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.

To obtain credit, please provide the requested information below:

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I do want to be placed on mailing list. Yes No (circle one)

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

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Carbon Tetrachloride
Chlordane
Cholinesterase Inhibitors
Chromium
Cyanide
Dioxins
Ethylene/Propylene Glycols
Exposure History
Gasoline
Jet Fuel
Lead
Mercury
Methanol
Methylene Chloride
Nitrates/Nitrites
Pentachlorophenol
Polyaromatic Hydrocarbons (PAHs)
Polychlorinated Biphenyls (PCBs)
Radiation
Radon
Reproductive and Developmental Hazards
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Trichloroethylene
Toluene
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CASE STUDIES IN ENVIRONMENTAL MEDICINE: BENZENE TOXICITY

If you wish CME credits or CEU, 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 benzene may be an acute and chronic health hazard.	1	2	3	4	5
Describe the factors that may contribute to benzene poisoning.	1	2	3	4	5
Identify potential environmental and occupational sources of benzene exposure.	1	2	3	4	5
Identify evaluation and treatment protocols for persons exposed to benzene.	1	2	3	4	5
List sources of information on benzene.	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: _____

POSTTEST: BENZENE TOXICITY

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

1. Which of the following statements about benzene exposure are true?
   a. The odor of benzene serves as an adequate warning property in the workplace.
   b. Benzene vapor may emanate from products in the home.
   c. In the United States, benzene is no longer found in commercial gasoline.
   d. Possible routes of benzene exposure include dermal absorption.
   e. Benzene in the water supply could expose persons by ingestion, inhalation, and dermal absorption.
2. Smokers may be at increased risk of benzene exposure because
   a. carbon monoxide potentiates the effects of benzene
   b. cigarette smoke contains toluene, which is metabolized to benzene
   c. smokers drink less alcohol as they smoke
   d. inhaled cigarette smoke contains benzene
   e. smokers are more sensitive to benzene's CNS effects
3. An appropriate biologic measure of high-dose benzene exposure may be
   a. blood benzene concentration
   b. benzene levels in end-expired air
   c. thyroid function tests
   d. tissue benzene concentration
   e. urinary phenol level
4. Hematologic abnormalities associated with benzene toxicity may include
   a. leukopenia
   b. myelogenous leukemia
   c. aplastic anemia
   d. thrombocytopenia
   e. erythrocytosis
5. Which of the following statements about benzene metabolism are true?
   a. The metabolic fate of absorbed benzene depends on the route of exposure.
   b. Benzene's hematotoxicity is probably due to the effects of active metabolites.
   c. Only the liver can metabolize benzene.
   d. Benzene's metabolites may bind covalently to cellular macromolecules.
   e. Ethanol prevents the metabolism of benzene.
6. Pancytopenia may be caused by
   a. certain medications such as aspirin
   b. heavy metals such as arsenic
   c. nonionizing radiation
   d. viral infections such as hepatitis
   e. certain insecticides
7. Treatment of chronic benzene toxicity would include
   a. administration of pressor agents to sustain blood pressure
   b. immediate removal of the patient from the source of exposure
   c. administration of large doses of catecholamines
   d. administration of hyperbaric oxygen and intravenous fluids
   e. symptomatic and supportive measures
8. Benzene exposures have been reported to occur during
   a. shoe manufacturing
   b. rocket fuel formulating
   c. blueprint drawing
   d. manufacturing of certain synthetic polymers
   e. gasoline transfer

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 1 hour per issue of ACEP Category 1 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 1.0 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

NOTE FROM NLM: 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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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.

Adequate nutrients (vitamins and protein source) in his diet should be assured. Care to prevent injury and bleeding must be exercised until proper blood coagulation (platelets and other factors) has returned, and the patient should be carefully monitored for infection in the event of severe granulocytopenia. Prophylactic antibiotics and blood transfusions should be avoided unless a significant deterioration of his condition becomes evident.

(7) The prognosis is generally good for the resolution of the macrocytosis. Although this patient has a significant aplastic anemia, it is possible for his bone marrow to recover slowly if the damage has not reached an irreversible stage. Supportive treatment will be needed for many months. Because of the continued risk of leukemia, the patient should receive medical surveillance consisting of regularly scheduled examinations and appropriate testing of hematologic function. The peripheral smear and blood count will permit monitoring of early changes of the patient's condition. Bone marrow biopsy should be repeated in a few weeks to confirm initial findings and observe an expected bone marrow recovery.

