The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and is often uncertain. In this monograph, the Agency for Toxic Substances and Disease Registry (ATSDR) has made a diligent effort to ensure the accuracy and currency of the information presented but makes no claim that the document comprehensively addresses all possible situations related to this substance. This monograph is intended as an additional resource for physicians and other health professionals in assessing the condition and managing the treatment of patients potentially exposed to hazardous substances. It is not, however, a substitute for the professional judgment of a health care provider and must be interpreted in light of specific information regarding the patient available to such a professional and in conjunction with other sources of authority.

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Please send me the following Case Studies in Environmental Medicine. (Circle selected subjects.)

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CASE STUDIES IN ENVIRONMENTAL MEDICINE: VINYL CHLORIDE TOXICITY

If you wish CME credits or CEUs, please indicate your answers to the Posttest questions on the previous page by circling the letters below for the correct answers. Complete the evaluation questionnaire and fill in the information requested on the following page.

Mail your answer sheet, evaluation questionnaire and the information page which follows to: Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, NE, Atlanta, GA 30333.

1. a b c d e
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Evaluation Questionnaire

Please complete the following evaluation by circling the appropriate number.

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
1. As a result of completing this monograph, I will be able to:					
Explain why vinyl chloride is a chronic health hazard.	1	2	3	4	5
Describe the known factors contributing to vinyl chloride poisoning.	1	2	3	4	5
Identify potential environmental or occupational sources of exposure to vinyl chloride.	1	2	3	4	5
Identify evaluation and treatment protocols for persons exposed to vinyl chloride.	1	2	3	4	5
List sources of information on vinyl chloride.	1	2	3	4	5
2. The monograph addressed the objectives listed under "How to use this issue . . ."	1	2	3	4	5
3. I am more likely to ask patients questions regarding possible environmental exposure as a result of reading this issue.	1	2	3	4	5
4. Independent study was an effective teaching method for the content.	1	2	3	4	5
5. How much time (in minutes) was required to read this monograph and complete the posttest?	40	60	80	100	120

Comments: _____

7. Which is (are) important in the history and examination of patients exposed to vinyl chloride?
   a. a baseline chest X ray
   b. thorough evaluation of the liver and spleen
   c. alcohol consumption
   d. location of residence
   e. prior use of contraceptive steroids
8. Which of the following tests might be used to evaluate a patient exposed to vinyl chloride?
   a. serum bilirubin
   b. urinary coproporphyrin
   c. liver enzymes
   d. cardiac enzymes
   e. arterial pO_2

Your confidential test score will be returned with an indication of where the correct answers can be found in the text. Validation of earned CME credit and CEU will also be forwarded to participants, and their names, if requested, will be placed on the mailing list to receive other issues in the *Case Studies in Environmental Medicine* series.

POSTTEST: VINYL CHLORIDE TOXICITY

Circle all correct answers and transfer your answers to the answer sheet immediately following.

1. Which is true regarding the risk of exposure to vinyl chloride?
   a. there is no risk today
   b. workers in the PVC industry may be at increased risk
   c. chronic exposure may produce angiosarcoma of the liver
   d. those suffering from cardiovascular disorders have increased risk
   e. excessive alcohol consumption may increase the risk
2. Vinyl chloride is distributed in the body
   a. slowly because it is not well absorbed
   b. rapidly because it is very water-soluble
   c. rapidly because it is soluble in blood lipids and lipoproteins
   d. rapidly because of uptake by the erythrocytes
   e. slowly because it is excreted as a glucuronide
3. Chronic inhalation of vinyl chloride may result in
   a. malignant and nonmalignant liver injury, depending on exposure level
   b. a prehepatic sclerosis unique to toxic chemical exposure
   c. dermatitis
   d. hepatic fibrosis
   e. angiosarcoma of the liver
4. Neurologic effects due to vinyl chloride
   a. are not as great as once thought, which is why it is no longer used as an anesthetic
   b. may include peripheral neuropathy in chronic exposures
   c. can result in Parkinson's disease
   d. may result from vascular occlusions
   e. may include electroencephalographic changes
5. Angiosarcoma of the liver (ASL)
   a. is a common illness often associated with exposure to vinyl chloride
   b. will not result if the exposure to vinyl chloride ceases
   c. is a rare disease
   d. has occurred less frequently since workplace levels for vinyl chloride have been reduced
   e. has a latency period of 15 to 40 years
6. In the management and treatment of vinyl chloride-exposed patients
   a. the administration of a quick-acting antidote is essential in acute exposures
   b. recovery from a sublethal, short-term exposure is usually rapid and complete with supportive therapy
   c. patients should be encouraged to avoid alcohol
   d. viral hepatitis is often a complication
   e. the organ of primary concern is the liver

International Association for Continuing Education and Training (IACET) to sponsor continuing education units for other health professionals.

