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UNIVERSITY of LOUISVILLE

October 31, 1989

Mr. Ron Martin
B. F. Goodrich Chemical Group
P.O. Box 32950
Louisville, Kentucky 40232

RE: Manuscript review

Dear Ron:

The Agency for Toxic Substances and Disease Registry of Center for Disease Control asked me to review DeLima Associates development of Case Studies in Environmental Medicine on vinyl chloride toxicity due out in 1990.

I would appreciate your comments and suggestions, etc.

Please feel free to indicate any changes you might suggest by writing directly on to the manuscript or by telephone.

Kind regards,

Carlo H. Tamburro, M.D./bjd

Carlo H. Tamburro, M.D., M.P.H.
Professor of Medicine and
Community Health
Acting Chairman, Department of
Community Health
Chief, Division of Occupational
Health
Director, Liver Research Center

CHT/bjd

SPI-01201

AUG 28 1989

DeLIMA ASSOCIATES
4340 Redwood Highway, Suite 222, San Rafael, California 94903 Telephone (415) 499-1065

August 25, 1989

Dr. Carlo Tamburro
Health Science Center, Suite 119A
School of Medicine
University of Louisville
Louisville, KY 40292

Dear Dr. Tamburro:

Enclosed please find a final draft of the vinyl chloride monograph of which we spoke. You have been very helpful and have contributed significantly to its contents and tone. We would like to add your name as an additional Guest Editor, if that is your choice also.

I look forward to your comments.

Sincerely,

DeLIMA ASSOCIATES

Lois L. Gerchman, Ph.D.
Program Manager

Enclosure

SPI-01202

ATSDR *Case Studies in Environmental Medicine*

VINYL CHLORIDE TOXICITY

March 1990

2

Current ALERT...

- ☑ *Chronic, low-level vinyl chloride exposure may cause angiosarcoma of the liver (ASL), an extremely rare form of cancer.*
- ☑ *ASL is associated with a minimum exposure period to vinyl chloride of 3 to 8 years, followed by a latency period of up to 40 years.*
- ☑ *No case of hepatic angiosarcoma has been reported in any worker who has been exposed to vinyl chloride only since allowable workplace air -- levels were drastically reduced in 1974. This finding, however, may reflect the passage of an incomplete latency period.*

This monograph is one in a series of self-instruction publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients.

The Centers for Disease Control designates this continuing medical education activity for 1 credit hour in Category 1 of the Physician's Recognition Award of the American Medical Association.

Each monograph of the series, Case Studies in Environmental Medicine, has been approved by XXXX for 1 hour of Category 1 credit.

Guest Contributors: *Robert Harrison, MD, MPH; Gloria Hathaway, PhD*
Guest Editor: *Laura Welch, MD*

Peer Reviewers: *Charles Becker, MD; Jonathan Borak, MD; Joseph Cannella, MD; Bernard Goldstein, MD; Alan Hall, MD; Richard J. Jackson, MD, MPH; Jonathan Rodnick, MD; Linda Rosenstock, MD, MPH; Robert Wheater, MS; Brian Wummer, MD*

U. S. Department of Health and Human Services
Public Health Service
Agency for Toxic Substances and Disease Registry
Atlanta, Georgia 30333

SPI-01203

How to use this issue...

This issue begins with a hypothetical Case Study that describes a realistic encounter with a patient. The case is then developed throughout the publication by way of the Challenge questions at the end of each section. The answers to the Pretest are incorporated in (11) through (14) of the Challenge answers, which begin on page 20. To fully benefit from this monograph, you are urged to answer each Challenge question as it is presented.

Objectives for this monograph on vinyl chloride toxicity:

- ❑ **Realize why vinyl chloride continues to be a hazard of great concern**
- ❑ **Understand the known factors contributing to vinyl chloride poisoning**
- ❑ **Assess a patient's environmental or occupational exposure to vinyl chloride**
- ❑ **Effectively evaluate and manage vinyl chloride-exposed patients**
- ❑ **Utilize a variety of sources to locate further information on vinyl chloride**

Contents

Case Study

A 55-year-old male comes to your office for an initial visit. He complains of fatigue, a 20-pound weight loss and anorexia over the past 2 to 3 months. He has been in good health prior to this, except for a history of hypertension, for which he has been treated with hydrochlorothiazide, 50 mg a day, for the past 3 years. He consumes about 2-3 beers per week and does not smoke tobacco.

Questioning reveals that he has been a car salesman for 25 years. He is married, has 3 children, and has lived near an industrial park for the last 18 years. Three and one-half years ago, he and his family were evacuated from their home for several days after a railroad tanker car derailed and ruptured on the nearby railroad tracks. He and his family were treated at a local emergency room for sore throat and cough; acute respiratory complaints resolved within 2 weeks. He does not recall the name of the chemical that was released, but he remembers it had a slightly sweet odor, an odor he has occasionally noticed while in the backyard. His youngest daughter, who has just turned 19, presented him with a grandson last week. The pregnancy was troubled, but the baby is fine. The rest of his family is in good health.

On physical examination, you find a chronically ill-appearing male. Blood pressure is 140/80; pulse is 72 and regular. He is afebrile. Weight is 174 pounds. There are no skin rashes or lesions. Sclerae are slightly icteric; the remainder of the HEENT examination is normal. There is no thyromegaly, and the neck is supple. No lymphadenopathy is felt. Abdominal exam shows a liver 12 cm in span, with a smooth margin and slightly tender to palpation. The spleen is not enlarged, and there are no other abdominal masses. Extremities and joints are unremarkable, and the neurological examination is completely normal. Rectal exam shows a normal-sized prostate; no masses are felt, and the stool is negative for occult blood.