(8) One step in your quest to establish a causal relationship between benzene-contaminated home water and the patient's condition would be to further investigate competing causes of low blood counts for this patient (e.g., drugs, radiation exposure, family history), keeping in mind that most cases of aplastic anemia are idiopathic. You would also need to explore the patient's potential exposure to chemicals other than benzene that might cause hematologic disorders. Finally, assuming the patient's condition is due to benzene exposure, you would need to weigh the significance of benzene sources other than the drinking water. For example, the patient is a diesel mechanic and most likely has inhalation and dermal exposure to gasoline (which contains benzene) at work. You would need to determine the amounts of benzene each source might have contributed to the patient's exposure. (See answer number 1 above.)

For the patient in the case study, as for most exposure cases, it will not be an easy matter to establish causality, and there is no precedent for a person developing hematologic abnormalities from benzene in drinking water.

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 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 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:

Answers to Pretest and Challenge Questions

(1) Some important areas to explore include amounts and duration of exposure from the following sources:

- water supply (ingestion)
- water supply (inhalation or dermal absorption during bathing and laundering)
- ambient air (fugitive emissions from the chemical plant during its operation and since it was abandoned 9 years ago)
- occupation (activities, conditions, and time spent as a diesel mechanic)
- workplace conditions (cleaning of machinery parts, solvents used, protective equipment worn, and the adequacy of ventilation)
- home environment (use of consumer products that might contain benzene, exposure to personal or passive cigarette smoke)

(For more information, see Case Studies in Environmental Medicine: Taking an Exposure History, ATSDR, October 1992.)

(2) Theoretically, a person could be at increased risk of benzene's adverse effects if he or she encountered agents or conditions that increased the rate of formation of toxic benzene metabolites through induction of the MFO system. Potential agents include MFO-inducing drugs (e.g., phenobarbital, alcohol); conditions include those causing rapid synthesis of bone marrow. The patient only occasionally drinks beer and did not take medications before his illness, and so he avoids the risk factors of alcohol and medications. However, if the patient is suffering from a hematologic abnormality, as his symptoms and laboratory evaluation suggest, he will have increased risk if benzene exposure continues.

Other persons in the case who may be at increased risk of benzene exposure are those who have had contact with the water supply for a prolonged period of time, although no data exist to quantitate the risk. Included are persons who have lived in the patient's household and members of the community who share the water supply. Community and household members who are at increased risk of benzene's adverse effects theoretically include those with rapidly synthesizing bone marrows and persons with increased MFO-mediated metabolism (e.g., heavy drinkers).

(3) The patient's problem list includes a clotting disorder, fatigue, ecchymoses and petechiae, and anorexia with concomitant weight loss.

(4) The hematology study reveals significant thrombocytopenia, leukopenia, and erythropenia. Pancytopenia is caused by the accelerated destruction or decreased production of all cell lines including red blood cells, white blood cells, and platelets. Bone marrow disorders are likely to be the cause, and could result from the following: drug and chemical toxicity (such as benzene toxicity), radiation, infection, nutrient deficiencies (e.g., vitamin B12 and folate), hypersplenism, and marrow replacement syndromes.

(5) Additional testing for the patient might include coagulation factors, evaluation for infectious agents, and assessment of nutrient status. Evaluation of the bone marrow should include a search for malignant cells. Cytogenetic abnormalities, if observed, may be helpful in the evaluation but are not definitive.

(6) The patient must be removed from exposure to benzene and other hematologic toxicants. His home water for drinking and personal purposes should be obtained from a source with no detectable level of benzene. Work exposure to toxic chemicals must be carefully evaluated.

Hematologic Effects

Aksoy M. Benzene as a leukemogenic and carcinogenic agent. Am J Ind Med 1985; 8:9-20.

Infante PF, Rinsky RA, Wagoner JK, Young RJ. Leukaemia in benzene workers. Lancet 1977; 2:76-8.

Infante PF, White MC. Projections of leukemia risk associated with occupational exposure to benzene. Am J Ind Med 1985; 7:403-13.

Runion HE, Scott LM. Benzene exposure in the United States, 1978-1983: an overview. Am J Ind Med 1985; 7:385-93.