The Agency for Toxic Substances and Disease Registry, in joint sponsorship with CDC, is offering 1 hour of CME credit in Category 1 of the Physician's Recognition Award of the American Medical Association and 0.1 hour of CEU for other health professionals upon completion of this monograph.

In addition, the series *Case Studies in Environmental Medicine* has been reviewed and is acceptable for credit by the following organizations:

The **American Academy of Family Physicians (AAFP)**. This program has been reviewed and is acceptable for 1 prescribed hour by the American Academy of Family Physicians. (Term of Approval: beginning January 1992.) For specific information, please consult the AAFP Office of Continuing Medical Education.

The **American College of Emergency Physicians (ACEP)**. Approved by the American College of Emergency Physicians for one hour per issue of ACEP Category I credit.

The **American Osteopathic Association (AOA)**. AOA has approved this issue for 1 credit hour of Category 2-B credit.

The **American Association of Occupational Health Nurses (AAOHN)**. AAOHN has approved this program for 1.2 contact hours. Applicant will receive the assigned code number in the award letter.

The **American Board of Industrial Hygiene (ABIH)**. ABIH has approved this program for 0.5 certification maintenance (CM) point per 3 Case Studies. The CM approval number is 2817.

To receive continuing education credit (CME or CEU), complete the following Posttest in the manner shown in the sample question below. **Circle all correct answers.**

Which of the following is known to precipitate migraine headaches?

(a.) fatigue
(b.) alcohol
c. grapefruit
(d.) sunlight
e. sleep

<u>NOTE FROM NLM</u>: TO RECEIVE CONTINUING EDUCATION CREDITS, YOU MUST RETURN A HARD COPY OF THE COMPLETED ANSWER SHEET AND EVALUATION TO THE CONTINUING EDUCATION COORDINATOR AT ATSDR. BE SURE TO INCLUDE YOUR NAME, ADDRESS, AND OTHER INFORMATION REQUESTED.

After you have finished the Posttest, please transfer your answers to the answer sheet and complete the evaluation on the lower half of that page. Mail the completed pages to:

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(9) The differential diagnosis now most likely includes cirrhosis and malignancy. Hepatic angiosarcoma is not normally prominent in the differential diagnosis of liver function abnormalities. However, the test results thus far and the fact that this is a nonoccupational exposure to vinyl chloride (nonmalignant liver injury has not been reported in environmental exposures) make angiosarcoma of the liver a possibility. In the case of angiosarcoma of the liver, 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 6 to 12 months after diagnosis. The only long-term survivors have had the tumor successfully resected. As a precaution you might suggest that the patient 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 periodic testing of transaminases, alkaline phosphatase, and serum bile acids to detect latent chemical injury. If these tests or an ICG clearance rate are positive for hepatic injury, biopsy may also be helpful. If the drinking water is not contaminated and there is no vinyl chloride waste disposal source to contaminate the water in the future, the exposure to the family and community has likely terminated.

(12) Your local, county, or state health department should be contacted and notified of the possible 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 former workers at the plant as well as in the community. Public health authorities may also want to evaluate the potential for groundwater contamination around the plant.

Sources of Information

More information on the adverse effects of vinyl chloride and the treatment and management of vinyl chloride-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Vinyl Chloride Toxicity* is one of a series. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Posttest and Credits

Continuing education credit is available to health professionals who use this monograph and complete the posttest. The criterion for awarding continuing medical education (CME) credits and continuing education units (CEU) is a posttest score of 70% or better.

The Centers for Disease Control (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians, and by the

Answers to Pretest and Challenge Questions

(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 doses on those occasions. You may want to determine if others smelled the vinyl chloride. In cases where plant records are available, it is desirable to obtain the frequency and extent of contamination from them. The drinking water in your patient's home should be tested since groundwater contamination, caused by a release 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 such as PVC food packaging and flooring are of little concern.

(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 occur only a limited distance from the plant. If the groundwater has been contaminated, on the other hand, the number of persons affected could be far greater, and they could be located at some distance from the plant.

(4) Your patient has lived near the vinyl chloride plant for 18 years. His children may have been periodically exposed in their younger years, depending on their ages. Data from animal studies suggest that exposure at an early age may increase the risk of cancer later; however, there is no supportive human evidence. The patient's grandson has not been exposed to contaminated air because the plant shut down 2 years ago. There is no evidence that vinyl-chloride contaminated water would have any effect on the child, pre- or postnatally.

(5) Yes. It would be prudent to investigate all potentially involved organ systems, although there is no conclusive evidence that environmental exposures to vinyl chloride result in neurotoxicity or cancers other than hepatic.