The initial laboratory results include hemoglobin, PT, PTT, white blood cell count, and urinalysis, all normal. The SGPT is 372 IU/L and SGOT is 293 IU/L. The bilirubin, ferritin, alkaline phosphatase, and serum protein are reported to be within normal limits.

PRETEST

What should be included in this patient's problem list?
What is the differential diagnosis for this patient?
What tests would you order to confirm or rule out these diagnoses?

Vinyl chloride released from point sources to the ambient air is degraded in a matter of hours; that released to lakes, streams, or rivers will volatilize in several hours to a few days, depending on the water's temperature and aeration rate. Vinyl chloride may remain in groundwater, however, for months or years. Of all potential sources of vinyl chloride exposure to the general population today, contaminated groundwater is the most enduring. The Environmental Protecton Agency (EPA) estimates that less than 2% of the country's drinking water supply is contaminated with vinyl chloride at sufficent levels to be of concern.

(1) Additional history to the Case Study: After checking with the local fire department, you find that vinyl chloride was contained in the overturned tanker car and that there was an airborne release of approximately 10,000 gallons of vinyl chloride. Furthermore, you learn from the regional office of the EPA that significant leaks in the reactor vessels may have been occurring over the course of several decades, resulting in frequent environmental contamination. No air monitoring had been done outside the plant. Following the tanker car accident, the complex permanently closed. What further information will you request in order to evaluate the extent of your patient's exposure?

(2) What are the significant sources of vinyl chloride exposure for this patient?

Who's at Risk

Those at greatest risk of vinyl chloride exposure are the 2.2 million workers concerned with the production, use, transport, storage, and disposal of this material. The highest health risk has been to those workers exposed as a result of the polymerization process, especially to individuals who were lowered directly into the reactor vessels after polymerization to remove solid polymer adhering to the inside. During this cleaning process, the exposure levels to vinyl chloride monomer were typically in the range of a hundred ppm or more.

- **Of the 2.2 million workers exposed to vinyl chloride, autoclave cleaners have the highest health risk.**

Vinyl chloride is well absorbed. Following absorption by all routes, it is rapidly distributed via lipids or lipoproteins in the bloodstream to all tissues. The liver and kidneys receive the highest concentrations, followed by the brain, lungs, spleen, and small intestine.

Experimental evidence suggests that the toxicity of vinyl chloride is related to its transformation by the liver to one or several reactive metabolite(s). Suspected intermediate metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, can bind to cellular macromolecules such as DNA and proteins, presumably causing liver damage. These metabolites can also undergo further oxidation to compounds such as 2-chloroacetic acid and thiodiglycolic acid, which are mainly excreted in the urine.

- Following absorption, vinyl chloride is metabolized in the liver. The primary metabolites can cause cellular damage or be further metabolized to compounds that are excreted in the urine.

Physiological Effects

Acute Exposure

The only data regarding acute exposure to vinyl chloride are early reports among occupationally exposed workers. Deaths appeared to be due to narcosis, but no specific exposure levels have been reported. Presumably, these exposure levels exceeded 10,000 ppm. Autopsies revealed congestion of the liver, spleen, and kidneys.

- With acute exposure to vinyl chloride, the nervous system is the primary target.

Chronic Exposure

Several epidemiological studies have convincingly associated chronic vinyl chloride exposure with liver tumors, both malignant and non-malignant, and have suggested an increased incidence of cancers in other parts of the body. Subtle neurological affects have also been noted in some workers chronically exposed to vinyl chloride at relatively low levels.

- With subacute or chronic exposure, the primary target organ is the liver.

SPI-01207

rare form of cancer were employed as reactor cleaners; exposure levels then were presumably much greater than those seen today. Most of the cases of vinyl chloride-induced ASL have been associated with chronic exposures on the order of 100 ppm.

There have been no cases of ASL recorded in individuals who have been occupationally exposed only since allowable workplace air levels were drastically reduced in 1974. However, this may be due to the fact that a sufficient latency period has not yet elapsed for carcinogenic effects to have presented. The few cases of ASL reported to be due to environmental contamination are suspect because of the statistically small numbers involved and the fact that this disease can arise spontaneously.

Increased incidence of several cancers, other than hepatic, have been suggested by various epidemiological studies of vinyl chloride-exposed workers and by animal studies. Presently, there is insufficient evidence to establish a causal relationship in humans between environmental vinyl chloride exposures and suggested increased incidences of cancer of the brain, breast, lung, thyroid, lymphatic or hematopoietic tissues, and malignant melanoma.

Increased frequencies of chromosomal aberrations in circulating peripheral lymphocytes, including fragments, rings, breaks, and gaps, have been reported in vinyl chloride workers. In general, these aberrations have not been associated with vinyl chloride levels of less than 5 ppm. Strong evidence of genotoxicity in a number of biological assay systems suggests that the reported carcinogenicity of vinyl chloride may proceed via genotoxic mechanisms.

Challenge

5
~~6~~ *Referring to the Case Study, would you examine your patient for CNS damage? For malignancies other than hepatic? Explain.*

NO

The physical examination for vinyl chloride-exposed persons includes a thorough evaluation of the liver and spleen. The renal, nervous, hematopoietic, gastrointestinal, cardiovascular, and respiratory systems should also be carefully examined for abnormalities. The extremities of vinyl chloride workers, particularly the hands, should be examined for signs of acroosteolysis, a result of "vinyl chloride disease," discussed under Signs and Symptoms below.

Signs and Symptoms

Acute Exposure. Vinyl chloride has little acute toxicity, and air levels between 8,000 ppm and 13,000 ppm may be tolerated for 5 minutes without the development of symptoms. Longer high-level exposures have been associated with headache, dizziness, euphoria, ataxia, and narcosis; cardiac, circulatory, and respiratory irregularities have also been noted. Depressed myocardial contractility and cardiac dysrhythmias have been reported in animals following acute exposure at anesthetic levels. Such exposure may sensitize the myocardium to catecholamines and may predispose to ventricular fibrillation.