Risk Assessment

Rinsky RA, Smith AB, Hornung R, et al. Benzene and leukemia: an epidemiologic risk assessment. N Engl J Med 1987; 316:1044-9.

Related Government Publications

Agency for Toxic Substances and Disease Registry. Toxicological profile for benzene. Atlanta: US Department of Health and Human Services, Public Health Service, 1989. NTIS report no. PB/89/209464/AS.

Environmental Protection Agency. Health effects assessment for benzene. Cincinnati, OH: US Environmental Protection Agency, Office of Health and Environmental Assessment, 1984. Report no. EPA/540/1-86/037.

Sources of Information

More information on the adverse effects of benzene and the treatment and management of benzene-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Benzene Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

In addition to other resources, ATSDR has created a National Exposure Registry for benzene. This registry is one of a series mandated by the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA). ATSDR, in cooperation with the states, will establish and maintain national registries of (1) persons exposed to substances and (2) persons with serious illness or diseases possibly due to exposure. The registries will collect information on the effects of low-level exposures of long duration (i.e., the exposures typically found in populations surrounding hazardous waste sites) and the health outcomes for populations receiving a one-time, high-level environmental exposure (such as those experienced at chemical spill sites). The registries will facilitate the identification and subsequent tracking of persons exposed to a defined substance at selected sites and will coordinate the clinical and research activities involving the registrants. For further information on the benzene registry, please contact ATSDR Division of Health Studies, Office of the Director, at (404) 639-6200.

regulations have been proposed that would control benzene emissions from industrial solvent use, waste operations, transfer operations, and gasoline marketing. At gas stations, proposed rules would require new equipment restricting benzene emissions while dealers' storage tanks are being filled.

Water

The maximum contaminant level of benzene in drinking water is 5 ppb.

The National Primary Drinking Water Regulations promulgated by EPA in 1987 set a maximum contaminant level for benzene of 0.005 ppm (5 ppb). This regulation is based on preventing benzene leukemogenesis. The maximum contaminant level goal (MCLG), a nonenforceable health goal that would allow an adequate margin of safety for the prevention of adverse effects, is zero benzene concentration in drinking water.

Food

FDA prohibits the use of benzene in foods.

Effective April 1988, the Food and Drug Administration has mandated that benzene can only be an indirect food additive in adhesives used for food packaging.

Challenge

(8) The lawyer for the family of the patient in the case study approaches you and asks you to establish causality between the patient's condition and the benzene in the drinking water. How would you do so?

_____

_____

_____

Suggested Reading List

Reviews

Austin H, Delzell E, Cole P. Benzene and leukemia. A review of the literature and a risk assessment. Am J Epidemiol 1988; 127(3):419-39.

Goldstein BD. Benzene toxicity. State Art Rev Occup Med 1988; 3:541-54.

Goldstein BD. Introduction: Occam's razor is dull. Environ Health Perspect 1989; 82:3-6.

Marcus WL. Chemical of current interest-benzene. Toxicol Ind Health 1987; 3(1):205-66.

lifetime has been estimated to be 5 excess leukemia deaths per 1000 employees exposed. (This estimate assumes no threshold for benzene's carcinogenic effects.) OSHA has also established an action level of 0.5 ppm to encourage even lower exposures in the workplace.

The National Institute for Occupational Safety and Health (NIOSH) recommends an exposure limit of 0.1 ppm as a 10-hour TWA. NIOSH also recommends that benzene be handled in the workplace as a human carcinogen.

Table 1. Standards and regulations for benzene

Agency*	Focus	Level	Comments
ACGIH	Air-workplace	10ppm	Advisory; 8-hour TWA †; suspected human carcinogen
NIOSH	Air-workplace	0.1 ppm	Advisory; 10-hour TWA
		1.0 ppm	15-min ceiling limit
OSHA	Air-workplace	1 ppm	Regulation; 8-hour TWA
		5 ppm	15-min STEL§
EPA	Drinking water	5 ppb	Regulation; maximum contaminant level
FDA	Food	N/A	Regulation; may be used only as a component of packaging adhesives

* 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 workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

§ STEL (short-term exposure limit) = usually determined by a 15-minute sampling period.

Environment

Air

EPA restricts benzene emissions from specific point sources.