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

(7) The differential diagnosis at this point might include the following:

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

Among causes of acute hepatitis, alcohol is less likely because the SGPT level is greater than the SGOT level. With normal alkaline phosphatase, primary biliary cirrhosis or bile duct obstruction are also not probable.

(8) Viral hepatitis should be ruled out by serologic testing. Imaging studies such as CAT, MRI, or liver-spleen scan would be appropriate. An angiogram would be helpful if angiosarcoma is suspected. Direct indicators, such as urinary thiodiglycolic acid or vinyl chloride levels, would be helpful only if exposure to vinyl chloride were recent. Negative results in tests measuring these direct indicators, however, would not rule out drinking water contamination, for example.

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Carcinogenicity

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Guengerich FP, Crawford WM Jr, Watanabe PG. Activation of vinyl chloride to covalently bound metabolites: roles of 2-chloroethylene oxide and 2-chloroacetaldehyde. Biochemistry 1979;18(23):5177-82.

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Heath CW Jr, Falk 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.

International Agency for Research on Cancer. Some monomers, plastics and synthetic elastomers and acrolein. Lyon: IARC,1979:377-438. (IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans; vol 19).

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.

Teratologic Effects

Edmonds LD, Anderson CE, Flynt JW Jr, James LM. Congenital central nervous system malformations and vinyl chloride monomer exposure: a community study. Teratology 1978;17:137-42.

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. NTIS report no. PB/90/103810/AS.

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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?

_____

_____

_____

_____

Suggested Reading List

General

Bolt HM, Laib RJ, Kappus H, Buchter A. Pharmacokinetics of vinyl chloride in the rat. Toxicology 1977;7:179-88.

Buchter A, Filser JG, Peter H, Bolt HM. Pharmacokinetics of vinyl chloride in the Rhesus monkey. Toxicol Lett 1980;6:33-6.

Dinman BD, Cook WA, Whitehouse WM, Magnuson HJ, Ditcheck T. Occupational acroosteolysis. An epidemiological study. Arch Environ Health 1971;22:61-73.

Doll R. Effects of exposure to vinyl chloride. An assessment of the evidence. Scand J Work Environ Health 1988;14:61-78.

Environmental Health Associates. An update of an epidemiological study of vinyl chloride workers 1942-1982. Oakland, CA: EHA Inc; 1986. Final report to the Chemical Manufacturers Association.

Fox AJ , Collier PF. Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. Br J Ind Med 1977;34:1-10.

Perticoni GF, Abbritti G, Cantisani TA, Bondi L, Mauro L. Polyneuropathy in workers with long exposure to vinyl chloride. Electrophysiological study. Electromyogr Clin Neurophysiol 1986;26:41-7.

Preston BJ, Jones KL, Grainger RG. Clinical aspects of vinyl chloride disease: acro-osteolysis. Proc R Soc Med 1976;69:284-6.

Hepatotoxicity

Berk PD, Martin JF, Young RS, et al. Vinyl chloride-associated liver disease. Ann Intern Med 1976;84:717-31.

Workplace

Air

The PEL set by OSHA is 1 ppm averaged over an 8-hour workday.

The Occupational Safety and Health Administration (OSHA) requires that a worker's exposure to airborne vinyl chloride monomer not exceed 1 ppm averaged over any 8-hour period and that a worker not be exposed to greater than 5 ppm for any period of time exceeding 15 minutes. Direct contact with the liquid is prohibited.

NIOSH recommends a zero exposure limit for vinyl chloride.

The American Conference of Governmental Industrial Hygienists 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. NIOSH has recommended that workers exposed to vinyl chloride wear an air-supplied respirator.

Environment

Air

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

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

Water

The maximum contaminant level for vinyl chloride in drinking water is 2 ppb.

Pursuant to the Safe Drinking Water Act, EPA has issued a maximum contaminant level for vinyl chloride of 2 micrograms per liter (µg/L) or 2 parts per billion (ppb), effective January 9, 1989. This regulation applies to all community drinking water systems that regularly serve the same 25 persons for at least 8 months of the year.

Food

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

The Food and Drug Administration (FDA) proposed in 1986 that the vinyl chloride monomer content of polymers used in food packaging or processing be limited to 5 to 50 ppm, depending on the nature of the polymer and its use. These levels would produce negligible amounts of vinyl chloride in the food.

Standards and Regulations

The table below summarizes the standards and regulations for vinyl chloride, which are then discussed in greater detail.