- Short-term vinyl chloride exposure at relatively high concentrations may be tolerated without lasting adverse effects.

Exposures to very high levels (probably in the range of 70,000 to 120,000 ppm) have resulted in death, presumably due to narcosis.

Chronic Exposure. Heavy, long-term occupational exposure to vinyl chloride may lead to "vinyl chloride disease," a condition involving a number of organ systems and tissues and resulting in a variety of clinical symptoms. The reported period of exposure before the onset of this disease has ranged from 1 month to 3 years. New cases of "vinyl chloride disease" have not been reported since acceptable workplace exposure levels were reduced to 1 ppm in 1974.

- "Vinyl chloride disease" is a condition affecting a number of organ systems and tissues.
- The onset of vinyl chloride-induced liver damage is insidious, with a clinical picture of nonspecific hepatic injury.

The signs of "vinyl chloride disease" include a scleroderma-like condition of the connective tissue of the fingers, accompanied by thickening of the dermis. Acroosteolysis, a rare bone disease resulting in decalcification of the terminal phalanges of the hand, may also be seen. Acroosteolysis has frequently been preceded by a Raynaud-type phenomenon in which there is reversible constriction of the arterioles of the fingers leading to numbness, pallor, and cyanosis of the fingers. Vascular occlusions, stenosis, and narrowing of the digital arteries with the development of collateral circulation have been prominent angiographic findings.

Direct Indicators. No reliable direct method exists for monitoring exposure to low levels of vinyl chloride. Attempts have been made to correlate vinyl chloride exposure levels with urinary output of thiodiglycolic acid, a major urinary metabolite that peaks approximately 20 hours after exposure to vinyl chloride. Because of wide individual variations in excretion patterns, however, urinary thiodiglycolic acid is not reliable with exposure to vinyl chloride at concentrations less than 5 ppm, nor several days post-exposure. Likewise, no correlation has been found between the amount of vinyl chloride in breath or urine samples and the inspired air at air concentrations less than 5 ppm.

- There is no reliable direct indicator for vinyl chloride at low exposure levels.

Biological Effect Indicators. Overt liver injury is a relatively late occurrence in vinyl chloride-related hepatic disease, and detection of early chemical injury in asymptomatic individuals is difficult. Standard biochemical enzyme studies (alkaline phosphatase (AP), aspartate aminotransferase (SGOT, AST), alanine aminotransferase (SGPT, ALT) and gamma-glutamyl transpeptidase (GGTP, GGT)) when used alone are of limited value in identifying the early phases or progression of liver injury. These enzymes primarily reflect acute disruption in cell membrane integrity rather than alterations in the uptake, metabolism, storage, or excretion functions of hepatic cells. Furthermore, these enzyme levels may be elevated in nonhepatic diseases, or may return to normal after initial elevation in subacute, chronic or end-stage liver disease, thus complicating their interpretation. The ratio of SGOT to SGPT has been reported to be of some value in predicting early liver disease.

- Except in an ongoing medical surveillance program, standard biochemical and liver function tests alone may be of limited value in evaluating vinyl chloride-induced liver injury.

A correlation has been noted between slightly to moderately elevated total urinary porphyrins and secondary urinary coproporphyrin elevations in the early stages of toxic liver disease. Similar findings seem to be common in vinyl chloride-related liver disease, and periodic determination of these values may aid in monitoring the progress of a known clinical case.

- A rise in urinary coproporphyrin and total urinary porphyrins can signal the early stages of hepatocellular disease.

Recent studies have suggested that measuring clearance rates of substances removed from the circulation by the liver provides the most sensitive and specific indicator of early chemical liver injury. Indocyanine green (ICG) is a synthetic dye used for this purpose. When expressed as half-time, ICG clearance rates are directly related to the severity of chemical hepatic injury. However, the test has certain limitations: it is invasive, involves intravenous injection of a synthetic dye, and necessitates drawing multiple blood samples with same-day analysis.

- Recent studies suggest that fasting serum bile acids, in conjunction with an indocyanine green clearance rate, is sensitive and specific for latent chemical liver injury. Only biopsy is more definitive.

SPI-01210

Management and Treatment

Acute Exposure

Following acute vinyl chloride exposure, the individual should be immediately removed from the source of exposure and given oxygen or artificial resuscitation, if indicated. Any persistent effects should be treated symptomatically. Recovery from acute effects is usually rapid and complete with supportive therapy; there is no specific treatment or antidote for vinyl chloride exposure.

- ❑ **There are no specific treatments for patients with acute exposure to vinyl chloride.**

Chronic Exposure

Symptoms associated with "vinyl chloride disease" tend to disappear after 1 or 2 years following removal from exposure. Hepatic angiosarcoma, on the other hand, grows rapidly and carries a poor prognosis; if untreated, most patients die within six to twelve months of diagnosis. Results of radiation therapy and chemotherapy have been disappointing, and only those patients who have had the tumor successfully resected have been long-term survivors. Patients with chronic liver injury should avoid exposure to vinyl chloride, ethanol, acetominophen, INH, and other hepatotoxins. Followup may require treatment for complications such as ascites, diabetes, and bleeding varices.

- ❑ **Abnormalities due to "vinyl chloride disease" disappear within a few years if the worker is removed from the exposure.**
- ❑ **Unlike "vinyl chloride disease," hepatic angiosarcoma carries a poor prognosis.**

Challenge

(10) What can you tell your patient about hepatic angiosarcoma? How will you advise him?

(11) What is the danger to other members of your patient's family and the community? What tests could you use to evaluate and monitor these individuals?