Benzene has been designated as a hazardous air pollutant under section 112 of the Clean Air Act. EPA has not promulgated a specific ambient air standard for benzene but has imposed restrictions designed to lower industrial emissions of benzene by 90% over the next 20 years. In addition,

benzene can produce a severe chemical pneumonitis. Gastric lavage may be preferable to emesis if large amounts of benzene have been ingested or if the patient is seen more than 1 hour after ingestion. Activated charcoal decreases benzene absorption in experimental animals, and the benefits are likely to be similar in humans.

When medically indicated, epinephrine should be used cautiously with careful cardiac monitoring. Benzene is one of several solvents that may increase the susceptibility of the myocardium to the dysrhythmogenic effects of catecholamines.

Chronic Exposure

Once chronic exposure to benzene ceases, hematologic test results typically return to normal.

In treating persons chronically exposed to benzene, the most important actions are to remove the patient from the source of benzene exposure and to prevent further exposure. Benzene-induced depression of blood elements generally reverses after exposure is terminated. Chronically exposed patients whose hematologic results do not return to normal despite removal from exposure should be managed in consultation with a hematologist or oncologist. Chemotherapy and bone marrow transplants are therapeutic options for leukemia and aplastic anemia, respectively.

Challenge

(6) What are some key considerations in the treatment for the patient in the case study?

_____

_____

(7) What is the prognosis for this patient? What follow-up care should he receive?

_____

_____

Standards and Regulations

Workplace

Air

The current permissible exposure limit for benzene is 1 ppm.

In 1987, the Occupational Safety and Health Administration (OSHA) instituted a permissible exposure limit for benzene of 1 ppm, measured as an 8-hour time-weighted average (TWA), and a short-term exposure limit of 5 ppm (Table 1). These legal limits were based on studies demonstrating compelling evidence of health risk to workers exposed to benzene. The risk from exposure to 1 ppm for a working

Challenge

(3) What should be included in the problem list of the patient described in the case study?

_____

_____

(4) Additional Information for the Case Study: A bone marrow aspiration reveals fibrous and fatty structures with very few spicules including mononuclear phagocytes, reticulum cells, and plasma cells. Rare promyelocytes and megaloblastic nucleated erythroid cells are present. No megakaryocytes are observed.

What differential diagnosis do the patient's hematologic results suggest?

_____

_____

(5) What additional laboratory testing would you recommend?

_____

_____

Treatment and Management

Acute Exposure

There is no antidote for acute benzene poisoning.

Treatment for benzene toxicity is supportive and symptomatic.

Treatment for persons acutely exposed to benzene is generally supportive and symptomatic. Immediate removal of the patient from exposure and administration of oxygen and cardiopulmonary resuscitation measures are the first consideration. In cases of ingestion, respiratory distress may indicate pulmonary aspiration of gastric contents.

Contaminated clothing and shoes should be removed from an exposed person as soon as possible. If the skin or eyes have contacted liquid benzene, immediately wash the exposed skin with soap and copious water, and irrigate the eyes with running water for 3 to 5 minutes or until irritation ceases.

In cases of ingestion, emesis is recommended in alert adult patients if less than 1 hour has passed since ingestion. However, if CNS or respiratory depression are present or likely, emesis is contraindicated. Care must be taken to avoid aspiration of stomach contents during vomiting because

The above laboratory tests will detect hematologic abnormalities that have been associated with relatively high levels of exposure to benzene. Persons with blood dyscrasias that persist after removal from exposure should be evaluated by a hematologist. Bone marrow aspiration and biopsy may be useful in narrowing the differential diagnosis in some cases.

Direct Biologic Indicators

Measurement of benzene in blood and breath is generally not clinically useful in nonoccupational settings.

Urinary phenol concentrations do not correlate with airborne benzene levels below 10 ppm.

Measurement of benzene in breath and blood can be useful in certain occupational settings. Because of benzene's relatively short biologic half-life, blood levels do not reflect cumulative body burden. A less invasive measurement of exposure in the workplace may be the benzene concentration in end-expired air. Studies show that 16 hours after an 8-hour exposure to benzene levels of 10 ppm and 1 ppm, steady-state exhaled benzene concentrations are 50 ppb and 10 ppb, respectively. However, these methods are not clinically useful for patients exposed to the low levels of benzene typically found in ambient air.

Urinary phenol concentrations generally correlate well with benzene exposure at concentrations above 10 ppm. Exposure to 10 ppm for 8 hours typically produces a postshift urinary phenol level of 45 to 50 milligrams per liter (mg/L). With exposure to air levels below 10 ppm, high background excretion of phenol from dietary and other sources can render urinary phenol levels unreliable. Unexposed persons rarely have urinary phenol levels greater than 20 mg/L.