Table 1. Standards and regulations for vinyl chloride

Agency*	Focus	Level	Comments
ACGIH	Air-Workplace	5 ppm	Advisory; TWA†, confirmed human carcinogen
		10 ppm	Advisory; short-term limit, averaged over 15 minutes
NIOSH	Air-Workplace	0	Advisory; zero exposure because of carcinogenicity
OSHA	Air-Workplace	1 ppm 5 ppm	Regulation; PEL§ over 8-hour workday Regulation; short-term limit not to exceed 15 minutes
EPA	Air-Environment	10 ppm	Regulation; emission limit
EPA	Water	2 μg/L	Regulation; effective January 9, 1989, for all water systems that regularly serve the same 25 persons at least 8 months/year
FDA	Food	5-50 ppm	Proposal; monomer content of polymers used in food packaging or processing

*ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration

†TWA (Time-Weighted Average) = time weighted average concentration for a normal 8-hour workday and a 40-hour workweek to which nearly all workers may be repeated exposed.

§PEL (Permissible Exposure Limit) = highest level of vinyl chloride in air, averaged over an 8-hour workday, to which a worker may be exposed.

Treatment and Management

Acute Exposure

There is no specific treatment for patients with acute exposure to vinyl chloride.

After acute vinyl chloride exposure, the patient should be immediately removed from the source and given oxygen, 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.

Chronic Exposure

Unlike vinyl chloride disease, hepatic angiosarcoma has a poor prognosis.

In the past, symptoms associated with vinyl chloride disease tended to disappear within 1 or 2 years after the patient was removed from exposure. Hepatic angiosarcoma, on the other hand, grows rapidly and carries a poor prognosis; if untreated, most patients die within 6 to 12 months of diagnosis. Results of radiation therapy and chemotherapy have been disappointing. Patients who have had the tumor successfully resected have experienced long-term survival. Patients with chronic liver injury should avoid alcoholic beverages, tobacco use, and exposure to vinyl chloride, acetominophen, isoniazide, or other hepatotoxins. Follow-up may require treatment for complications such as ascites, diabetes, and bleeding varices.

Challenge

(10) What can you tell the patient described in the case study about the 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 persons?

_____

_____

it is invasive, involves intravenous injection of a synthetic dye, necessitates drawing multiple blood samples with same-day analysis, and is fairly expensive.

Serum bile acids are also cleared by the liver; measurement requires drawing a single fasting serum sample to obtain levels, usually by radioimmunoassay. These bile acids, cholylglycine and conjugates of cholic acid, have been shown to be significantly elevated in asymptomatic workers with chemical exposure and histologically proven chemical liver injury.

A screening panel of fasting serum bile acids and liver enzyme assays or ICG clearance rates is both sensitive (few false negatives) and specific (few false positives) for chemically induced hepatic injury. In asymptomatic persons, the presence of elevated liver enzymes or abnormal ICG clearance rates, in conjunction with normal bile acids, is characteristic of hepatic cellular injury due to alcohol, drugs, or viral hepatitis. On the other hand, elevated fasting serum bile acids, in conjunction with persistent enzyme abnormalities or elevated ICG clearance rates, are more indicative of subclinical hepatic injury due to low-grade chemical exposure. When serum bile acids, alkaline phosphatase, and SGPT (ALT) are all normal, there is a high probability of excluding latent liver disease due to any cause; only a liver biopsy is more definitive.

Challenge

(6) What should be included in the problem list for the patient described in the case study?

_____

(7) What is the differential diagnosis?

_____

_____

(8) What additional diagnostic tests should be performed to restrict the differential diagnosis?

_____

_____

(9) Additional information: Hepatitis A antibody is negative, as are hepatitis B core antibody and antigen and surface antigen. What is included in the differential diagnosis now?

_____

_____

_____

Urinalysis

Hepatitis serology

Specialized Tests

Vinyl chloride in breath or urine, if exposure is recent

Urinary thiodiglycolic acid, if exposure is recent

Direct Biologic Indicators

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

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

Indirect Biologic Indicators

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

Recent studies suggest that fasting serum bile acids, in conjunction with an indocyanine green clearance rate, are sensitive and specific for latent chemical liver injury.

Overt liver injury is a relatively late occurrence in vinyl chloride-related hepatic disease, and detection of early chemical injury in asymptomatic persons is difficult. Standard biochemical enzyme studies (alkaline phosphatase , aspartate aminotransferase [SGOT or AST], alanine aminotransferase [SGPT or ALT] and gamma-glutamyl transpeptidase [GGTP or 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.

A correlation has been noted between slightly to moderately elevated total urinary porphyrins or secondary urinary coproporphyrin and the early stages of toxic liver disease. However, no similar observations have been reported in patients with vinyl chloride-related liver 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 chemically induced liver injury. Indocyanine green (ICG) is a synthetic dye used for this purpose, and ICG clearance rates are directly related to the severity of chemical hepatic injury. This test, however, has certain limitations:

Chronic Exposure

Vinyl chloride disease appears to be a disease of the past.