SPI-01211

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends an exposure limit of 5 ppm for an 8-hour day and a short-term exposure limit of 10 ppm. The National Institute for Occupational Safety and Health (NIOSH) has concluded that an exposure level for vinyl chloride is inappropriate because of its carcinogenicity.

Air in the Environment

The 1982 Environmental Protection Agency (EPA) emission standards for chemicals released to the atmosphere set a limit for vinyl chloride of 10 ppm, measured at the source.

- **The EPA has set an emission standard of 10 ppm for vinyl chloride.**

Water

Pursuant to the Safe Drinking Water Act, the EPA has issued a maximum contaminant level for vinyl chloride of 2 µg/L, effective January 9, 1989. This applies to all community drinking water systems that regularly serve the same 25 persons for at least 8 months of the year, and corresponds to an estimated cancer risk of 1 additional case in 100,000 persons exposed to this level for a lifetime.

- **The maximum contaminant level for vinyl chloride in drinking water is 2 µg/L (2 parts per billion).**

Food

The Food and Drug Administration (FDA) proposed in 1986 that the vinyl chloride monomer content of polymers used in food packaging or processing may range from 5 to 50 ppm, depending on the nature of the polymer and its use.

- **The FDA limits the content of vinyl chloride monomer in PVC that is used for food packaging.**

Challenge

(12) Where would you get help in order to evaluate others living or working in the community near the former vinyl chloride facility, and the workers who were employed at the plant?

11. Popper H, Thomas LB. Alterations of liver and spleen among workers exposed to vinyl chloride. Ann NY Acad Sci 1975; 246:172-94.

Carcinogenicity.

12. Technical Report No. 31. The mutagenicity and carcinogenicity of vinyl chloride: a historical review and assessment. Brussels, Belgium: European Chemical Industry Ecology and Toxicology Centre; 1988.
13. Bolt HM. Metabolic activation of vinyl chloride, formation of nucleic acid adducts and relevance to carcinogenesis. IARC Sci Publ. 1986;70:261-8.
14. Guengerich FP, Watanabe PG. Activation of vinyl chloride to covalently bound metabolites: roles of 2-chloroethylene oxide and 2-chloroacetaldehyde. Biochemistry 1979;18:5177-82.
15. Hansteen IL, Hillestad L, Thiis-Evensen E, Heldaas SS. Effects of vinyl chloride in man: a cytogenetic follow-up study. Mutat Res 1978;51:271-8.
16. Heath CW, Jr, Fable H, Creech JL, Jr. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. Ann NY Acad Sci 1975;246:231-6.
17. IARC (International Agency for Research on Cancer). Monograph on the Evaluation of the Carcinogenic Risk of Chemicals in Humans. Vinyl Chloride. Lyons, France: WHO, IARC 1979;19: 377-401.

Teratological Effects

18. Edmonds LD, Anderson CE, Flynt JW, James LM. Congenital central nervous system malformations and vinyl chloride monomer exposure: a community study. Teratology 1978;17:137-42.
19. Theriault G, Iturra H, Gingras S. Evaluation of the association between birth defects and exposure to ambient vinyl chloride. Teratology 1983;27:359-70.

Related Government Documents

Agency for Toxic Substances and Disease Registry. Toxicological Profile for Vinyl Chloride. Atlanta: US Department of Health and Human Services, Public Health Service, 1989; DHHS document no. XX-XXXX.

Environmental Protection Agency. Health Effects Assessment for Vinyl Chloride. Cincinnati: US Environmental Protection Agency, Office of Environmental Criteria and Assessment, 1984; EPA report no. EPA 540/1-86-036.

Centers for Disease Control. Recommended Standard. Occupational Exposure to Vinyl Chloride. Atlanta: US Department of Health, Education, and Welfare, Public Health Service, 1978; document no. (NIOSH) XX-XXX.

Answers to Challenge Questions

These questions begin on page 3.

(1) Since the odor of vinyl chloride was detected by your patient, you can conclude that the air concentration must have been high (300 to 5000 ppm) and that your patient received toxic or near-toxic doses on those occasions. You may want to determine if others smelled the vinyl chloride and obtain the frequency and extent of environmental contamination from plant records, if they are obtainable. The drinking water in your patient's home should be tested since groundwater contamination, caused by releases from the plant, is a possibility.

(2) In addition to exposure through possible contamination of the air and water at home, your patient may be exposed to vinyl chloride at work. As a car salesman, he may daily spend time inside new cars where the ambient air can contain significant amounts of vinyl chloride (1 to 10 ppm) released from plastic and upholstery including the dashboard and seats. To the general population, this and other sources of consumer exposures to the monomer released from polyvinyl chloride products such as food packaging, flooring, etc. are normally of little concern. Your patient is a nonsmoker, and so does not receive the added insult of the 28 nanograms of vinyl chloride present in the smoke from each cigarette.

(3) Those closest to the source of vinyl chloride, i.e., the former workers at the plant, are at highest risk. Assuming only air emissions from the plant, your patient's immediate family, the surrounding community and especially those residents immediately downwind have probably been periodically exposed. Since airborne vinyl chloride normally photodegrades within a few hours, ambient air exposure is likely to be limited in distance from the plant. If the groundwater has been contaminated, on the other hand, the number of persons affected could be far greater and be located at some distance from the plant.

(4) Your patient has lived near the vinyl chloride plant for 18 years. Depending on the ages of his children, they may have been periodically exposed in their younger years. Animal data suggest that exposure at an early age may increase the risk of cancer later on. If your patient's daughter spent much time at the residence during her pregnancy, there is a chance that his grandson was exposed *in utero*. This fact may increase the risk of cancer for the grandson, even assuming cessation of exposure following the plant shutdown.

