Early dyspnea can indicate upper airway obstruction from epiglottic swelling, reflex bronchospasm or direct pulmonary injury, which require very different treatments. Patients require careful assessment for stridor, wheezing, and rales (for each of the mentioned diagnoses) in addition to use of X-ray, blood-gas, and pulmonary function testing.

Administer high concentrations of humidified oxygen to patients with shortness of breath, monitoring with ABG and/or oximetry determinations. Early and aggressive bronchodilator therapy is recommended for patients with asthma.

Monitor fluid status closely. Over hydration should be avoided to avoid contributing to pulmonary edema.

Inhalation Exposure

Continue to support oxygenation and ventilation as required.

Skin Exposure

Liquid vinyl chloride may cause frostbite. If frostbite is present, treat in the conventional matter. There may also be chemical irritation or thermal injury that should be managed as the burns from any other cause. Airway compromise from mucosal injury may be a concern for the first days in cases of high-concentration exposure.

Eye Exposure

Eye exposure to vinyl chloride is unlikely, because it is gaseous at room temperature and a liquid when kept under pressure.

Ingestion Exposure

Ingestion of vinyl chloride is largely impossible, because it is gaseous at room temperature and a liquid when kept under pressure.

Antidotes and Other Treatments

There are no known antidotes for vinyl chloride exposure effects.

Laboratory Tests

Patients who have respiratory complaints should be evaluated with pulse oximetry (or ABG measurements) and chest radiography.

Vinyl chloride blood or plasma levels are not clinically useful but may be used to document an exposure.

Disposition and Follow-up

Delayed Effects

Recovery from acute exposure effects is usually rapid and complete. The only intervention necessary is supportive. Any persistent effects should be treated symptomatically.

Patient Release

Patients who remain medically stable and asymptomatic 12 hours after exposure may be discharged. They should be informed as to what symptoms to look for that would mandate immediate return (see the reverse side of *Vinyl Chloride Patient Information Sheet*).

Follow-Up

No follow-up is generally necessary as recovery is usually rapid and complete. Any persistent effects should be treated symptomatically.

Reporting

If a work-related incident has occurred, file a clinical report to Workers' Compensation. In some states and circumstances, additional reports to Public Health authorities are mandatory; contact your state or local health department.

Other persons may still be at risk in the setting where this incident occurred. If the incident occurred in the workplace, discussing it with company personnel may prevent future incidents. If a public health risk exists, notify your state or local health department or other responsible public agency. When appropriate, inform patients that they may request an evaluation of their workplace from OSHA or NIOSH.

Vinyl Chloride (C_2H_3Cl)
Patient Information Sheet

This handout provides information and follow-up instructions for persons who have been exposed to vinyl chloride.

What is vinyl chloride?
Vinyl chloride is primarily a manufactured chemical. It is a colorless vapor at room temperature with a mild sweet odor. Vinyl chloride can exist as a liquid when kept under high pressure. Vinyl chloride is used in the production of polyvinyl chloride (PVC) which in turn is used to make a variety of plastic products including pipe and packing materials.

What immediate health effects can be caused by exposure to vinyl chloride?
Inhaling vinyl chloride causes sleepiness and/or dizziness and exacerbation of pre-existing asthmatic conditions. Breathing high concentrations of vinyl chloride may result in loss of consciousness. Extremely high concentrations of vinyl chloride, when breathed, may cause death. If the skin comes in contact with liquid vinyl chloride, it can produce frostbite (numbness, redness, and blistering of the skin).

Can vinyl chloride poisoning be treated?
There is no known antidote for vinyl chloride. There is usually rapid and complete recovery from the acute effects of exposure with supportive care.

Are any future health effects likely to occur?
A single small exposure from which a person recovers quickly is not likely to cause delayed or l ng-term effects. Symptoms due to chronic exposure may be delayed for years. The liver is the main target of chronic exposure. Vinyl chloride is a known human carcinogen causing a rare form of cancer of the liver.

What tests can be done if a person has been exposed to vinyl chloride?
There are several tests that can show if you have been exposed to vinyl chloride. These specialized tests are generally not available in your doctor's office and must be obtained at a medical center.

Where can more information about vinyl chloride be found?
More information about vinyl chloride can be obtained from your regional poison control center; your state, county, or local health department; the Agency for Toxic Substances and Disease Registry (ATSDR); your doctor; or a clinic in your area that specializes in occupational and environmental health. If the exposure happened at work, you may wish to contact your employer, the Occupational Safety and Health Administration (OSHA), or the National Institute for Occupational Safety and Health (NIOSH). Ask the person who gave you this form for help in locating these telephone numbers.

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Follow-up Instructions

Keep this page and take it with y u to your next appointment. Follow *only* the instructions checked below.

[ ] **Call your doctor or the Emergency Department if you develop any unusual signs or symptoms within the next 24 hours, especially:**
- **shortness of breath limiting normal activity**
- **coughing, wheezing, or chest tightness**
- **persistent pain or irritation in your eyes**
- **increased redness or pain or a pus-like discharge in the area of your skin that has come in contact with vinyl chloride.**

[ ] **No follow-up appointment is necessary unless you develop any of the symptoms listed above.**

[ ] **Call for an appointment with Dr. _____ in the practice of _____. When you call for your appointment, please say that you were treated in the Emergency Department at ___ _____ Hospital by _____ and were advised to be seen again in ___ days.**

[ ] **Return to the Emergency Department/_____ Clinic on (date) _____ at _____ _____ AM/PM for a follow-up examination.**

[ ] **Do not perform vigorous physical activities for 1 to 2 days.**

[ ] **You may resume everyday activities including driving and operating machinery.**

[ ] **Do not return to work for _____ days.**

[ ] **You may return to work on a limited basis. See instructions below.**

[ ] **Avoid exposure to cigarette smoke for 72 hours; smoke may worsen injury to your stomach or have other effects.**

[ ] **Avoid drinking alcoholic beverages for at lease 24 hours; alcohol may worsen injury to your stomach or have other effects.**

[ ] **Avoid taking the following medications: _____**

_____

[ ] **You may continue taking the following medication(s) that your doctor(s) prescribed for you: _____**

_____

[ ] **Other instructions: _____**

_____

_____

_____

Signature of patient _____ Date _____

Signature of physician _____ Date _____

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