Indirect Biologic Indicators

MCV and lymphocyte count may aid in the diagnosis of benzene toxicity.

A bone marrow aspiration and biopsy will aid in identifying aplastic anemia.

An increase in MCV and a decrease in total lymphocytes may be early signs of benzene toxicity. A finding of benzene-induced hematotoxicity in a patient should trigger consideration that this represents a sentinel event, indicating that other persons may have been similarly exposed.

If aplastic anemia is suspected, a bone marrow aspiration and biopsy should be performed. Aspiration of the marrow space often produces no sample (dry tap) in patients with aplastic anemia; however, a dry tap is not diagnostic of aplastic anemia; therefore, a biopsy specimen should be obtained as well and examined for architecture and cellularity. In aplastic anemia, only the empty reticular meshwork of the marrow is evident with fat cells replacing all or most of the hematopoietic tissues. Islands of residual hematopoiesis may be seen, but the overall cellularity typically is less than 25%. Chromosomal changes consistent with myelo-dysplasia are seen on cytogenetic analysis.

function of formed blood elements; an environmental history focusing on activities and possible sources of benzene exposure at home; and an occupational history, including past exposures to hematologic toxicants such as solvents, insecticides, and arsenic. A history of ionizing radiation exposure, medications, and smoking should also be explored.

Signs and Symptoms

Acute Exposure

Acute benzene exposure causes CNS depression.

Acute benzene toxicity is characterized by central nervous system depression. Symptoms may progress from light-headedness, headache, and euphoria, to respiratory depression, apnea, coma, and death. Benzene concentrations of about 20,000 ppm are fatal to humans within 5 to 10 minutes.

"Benzol jag" is a term workers use to describe symptoms of confusion, euphoria, and unsteady gait associated with acute benzene exposure. Depending on the magnitude of the dose, persons who have ingested benzene may experience these effects 30 to 60 minutes after benzene ingestion. In one case report, an oral dose of 10 milliliters (mL) was reported to produce staggering gait, vomiting, tachycardia, pneumonitis, somnolence, delirium, seizures, coma, and death.

Chronic Exposure

Symptoms of chronic benzene exposure may be nonspecific, such as fatigue and anorexia.

Early symptoms of chronic benzene exposure are often nonspecific but show marked individual variability. By the time a physician is consulted, the bone marrow may have been affected significantly. For example, conditions that first bring the patient to medical attention are typically fever due to infection or manifestations of thrombocytopenia, such as hemorrhagic diathesis with bleeding from the gums, nose, skin, gastrointestinal tract, or elsewhere.

The clinical picture of patients chronically exposed to benzene was described well in 1938 in a cohort study of about 300 workers in the rotogravure printing industry. At that time, ink solvents and thinners containing 75% to 80% benzene by volume were used in the pressroom. Initial physical examination of the workers was relatively unrevealing, but of those tested, 22 persons had severe hematologic abnormalities. Follow-up of the workers a year after exposure ceased suggested that the effects of benzene can persist or can evolve over time. Most patients recover after exposure ceases.

Laboratory Evaluation

Hematologic abnormalities are the primary concern in benzene exposure.

Laboratory evaluation of benzene-exposed persons should include the following:

> CBC with differential, hematocrit, hemoglobin, erythrocyte count, erythrocyte indices (MCV, MCH, MCHC), and platelet count.

Plasma folate and vitamin B_{12} levels may be used to rule out megaloblastic anemia if the MCV is elevated.

inadequate number of all cell lines. Generally, benzene-induced aplastic anemia is caused by chronic exposure at relatively high doses. No overt cytopenic effects have been observed in persons exposed at the previous workplace permissible exposure limit of 10 ppm. Severe aplastic anemia typically has a poor prognosis and can progress to leukemia, whereas pancytopenia may be reversible.

Leukemia

Benzene-induced leukemia has a usual latency period of 5 to 15 years and, in many cases, is preceded by aplastic anemia.