(5) It would be prudent to investigate all potentially involved organ systems, even though there is limited evidence to suggest that chronic environmental exposure to vinyl chloride may result in neurotoxicity or cancers other than hepatic.

(6) The patient's problem list includes fatigue, weight loss, slightly icteric sclerae, and liver enlargement.

(7) The differential diagnosis at this point might consist of:

acute hepatitis (viral, alcohol, or chemical- or drug-induced)
chronic active hepatitis
granulomatous or neoplastic infiltration

Cirrhosis is less likely since transaminases are high, but it cannot be ruled out. In light of the normal alkaline phosphatase, primary biliary cirrhosis or bile duct obstruction are not considered.

(8) Viral hepatitis should be ruled out with the appropriate serologies and a liver-spleen scan performed. An MRI (magnetic resonance imaging) scan and an angiogram might also be helpful. Direct indicators, such as urinary thiodiglycolic acid or vinyl chloride levels, would only be helpful if significant quantities of vinyl chloride are presently being consumed in the drinking water. However, negative results, in tests using these direct indicators, do not rule out drinking water contamination.

(9) The differential diagnosis now most likely includes:
cirrhosis
malignancy
Hepatic angiosarcoma is not normally prominent in the differential diagnosis of liver function abnormalities. However, the known exposure to vinyl chloride and the test results thus far make it a probability. In that case, hepatic arteriography would reveal a characteristic appearance, with displacement of hepatic arteries, and a blush and "puddling" during the middle of the arterial phase. Percutaneous liver biopsy is contraindicated in cases of angiosarcoma because of the vascular nature of the tumor and the possibility of complicating thrombocytopenia or significant bleeding; laparoscopic biopsy would be more appropriate.

(10) Hepatic angiosarcoma grows rapidly and carries a poor prognosis. If untreated, most patients die within six to twelve months of diagnosis. The only long-term survivors have had the tumor successfully resected. You might assure your patient that there is no evidence that the vinyl chloride exposure at work will influence the evolution of his disease. As a precaution you might suggest that he ventilate new cars before entering them for prolonged periods and drive with the window open to maintain ventilation. Until the drinking water at his home is tested, the family should use bottled water to avoid any possible exposure there.

(11) Since the rest of the family and the nearby community may have had similar exposure to vinyl chloride, all should undergo testing for transaminases, alkaline phosphatase, and serum bile acids to detect latent chemical injury. If these tests or an indocyanine green clearance rate are positive for hepatic injury, biopsy may also be helpful. If the drinking water is not contaminated and there is no waste disposal source to contaminate the water in the future, the exposure for the family and community has likely terminated.

(12) Your local, county, or state health department should be contacted and notified of the suspect case. Because hepatic angiosarcoma is an extremely rare disease, even one case would alert public health authorities to a potential risk to the community around this plant. Your report should initiate case-finding investigations among the workers at this plant as well as in the community. Public health authorities may also want to evaluate the potential for groundwater contamination around the plant.

File: VCM: Health Effects

The Vinyl Institute

A Division of The Society of The Plastics Industry, Inc.

Roy T. Gottesman
Executive Director

October 10, 1989

Dr. Robert Hinderer
BFGoodrich Company
3925 Embassy Parkway
Akron, Ohio 44313

Re: Human Carcinogens - Vinyl Chloride

Dear Bob:

Dr. Brian Bennett of ICI, who maintains the angiosarcoma registry visited with me in Wayne on October 5th. He kindly provided me with the enclosed paper from Environmental Research 49, 143-151 (1989). The marginal notes on this copy are those of Dr. Bennett who has met with the author, Dr. Benjamin Van Duuren at NYU Medical Center.

Also, Dr. Bennett advises me that because of some apparent errors in the publication, he plans to write a letter to the editor, pointing out the mis-interpretations/errors. This is for your information and files.

Sincerely yours,

Roy

RTG/pmb

SPI-01216

ENVIRONMENTAL RESEARCH 49, 143–151 (1989)

With Compliments
Ben Van Duuren.

REVIEW

Comparison of Potency of Human Carcinogens: Vinyl Chloride, Chloromethylmethyl Ether and Bis(chloromethyl)ether

BENJAMIN L. VAN DUUREN

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Received November 4, 1988

The α-chloroether carcinogen chloromethylmethyl ether (CME) and its impurity bis(chloromethyl)ether (BCME) are direct-acting alkylating agents. Vinyl chloride (VC) is an indirect-acting carcinogen but its accepted carcinogenic intermediate, chloroethylene oxide, is also an α-chloroether. Both CME–BCME and VC have been in industrial use since about 1950. Hence, they were selected for comparison of potency as human carcinogens using numerous epidemiologic reports. There were 115 deaths due to angiosarcoma of the liver among several hundred thousand VC-exposed workers on the basis of reports from 10 countries during 1955 and 1984. Reports from five countries cited a total of 87 respiratory cancer deaths among only 3024 CME–BCME-exposed workers. If a recent court settlement in the United States is taken into account, the number of respiratory cancer deaths due to CME–BCME rises to 117. On the basis of these numbers of cancer deaths, and the levels and durations of exposure, it is concluded that VC is a weak human carcinogen compared to CME–BCME.

INTRODUCTION

Thirty-six chemicals or mixtures of chemicals are now classed as materials for which there is sufficient evidence of human carcinogenicity (IARC, 1987). They are referred to as Group 1 human carcinogens by the IARC. In most instances sufficient animal carcinogenicity data are also available for these 36 materials. Included in this group are chloromethylmethyl ether (CME), bis(chloromethyl)ether (BCME), and vinyl chloride (VC). The purpose of the present report is to compare the potency of these carcinogens to humans based on animal bioassay data and epidemiologic studies.