The onset of vinyl chloride-induced liver damage is insidious, with a clinical picture of nonspecific hepatic injury.

Chronic occupational exposures to vinyl chloride at levels of several hundred ppm have led, in the past, 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 ranged from 1 month to 3 years. New cases of vinyl chloride disease have not been reported since 1974, when permissible workplace exposure levels were reduced to 1 ppm.

The signs of vinyl chloride disease included a scleroderma-like condition of the connective tissue of the fingers, accompanied by thickening of the dermis. Acro-osteolysis, a rare bone disease resulting in decalcification of the terminal phalanges of the hand, was also seen. Acro-osteolysis was frequently preceded by a Raynaud-type phenomenon in which there was reversible constriction of the arterioles, leading to numbness, pallor, and cyanosis of the fingers.

The onset of vinyl chloride-induced liver disease (malignant or nonmalignant) can be insidious, with a clinical picture of nonspecific hepatic injury. Abdominal pain, followed by weakness, fatigue, and weight loss are the most common symptoms. Fibrosis and cirrhosis may develop, resulting in hepatomegaly, splenomegaly, portal hypertension, thrombocytopenia, and esophageal varices. These pathologic effects may occur singly or in any combination and may be accompanied by other less characteristic signs, such as hematologic changes and pulmonary effects.

Laboratory Tests

In the evaluation of vinyl chloride-exposed patients, it is important to exclude other etiologies for liver disease.

Short of liver biopsy, there are no definitive clinical clues to distinguish hepatic injury due to vinyl chloride from that of other etiologies such as viral hepatitis infection and ethanol toxicity. (Vitamin A overload, hemochromotosis, and carbon tetrachloride exposure have been reported to cause liver disease only rarely.) Biliary cirrhosis, cholelithiasis, and metastatic cancer should also be considered in the differential diagnosis of liver injury.

Laboratory tests can be used to evaluate patient health, confirm vinyl chloride exposure, and exclude other etiologies such as hepatitis virus.Tests that may be helpful are listed below. Since the histologic appearance of vinyl chloride-induced liver injury is distinct from that due to other agents, biopsy may be the best method to diagnose liver disease caused by this chemical.

Screening Tests

Urinary coproporphyrin and total urinary porphyrins

Liver enzymes

Liver function tests (see below)

Serum bilirubin

CBC with peripheral smear

BUN and creatinine

Clinical Evaluation

History and Physical Examination

The onset of symptoms due to chronic vinyl chloride exposure may be delayed for several years after the actual exposure has ceased.

A detailed occupational history should include any past exposure to vinyl chloride. The latency period for nonmalignant complications may be several months, while the latency period for angiosarcoma of the liver may be as long as 40 years. Workers exposed before 1974, when permissible workplace levels were still high, are at increased risk for the development of hepatic angiosarcoma into the next century. Individual susceptibility as well as intensity and duration of exposure may affect the interval before symptoms are manifested.

Persons who have been chronically exposed to vinyl chloride are likely to have worked or lived in locations where the chemical was produced, used, or stored. Such proximity to vinyl chloride plants operating before 1960, when engineering controls were inadequate, is particularly suspect. Although the number of symptomatic persons having this type of exposure is small, angiosarcoma of the liver is so rare that the incidence of even one case near such a plant may be initially regarded as evidence of environmental pollution. Documentation of environmental contamination, in air or drinking water, would suggest a need to monitor other potentially exposed members of the community, past and present residents, and workers connected with the source of exposure.

Two other chemical agents have been specifically associated with angiosarcoma of the liver, and exposure to them should be ruled out by history; these are inorganic arsenic and thorium dioxide (a component of the X-ray contrast medium Thorotrast). Anabolic and contraceptive steroids have also been associated with the induction of hepatic angiosarcoma, and their use should be determined. In addition to alcohol consumption and smoking habits, any medications that normally or adversely affect the liver should be noted. The possible use of homeopathic medications and so-called health foods should be investigated.

The physical examination for vinyl chloride-exposed persons includes a thorough abdominal and neurologic examination. The extremities of vinyl chloride workers, particularly the hands, should be examined for signs of acro-osteolysis, a result of "vinyl chloride disease," discussed in Signs and Symptoms section.

Signs and Symptoms

Acute Exposure

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

Vinyl chloride has little acute toxicity, and air levels over 8000 ppm may be tolerated for 5 minutes without the development of symptoms. Longer exposures have been associated with headache, dizziness, euphoria, ataxia, and narcosis. Cardiac, circulatory, and respiratory irregularities have also been noted with acute exposures. Acute, high-level exposures have resulted in death, presumably due to narcosis.