The causal relationship between benzene exposure and leukemia, which has been suspected for over 50 years, has only recently been accepted widely. Lack of adequate epidemiologic data and difficulty in producing hematologic carcinogenicity in animals impeded a consensus. Cohort studies of benzene-exposed workers in several industries (sheet rubber manufacturing, shoe manufacturing, rotogravure printing) have demonstrated significantly elevated risk of leukemia, predominantly acute myelogenous leukemia, but also erythroleukemia and acute myelomonocytic leukemia. For benzene-induced leukemia the latency period is typically 5 to 15 years after first exposure. Patients with benzene-induced aplastic anemia have been observed to progress to a preleukemic phase and develop acute myelogenous leukemia. However, a person exposed to benzene may develop leukemia without having aplastic anemia.

Studies addressing the risk of leukemia associated with low-level benzene exposures have been inconclusive. Death certificates do not reveal increased leukemia mortality among workers potentially exposed to low levels of hydrocarbons and other petroleum products. However, in one recent case-control study, significantly more patients with acute nonlymphocytic leukemia were employed as truck drivers, filling station attendants, or in jobs involving exposure to low levels of petroleum products than among the controls.

Other Effects

The evidence is insufficient to indicate a causal relationship between benzene and nonhematologic tumors.

Teratogenic effects due to benzene have been observed in animals only at high exposure levels.

Several reports relate benzene exposure to a variety of lymphatic tumors including non-Hodgkin's lymphoma and multiple myeloma. Although this is plausible, no scientific proof of a causal relationship exists. The association between exposure to benzene and development of nonhematologic tumors remains inconclusive.

Information on the reproductive toxicity of benzene in humans is meager. Benzene has not been proven teratogenic in humans or animals at doses that do not produce maternal toxicity.

Clinical Evaluation

History and Physical Examination

In addition to a thorough medical history and physical examination, important factors in evaluating a patient potentially exposed to benzene include a detailed family history of blood dyscrasias including hematologic neoplasms, genetic hemoglobin abnormalities, bleeding abnormalities, and abnormal

Approximately 50% of absorbed benzene is excreted unchanged via the lungs over a 36-hour period, depending on exercise level and amount of body fat. Respiratory elimination is triphasic, with approximate half-lives of 1 hour, 3 hours, and greater than 15 hours. Urinary excretion of metabolites, primarily phenol, is another important pathway for elimination. Most of the phenol is excreted in the form of sulfate esters and glucuronides. After a single exposure, urinary excretion of phenol and hydroquinone is highest within the first 24 hours and is essentially complete within 48 hours.

Physiologic Effects

Benzene affects primarily the CNS and hematopoietic system.

Benzene exposure affects the central nervous system (CNS) and hematopoietic system and may affect the immune system. Death due to acute benzene exposure has been attributed to asphyxiation, respiratory arrest, CNS depression, or cardiac dysrhythmia. Pathologic findings in fatal cases have included respiratory tract inflammation, lung hemorrhages, kidney congestion, and cerebral edema.

Central Nervous System Effects

At very high concentrations, benzene rapidly causes CNS depression, which can lead to death.

Acute benzene exposure results in classic symptoms of CNS depression such as dizziness, ataxia, and confusion. General agreement that benzene itself is responsible for central nervous system effects, and benzene metabolite(s) are responsible for the observed blood dyscrasias, has evolved from temporal studies and the fact that agents known to alter benzene metabolism also alter benzene hematotoxicity.

Hematologic Effects

All three blood cell lines may be adversely affected by benzene.

Pluripotential stem cells and lymphocytic cells are the probable targets of benzene toxicity.

All three cell lines--erythrocytes, leukocytes, and platelets--may be affected by benzene to varying degrees. Benzene's most likely target is the DNA of the pluripotential stem and lymphocytic cells. Hematologic abnormalities such as anemia, leukopenia, thrombocytopenia, or pancytopenia may occur after chronic exposure. Potentially fatal infections can develop if granulocytopenia is present, and hemorrhage can occur as a result of thrombocytopenia. Paroxysmal nocturnal hemoglobinuria, a rare paraneoplastic disorder, has been associated with benzene exposure. Cytogenetic abnormalities of bone marrow cells and circulating lymphocytes have been observed in workers exposed to benzene, abnormalities not unlike those observed after exposure to ionizing radiation. Myelodysplastic effects also can be seen in the bone marrow of persons chronically exposed to benzene.

Anemia

Benzene-induced aplastic anemia is caused by chronic exposure at relatively high levels.