These chemicals came into use in chemical industry at about the same time, 1950, although VC was used on a small scale prior to 1950. The animal and human carcinogenicity data on these chemicals first became known during the years 1968–1973. Since then, extensive studies on their animal carcinogenicity and epidemiologic studies on occupational exposure to them have been carried out. Thus, they provide a valuable series in which to compare potency as human carcinogens.

The animal carcinogenicity results on CME, BCME, and VC preceded publication of the first case reports and epidemiologic studies by several years. Thus, these human carcinogens are unusual in that the historical sequence of events for

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most human carcinogens is the reverse. For most of the 36 chemicals on the current list of Group 1 human carcinogens, epidemiologic studies provided the stimulus for subsequent laboratory animal carcinogenesis bioassays and related biochemical studies, as was pointed out in the preamble of the most recent compilation (IARC, 1987).

INDUSTRIAL PRODUCTION

CME is used on a small scale in chemical industry as an intermediate in the manufacture of anion-exchange resins from polystyrene and related polymers (Van Duuren *et al.*, 1968).

The resin made from polystyrene, CME, and trimethylamine, named Amberlite IRA-400, is used in the purification of household water and on a larger scale for deionization of water used by the electric power and pharmaceutical industries.

CME is synthesized from methyl alcohol, hydrochloric acid (HCl), and formaldehyde (CH_2O). The latter two reagents lead to the formation of BCME. Thus, CME as manufactured and used contains varying amounts of BCME, ranging from 1 to 10%, depending upon the exact conditions of manufacture (Van Duuren 1980). BCME was manufactured on a pilot-plant scale when CME first came into full-scale production, but it is not used in chemical industry because of its acute toxicity. Because CME as manufactured and used contains BCME, these two chemicals are referred to as CME–BCME in the discussion on occupational exposure that follows.

VC was used in industry from about 1930 but did not come into large-scale use until about 1950 for the manufacture of its polymer (PVC) and copolymers, e.g., with vinylidine chloride (Wessling and Edwards, 1971).

Production figures for CME–BCME or the anion-exchange resins for which it is used were not given in any of the published epidemiologic studies and could not be ascertained from industry sources. VC on the other hand, is No. 8 on the list of the top 10 organic chemicals manufactured in the United States (Anonymous *Chem. Eng. News*, 1988). In 1987, 8.23 billion pounds of VC was manufactured in the United States alone. It was estimated that in the same year 7.6 billion pounds of PVC was manufactured in the United States (Anonymous *Chem. Eng. News*, 1987). Because of the relatively limited use of anion-exchange resins compared to PVC, it can be safely concluded that the amount of CME–BCME manufactured worldwide is minuscule by comparison to the amount of VC produced. It should be noted that both CME and BCME are used in laboratory syntheses as alkylating agents in reaction with nucleophiles such as amines, as well as in displacement and addition reactions (Summers, 1955).

ANIMAL BIOASSAYS

Laboratory-purified CME is a weak carcinogen and an initiating agent in two-stage carcinogenesis on mouse skin. It also causes induction of fibrosarcomas by subcutaneous injection in rats. BCME is a mouse skin initiating agent and carcinogen and causes fibrosarcoma by subcutaneous injection in rats. In all three bioassays BCME was notably more potent than CME (Van Duuren *et al.*, 1968, 1969). In further studies subcutaneous injection of CME and BCME in newborn mice resulted in increased induction of lung adenomas in animals exposed to

BCME but not in those exposed to CME (Gargus *et al.*, 1969). In several subsequent studies the inhalation exposure of rats to CME and to BCME was studied. BCME proved to be a potent carcinogen for rats by this route at 0.1 ppm resulting in lung cancer and esthesioneuroepithelioma (Kuschner *et al.*, 1975). In other inhalation experiments in rats at various doses, induction of lung cancer was not observed but nasal tumors were induced (Leong *et al.*, 1981). These bioassays were recently reviewed (Van Duuren and Van Duuren, 1988).

On the basis of inhalation bioassays in which rats were exposed to mixtures of hydrochloric acid and formaldehyde (Sellakumar *et al.*, 1985) and hence to BCME it was subsequently concluded that BCME is markedly carcinogenic to rats in the dose range of only 0.1 to 0.4 parts per billion (Van Duuren and Van Duuren, 1988).

VC was first shown to be carcinogenic by inhalation exposure using Wistar rats at a dose level of 30,000 ppm (Viola *et al.*, 1971). Zymbal gland tumors were observed together with metastases to the skin, lung, and bone. Subsequently, a series of large-scale bioassays was undertaken using inhalation exposure of Wistar and Sprague–Dawley rats, Swiss mice, and golden hamsters (Maltoni *et al.*, 1984). Extensive dose–response studies were performed in these bioassays. Lung adenomas, angiosarcoma of the liver (ASL), and adenocarcinoma of the mammary gland in mice were observed. The same type of exposure in rats in the 50- to 10,000-ppm range led to induction of ASL, nephroblastoma, neuroblastoma, Zymbal gland tumors, and miscellaneous tumors at other sites.

From the above bioassays it is clear that BCME is a much more potent carcinogen by several orders of magnitude than VC in rat inhalation experiments, on the basis of numbers of animals with malignant tumors and doses used in the inhalation experiments. CME must be classed as a weak carcinogen and its carcinogenicity can be ascribed in part to the presence of BCME in industrial grade CME and to the formation of BCME from the hydrolysis products of CME.

Both CME and BCME are highly reactive direct-acting alkylating agents which do not need to be metabolized *in vivo* in order to exert their biological activity. Like other direct-acting carcinogens such as epoxides and β-lactones, they are expected to exert carcinogenic action at the site of contact in animal tests (Van Duuren, 1980). This is indeed the case, as shown by induction of nasal and lung tumors by inhalation exposure in rats, skin cancer by topical application in mice, and lung cancer by occupational exposure in humans.