Carcinogenic Effects

Vinyl chloride-induced angiosarcoma of the liver has a latency period from 15 to 40 years.

Numerous epidemiologic and experimental studies have indicated the carcinogenic potential of vinyl chloride. A worldwide register of histologically confirmed cases of hepatic angiosarcoma resulting from vinyl chloride exposure identified 120 cases from 1974 to 1986; additional cases are now being added at the rate of about 5 a year. Most of these cases were found 15 to 29 years after first exposure; the mean age of patients at diagnosis was 52 years, and the average length of exposure was 18.3 years. As of 1986, at least 43% (53/120) of the people with this rare form of cancer were employed as reactor cleaners; exposure levels then were presumably much greater than those seen today. Most of the workplace cases of vinyl chloride-induced hepatic angiosarcoma have been associated with chronic exposures on the order of 100 ppm or less; evidence for increased incidence of disease below 50 ppm has not been clearly documented in human studies.

There have been no cases of hepatic angiosarcoma recorded in workers due to vinyl chloride exposure after 1974, when allowable workplace air levels were drastically reduced. However, a sufficient latency period has not yet elapsed for carcinogenic effects to have appeared. Data on the few cases of hepatic angiosarcoma reportedly due to environmental contamination are inconclusive because of the statistically small numbers involved and because this disease can arise spontaneously.

Increased incidence of several cancers, other than hepatic, have been suggested by various epidemiologic 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, skin, lung, thyroid, lymphatic, or hematopoietic tissues.

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 exposure to vinyl chloride levels less than 5 ppm. Studies using a number of biologic assay systems suggest that the reported carcinogenicity of vinyl chloride may proceed by damage to the cell's genetic material.

Challenge

(5) Would you examine the patient described in the case study for CNS damage? For malignancies other than hepatic? Explain.

_____

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_____

_____

Most data regarding acute inhalation 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.

Chronic Exposure

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

Several epidemiologic studies have convincingly associated chronic vinyl chloride exposure with liver tumors, both malignant and nonmalignant, and have suggested, but not proved, an increased incidence of cancers in other parts of the body. Subtle neurologic effects have been noted in some workers chronically exposed to vinyl chloride. Vinyl chloride exposure also has been associated with decreases in pulmonary flow, interstitial pneumonitis, and "meat packers' asthma."

Hepatic Effects

Vinyl chloride can cause malignant or nonmalignant liver injury, depending on exposure level.

Hepatocellular injury of any kind is manifested only after months or years of vinyl chloride exposure. Epidemiologic studies suggest that chronic exposure to very high doses (on the order of 500 to 1000 ppm) leads more often to hepatotoxicity, while exposure to lower doses (100 ppm or less) results more often in carcinogenicity. At the higher levels hepatic cells often die rather than transform, which results in chronic liver disease.

Hepatic angiosarcoma is a multicentric lesion that typically occupies peripheral foci within the liver. The highly vascular nature of angiosarcomas causes the bruits and may result in massive peritoneal hemorrhage. Nonmalignant hepatic manifestations of vinyl chloride exposure include noncirrhotic portal hypertension and cirrhosis, depending on the nature of exposure. In cases of acute exposure, the resulting chemical hepatitis rarely progresses into fulminant hepatic necrosis. Chronic exposure results in periportal fibrosis without portal vein obstruction, collagen deposition in the space of Disse, and hyperplasia of the mesenchymal sinusoidal lining cells, which ultimately become fibrotic. Vinyl chloride exposure should be considered before the diagnosis of idiopathic portal hypertension is made. Exposure to arsenic, thorium, and copper may also cause portal hypertension without cirrhosis. Findings of capsular and subcapsular fibrosis are suggestive but not diagnostic of vinyl chloride exposure.

Neurologic Effects

Subtle signs of neurotoxicity have recently been associated with chronic exposure to vinyl chloride.

Vinyl chloride was once considered for use as an inhalation anesthetic agent, a result of its central nervous system effects at subacute exposures. Recent data suggest that more subtle signs of neurotoxicity can be associated with chronic exposure. Peripheral neuropathy of the legs has been reported in workers exposed to vinyl chloride at levels less than 50 ppm. Electroencephalographic changes have been noted in workers chronically exposed to vinyl chloride at high levels and in combination with other organic solvents. Further investigation in this area is needed.

Challenge

(3) Who in the case study, besides the patient, is at risk of being exposed to vinyl chloride?

_____

_____

(4) Do the children of this patient have an increased risk of developing cancer? Does his grandson? Why?

_____

_____

Biologic Fate

Primary routes of vinyl chloride entry in humans are inhalation and ingestion.

For vinyl chloride, the primary routes of entry in humans are inhalation and ingestion. Metabolic pathways are readily saturable, which limits systemic uptake at higher doses. Vinyl chloride that is not metabolized is exhaled.

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.

Animal studies indicate that inhalation absorption of vinyl chloride occurs readily and rapidly, but data are insufficient to determine the proportion of an inhaled dose that is absorbed. Absorption from the gastrointestinal tract is rapid and probably complete, as shown by several studies performed on rats.

Evidence suggests that the toxicity of vinyl chloride is related to its transformation in 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.

Physiologic Effects

Acute Exposure

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

Challenge

(1) *Additional information for 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 EPA that significant leaks in the reactor vessels of the nearby plant may have been occurring over the course of several decades, resulting in frequent environmental contamination, although no air monitoring had been done outside the plant. After 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

Of the 2.2 million workers exposed to vinyl chloride, autoclave cleaners in PVC production plants have the highest health 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 workers exposed as a result of the polymerization process, especially to those who were lowered directly into the reactor vessels 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 100 ppm or more.

Certain persons, such as alcoholics, have an increased risk of vinyl chloride toxicity.

During the childbearing years, women should avoid exposure since there is a possibility that vinyl chloride increases the incidence of congenital birth defects.

Prenatal or early exposure to vinyl chloride may increase the risk of cancer later.

Data from animal studies suggest that prior exposure to chemicals or drugs that stimulate the enzyme systems involved in vinyl chloride hepatic metabolism may result in increased risk of hepatotoxicity. The formation of scar tissue, which results from vinyl chloride-induced chronic liver disease, has been reported to cause hepatomas that can become malignant when ethanol is consumed.

The fetus may also be at increased risk. One human study suggests that maternal exposure to low ambient levels of vinyl chloride is associated with an increase in the incidence of congenital malformations, but these results have not been supported by the findings of at least two subsequent studies. Based on extrapolation of animal data, exposure to vinyl chloride either in the prenatal period or during early childhood years may result in an increased risk of developing cancer.

Exposure Pathways

The sweet odor of vinyl chloride can be detected only at concentrations too high to provide adequate warning of toxic levels.

Exposures may occur through air polluted with vinyl chloride from processing, polymerization, and fabrication plants or hazardous waste sites, and through groundwater contaminated by these sources.

Consumer sources of vinyl chloride may include release of the monomer from PVC plastic in new car interiors, packaging of certain foods and beverages, and pipes for drinking water.

Vinyl chloride (CH_2=CHCl) is a manmade chemical with no significant natural source. It is a colorless gas at room temperature but is normally stored under pressure and used as a liquid. It has a mild, sweet odor that can be detected at 300 to 5000 parts per million (ppm), too high to provide adequate warning of danger.Vinyl chloride is soluble in fats and organic solvents and is only slightly soluble in water. Synonyms include chloroethene, monochloroethylene, VC, and VCM (vinyl chloride monomer).Throughout the text, "vinyl chloride" refers to the vinyl chloride monomer, unless otherwise stated.

The primary use of vinyl chloride is in the production of polyvinyl chloride (PVC), a plastic that is used to make pipe, electrical wire and cable coatings, flooring, home furnishings, toys, packaging, apparel, and automobile parts and upholstery. Smaller amounts of vinyl chloride are used as a copolymer in the manufacture of other plastics, as an intermediate in the production of chlorinated compounds, and as a refrigerant. Historically, vinyl chloride has been used as an aerosol propellant and, at one time, was considered for use as an anesthetic.

Normally, the general population is exposed to negligible amounts of vinyl chloride. Amounts measured in ambient air near vinyl chloride production plants have been up to 1 ppm and, above hazardous waste sites, up to 0.4 ppm. Other sources of airborne exposure include volatilization from new plastic parts and upholstery in car interiors. Release of residual vinyl chloride monomer from most other solid PVC materials is generally of little consequence, although significant amounts of vinyl chloride may be released during burning of PVC products. Tobacco smoke also contains small amounts of vinyl chloride. In general, atmospheric environmental levels of vinyl chloride are not injurious and present no known risk.

Many consumer goods, including food and beverages, are packaged in various forms of polyvinyl chloride. Small amounts of residual vinyl chloride monomer can migrate into the packaged contents and be consumed. Residual monomer can also be leached into the drinking water supply from new PVC piping. Studies have shown, however, that the amount of vinyl chloride ingested from either of these sources is small.

Vinyl chloride released from point sources into the ambient air is degraded in a matter of hours; that released to lakes, streams, or rivers will volatilize in several hours to 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 majority of drinking water supplies in the United States contain no detectable amounts of vinyl chloride.