Unlike CME and BCME, VC is an indirect-acting carcinogen which is activated *in vivo* to chloroethylene oxide, a highly reactive and unstable epoxide. Extensive studies on metabolism of VC *in vitro* and *in vivo* and bioassays of the metabolites point to this epoxide as the activated carcinogenic intermediate of VC, as originally suggested on the basis of structure–activity considerations (Van Duuren, 1975). This subject has been reviewed (Singer and Grunberger, 1983). Because of its accepted mode of action, VC is expected to be a multipotential carcinogen in animals and humans. This is borne out by the animal carcinogenicity data and epidemiologic studies in workers exposed to VC.

OCCUPATIONAL EXPOSURE: CME–BCME

Three reports appeared in 1973 describing the occurrence of lung cancer, most frequently oat cell carcinoma, in workers exposed to CME–BCME (Figueroa *et*

al., 1973; Sakabe, 1973; Thiess *et al.*, 1973). On the basis of the animal carcinogenicity data available at the time and these three early reports, both CME and BCME were classed as human carcinogens by the U.S. Department of Labor in 1974 (U.S.D.L., 1974). They were classed as Group 1 human carcinogens by the International Agency for Research on Cancer in 1979 (IARC, 1979a). During the years 1973 and 1987 numerous epidemiologic studies dealing with CME–BCME were published (IARC, 1987). A report involving three worker deaths from lung cancer in a small BCME manufacturing facility in the United Kingdom appeared recently (Roe, 1985).

The number of respiratory cancer deaths ascribed to occupational exposure to CME–BCME and to BCME alone are summarized in Table 1. These data were culled from the literature up to 1987. The five countries reporting epidemiologic studies covered the total period 1948 through 1981.

Numerous interim epidemiologic studies appeared dealing with the same manufacturing facility in the United States. The first report concerning respiratory cancer among workers at this facility appeared in 1973 (Figueroa *et al.*, 1973). One of the 1987 reports (Collingwood *et al.*, 1987) gave findings on six other CME manufacturing facilities which are grouped together in Table 1. Thus the total number of respiratory cancer deaths from five countries was 87 out of 3024 exposed workers.

It is of considerable interest to compare the respiratory cancer deaths in one manufacturing facility in the United States as presented in Table 1 with the class-action settlement reached in 1987 in the Philadelphia Court of Common Pleas in Pennsylvania. According to this settlement 62 workers who died of respiratory cancer were deemed to have been exposed to CME–BCME and their estates were awarded monetary benefits. Twenty-five of these had oat cell carcinoma of the lung and 37 had other respiratory cancer. This settlement did not exclude the possibility that there were other workers exposed to CME–BCME who may have developed respiratory cancer. Monetary awards were based on the 62 workers having worked in certain buildings in the facility at specific times and developed

TABLE 1
RESPIRATORY CANCER DEATHS FROM EXPOSURE TO CME–BCME

Country	Period of exposure	Number of workers	Number of deaths[a]	Duration of exposure[b] (years)	Reference
U.S.	1948–1981	737	32	1–19	Maher, 1987
U.K.	1948–1980	221	10	1–15	McCallum, 1983
China	1958–1981	318	12	2–18	Hsueh, 1984
Japan[c]	1955–1970	32	5	7–12	Sakabe, 1973
Germany[c]	1954–1971	18	8	6	Thiess, 1973
U.S.	1948–1980	1,698	20	5–19	Collingwood, 1987

[a] Taking the legal settlement into consideration, the total number rises from 87 to 117 (see text).
[b] Years from first exposure to diagnosis of respiratory cancer.
[c] Exposure to BCME only; all others to CME–BCME.

respiratory cancer (Krimsky, 1987). It is notable that the number of workers compensated for this one manufacturing facility, 62, is almost double that given in the recent epidemiologic reports (Collingwood *et al.*, 1987, Maher and DeFonso, 1987).

It has been pointed out in some of these reports that (1) the respiratory cancers were mostly oat cell carcinoma of the lung and, (2) in a number of cases there was a remarkably short latent period between beginning of exposure and diagnosis of lung cancer and hence an unusually high incidence of this cancer among younger workers.

Smoking histories were examined in some of the studies summarized in Table 1 but were not considered in calculations of cancer risk, on the basis of the conclusion that this confounding factor is difficult to assess quantitatively (Doll, 1984).

The levels of exposure to CME–BCME were in earlier years, i.e., up to the early 1970s, rough estimates at best, and moreover, varied not only from one facility to the next, but also frequently within the same facility. It was only after these chemicals were known to be carcinogenic to animals and humans that exposure to them became monitored, regulated, and reduced. Before 1970 exposure to CME–BCME at certain stages of use in the manufacture of anion-exchange resins was so high that buildings had to be routinely evacuated three or four times during one 8-hr shift (Figueroa *et al.*, 1973).

During the process of manufacture of anion-exchange resin, excess CME was destroyed by addition of water to the reaction vessels. This step, referred to as quenching, is a highly exothermic reaction, which results in the release of HCl, CH_2O, methyl alcohol, and undoubtedly unreacted CME–BCME, all within the building where the resin was being manufactured, at times with inadequate ventilation.

Attempts were made in some of these studies to divide worker exposure into low-, medium-, and high-risk levels (Maher and DeFonso, 1987; McCallum *et al.*, 1983). This type of classification is difficult to evaluate because exposure levels are not available for at least the first 20 years that these chemicals have been in use. Moreover, the manufacture of CME is by its nature a batch-type operation. The number of batches and the quantities produced and used for any given length of time did not emerge from any of the studies reviewed here. It was also impossible to obtain with any degree of certainty the temporal exposure levels for the critical 20-year period, i.e., intense exposure for brief periods of time compared to long-term exposure to low levels of CME–BCME.