Case Study

A 55-year-old man with weight loss and hepatomegaly

A 55-year-old man seen at your office complains of fatigue, a 20-pound weight loss, and anorexia over the past 2 to 3 months. He has previously been in good health, except for a history of hypertension, for which he has been treated with hydrochlorothiazide, 50 mg a day, for the past 3 years. He takes no other medications, has never had a blood transfusion, and has not travelled outside the United States. He consumes 2 to 3 alcoholic beverages a 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 a 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, gave birth to a boy last week; the pregnancy was troubled, but the baby is fine. The rest of his family is in good health.

On physical examination, your patient appears to be in poor health. 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 or lymphadenopathy. The results of heart and chest examination are normal. The patient's liver is 14 cm in span, percusses at the midclavicular line, and is slightly tender to palpation; the lower border is palpable 4 cm below the costal margin. The spleen is not enlarged, and there are no other abdominal masses. Extremities and joints are unremarkable, and the results of neurologic examination are completely normal. Prostate is normal-sized; no masses are felt, and the stool is negative for occult blood.

The initial laboratory results include hemoglobin, white blood cell count, electrolytes, and urinalysis, all normal. The SGPT is 372 IU/L and SGOT is 293 IU/L. Bilirubin, alkaline phosphatase, and serum protein levels are within normal limits.

p_{retest}

(a) What should be included in this patient's problem list?

_____

(b) What is the differential diagnosis for this patient?

_____

(c) What tests would you order to confirm or rule out these diagnoses?

_____

Answers are incorporated in Challenge answers (6) through (9) located later in this document.

How to use this issue . . .

This issue begins with a composite study that describes a realistic encounter with a patient. This description is followed by a pretest. The case study is further developed through Challenge questions at the end of each section. To fully benefit from this monograph, readers are urged to answer each question when it is presented. (Answers to the Pretest and Challenge questions are found toward the end of this document.) The monograph ends with a posttest, which can be submitted to the Agency for Toxic Substances and Disease Registry (ATSDR) for continuing medical education (CME) credit or continuing education units (CEU). See the end of this document for further instructions on how to receive these credits.

The objective of this monograph on vinyl chloride is to help you:

- **Explain why vinyl chloride may be a hazard of great concern**
- **Describe the known factors contributing to vinyl chloride poisoning**
- **Identify potential environmental or occupational sources of exposure to vinyl chloride**
- **Identify evaluation and treatment protocols for persons exposed to vinyl chloride**
- **List sources of information on vinyl chloride**

Contents:

Case Study
Pretest
Exposure Pathways
Who's at Risk
Biologic Fate
Physiologic Effects
Clinical Evaluation
Treatment and Management
Standards and Regulations
Suggested Reading List
Answers to Questions
Sources of Information
Posttest and Credits

This issue is prepared with the assistance of those who share a common concern for physician education, public health, and the environment, including the following organizations: American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP), American College of Emergency Physicians (ACEP), American College of Occupational and Environmental Medicine (ACOEM), American Medical Association (AMA), Association of State and Territorial Health Officials (ASTHO), and the Society of Teachers of Family Medicine (STFM). Final responsibility for the contents and views expressed in this monograph resides with ATSDR.

Agency for Toxic Substances and Disease Registry
Project Officers: Max Lum, Ed.D., and Donna L. Orti, M.S.
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Case Studies in Environmental Medicine

Vinyl Chloride Toxicity

2

Environmental ALERT . . .

Chronic, low-level vinyl chloride exposure may cause angiosarcoma of the liver, an extremely rare form of cancer.

At higher doses, hepatic cells may die rather than transform, which results in chronic liver disease.

Hepatic angiosarcoma has not been reported in workers who were exposed to vinyl chloride after 1974, when permissible workplace air levels were drastically reduced. This finding, however, may reflect an incomplete latency period.

This monograph is one in a series of self-instructional 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. See Posttest section of this document for more information about continuing medical education credits and continuing education units..

Guest Contributors: *Robert Harrison, MD, MPH; Gloria Hathaway, PhD*
Guest Editors: *Laura Welch, MD; Carlo Tamburro, 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*

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Case Studies in Environmental Medicine

Vinyl Chloride Toxicity

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This case study and monograph have been edited for inclusion in the TEHIP Gopher. The pagination and layout of this document differ from that of the original case study as published by ATSDR because of data conversion. For example, **summary highlights**, appearing adjacent to relevant text in the ATSDR publication, are placed before the text to which they refer in the TEHIP gopher version. There may be other differences between this version and the official document.

The official ATSDR hard copy document is available from:

Continuing Education Coordinator
Agency for Toxic Substances and Disease Registry
Division of Health Education, E33
1600 Clifton Road, NE
Atlanta, GA 30333

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