OCCUPATIONAL EXPOSURE: VC

The first full report dealing with the occurrence of angiosarcoma of the liver (ASL) in VC–PVC workers (Creech and Johnson, 1974), appeared 3 years after the initial animal carcinogenicity bioassays were described (Viola *et al.*, 1971). Since then numerous papers have dealt with ASL and cancers in other organs and systems in workers in the VC–PVC industry (IARC, 1987).

The most recent compilation of worker deaths ascribed to ASL as a result of exposure to VC was reported by the Association of Plastics Manufacturers in

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Europe (APME) for the years 1955 through 1984. (Forman *et al.*, 1985). A total of 115 deaths from ASL were counted for Europe, North America, and Japan. Thirty-five of these cases were from 10 manufacturing facilities in the United States. The largest proportion of ASL cases occurred between 20 and 29 years from the beginning of exposure. The median latent period was given as 22.6 years. The authors concluded that additional cases may be expected after more than 30 years. Close to 77% of the ASL deaths occurred in autoclave cleaners and production operators where the highest levels of exposure to VC were encountered. The total number of workers exposed to VC was not given in this compilation.

During two-and-a-half decades, 1950–1975, i.e., before human carcinogenicity was established (IARC, 1979a), the major concerns in manufacturing industries were the narcotic properties of VC and the fact that at sufficiently high levels, 4% by volume (Weast and Astle, 1981), it becomes a fire and explosion hazard. As a result of these concerns some information is available on VC concentrations in components of some manufacturing facilities prior to the early 1970s. The highest concentration of VC was found in the polymerization reaction vessels after completion of the process. This has been reported to reach 3000 to 4000 ppm. Other areas in the facility gave measurements ranging from 1 to 1000 ppm (Barnes, 1976). These levels decreased markedly after the early 1970s (IARC, 1979b; Barnes, 1976; Purchase *et al.*, 1987).

Several recent reports present additional epidemiologic findings on cancer incidences in VC–PVC workers (Laplanche *et al.*, 1987; Heldaas *et al.*, 1984; Smulevich *et al.*, 1988). They present data on ASL, lung, stomach, skin, hematopoietic and lymphatic systems. Some of these cancers of organs and systems other than the liver were mentioned in earlier reports and reviews (IARC, 1987). Further studies in some of these areas are indicated because of marginal significances in some instances, e.g., malignant melanoma as pointed out by the authors (Heldaas *et al.*, 1984). There are indications that ASL may occur only at high levels of and/or prolonged exposure to VC (Forman *et al.*, 1985; Smulevich *et al.*, 1988). In one study increased deaths in VC-exposed workers were reported from cancers of the lymphatic, hematopoietic, digestive, respiratory systems, including bone, brain, and skin, but no ASL's were observed (Smulevich *et al.*, 1988).

CONCLUSIONS

The number of workers exposed to VC during the years 1948–1981 is probably two orders of magnitude higher than the number of those exposed to CME–BCME during the same period. In the latter case, and if the legal settlement reached for one manufacturing facility is taken into account, there were 117 respiratory cancer deaths reported from five countries from 1948–1981 among 3024 workers. By comparison there were 115 ASL deaths among several hundreds of thousands of VC workers from 1955–1984 in the APME compilation. The latter is undoubtedly much more complete than that given in Table 1 for CME–BCME respiratory cancer deaths.

Exposure levels to VC range from one to 4000 ppm with roughly 77% of ASL deaths occurring in workers exposed to a 3000- to 4000-ppm level. VC is a narcotic gas with a pleasant odor which leads to euphoria, unconsciousness, and sleep. On

the other hand CME-BCME is highly irritating and noxious in vapor form. Moreover, in air even at low levels of humidity, CME-BCME releases highly noxious fumes of HCl and CH_2O. CH_2O causes eye and mucous membrane irritation at 0.01 ppm to 2.0 ppm (NRC-NAS, 1981). The odor threshold concentration for HCl is about 0.1 ppm and irritancy becomes pronounced in the range of 5–20 ppm (NRC-NAS, 1976). Thus, unlike VC exposure, CME-BCME exposure forces a warning on workers to such an extent that they evacuate work areas when unbearable levels of these chemicals and their hydrolysis products appear. It is therefore reasonable to conclude that levels of exposure to CME-BCME were lower than those to VC by several orders of magnitude.

There is another factor which should be borne in mind. The Group 1 occupational carcinogens (IARC, 1987) are indirect-acting agents with the exception of CME-BCME, melphalan, and sulfur mustard. It is expected that the markedly higher human and animal carcinogenicity of CME-BCME compared to VC is ascribable to their high order of direct-acting alkylating reactivity; i.e., metabolic activation is not required for CME-BCME. In the case of the indirect-acting carcinogen VC, the delivered level of activated carcinogenic intermediate is undoubtedly substantially lower than the amounts of VC inhaled. A part of the VC inhaled is metabolized to innocuous products and the activated carcinogenic intermediate will also be partially removed by irrelevant reactions with glutathione, proteins, and other tissue constituents (Van Duuren and Van Duuren, 1988).

It is possible that additional information will be forthcoming concerning such matters as total number of workers exposed to VC or quantities of CME-BCME manufactured, in order to place the above observations and conclusions on a more solid foundation.

From the animal bioassays and epidemiologic studies summarized in this report it is clear that CME-BCME represents a much more potent animal and human carcinogen than VC.

ACKNOWLEDGMENTS

This work was supported by NIH center grants CA-13343 and ES-00260 and American Cancer Society grant No. 00009. This paper constitutes Contribution No. L235 from the Laboratory of Organic Chemistry and Carcinogenesis.

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