Fatal aplastic anemia was first reported in benzene-exposed workers in the nineteenth century. Aplastic anemia is a condition caused by bone marrow failure, resulting in hypoplasia with an

devices on delivery hoses, which, if used properly, significantly reduce exposure. Catalytic converters have significantly reduced the benzene in automobile emissions.

Benzene is converted to toxic metabolites mostly by mixed-function oxidases (MFO) in the liver and bone marrow. MFO-inducing drugs (e.g., phenobarbital, alcohol) and certain chemicals (e.g., chlordane, parathion) may increase the rate at which toxic metabolites of benzene are formed. Theoretically, persons with rapidly synthesizing marrows--the fetus, infants and children, persons with hemolytic anemia or with agranulocytosis--are at increased risk.

Challenge

(2) *Does the patient in the case study have any risk factors for the adverse effects of benzene? Is anyone else in the case at risk of benzene exposure or its adverse effects?*

_____

_____

Biologic Fate

Benzene is absorbed well after inhalation or ingestion; in comparison, dermal absorption is slow.

Benzene is metabolized in the liver and bone marrow.

Benzene excretion occurs via the lungs and urine.

Benzene is absorbed rapidly by inhalation and ingestion, and slowly through intact skin. After a 4-hour exposure to approximately 50 ppm benzene in air, human volunteers absorbed about 50% of the amount inhaled.

Distribution of benzene to tissues is dependent on relative perfusion rates. In humans, approximately half of an inhaled dose is distributed to the liver and bone marrow. Benzene accumulation is slow in fat, but the total potential uptake is great because of benzene's high lipid solubility.

Absorbed benzene is metabolized primarily in the liver. Benzene metabolism initially involves oxidation, with phenol as the major metabolite. Further metabolic products formed by the introduction of hydroxyl groups on the aromatic ring include hydroquinone, catechol, and 1,2,4-trihydroxybenzene. These hydroxylated metabolites can be further oxidized to their corresponding quinones or semiquinones. Urinary excretion of small amounts of muconic acid, a straight-chain dicarboxylic acid, indicates that the benzene ring also is opened during metabolism.

Bone marrow is the main target organ of benzene toxicity. It contains the MFO enzymes necessary to metabolize benzene, and although benzene metabolism in bone marrow is not clearly understood, one or more benzene metabolites are suspected as responsible for the hematotoxicity. The metabolites may bind covalently to cellular macromolecules (e.g., proteins, DNA, and RNA), causing disruption of cell growth and replication. The rate of benzene metabolism in bone marrow is lower than that in the liver.

water would correspond to, at most, 1 additional cancer case in 10,000 people exposed. (The current EPA maximum contaminant level [MCL] for benzene in drinking water is 5 ppb.) In addition to being ingested, benzene in water can also be absorbed through wet skin and inhaled as it volatilizes during showering or laundering.

Persons who smoke one pack of cigarettes a day inhale a daily dose of approximately 1 milligram of benzene, which is about one-thirtieth of the daily amount inhaled by a worker exposed at the currently permissible workplace level.

* Group A consists of agents for which sufficient evidence supports a causal association between exposure and cancer in humans and in experimental animals.

Challenge

(1) *Later, the patient in the case study tells you that his well water has always tasted "funny" and smells like "solvent." You learn that a chemical plant was adjacent to his property until 9 years ago when the company moved to another location. You are concerned about your patient's description of his drinking water, and you request that the state health department investigate the problem. The investigator contacts the chemical company that owns the abandoned site and learns that benzene is stored at the site in tanks that are above and below ground. Laboratory analyses of the patient's well water reveal an average concentration of 20 ppm benzene and traces of 1,1,1-trichloroethane and toluene.*

What areas will you explore in your questioning to gauge the extent of the patient's exposure to benzene?

_____

_____

_____

Who's at Risk

Two to three million U.S. workers are at risk of benzene exposure.

Alcohol and other drugs that induce the mixed function oxidase (MFO) enzymes may potentiate the effects of benzene.

Workers employed in industries using or producing benzene have the greatest likelihood of exposure. The National Institute for Occupational Safety and Health (NIOSH) estimates that approximately two to three million workers in the United States may be exposed to benzene during refining operations; gasoline storage, shipment, and retail operations; chemical manufacturing; plastics and rubber manufacturing; shoe manufacturing; printing; and activities in chemical laboratories. A review of benzene exposure in the U.S. petroleum industry from 1978 to 1983 indicated that 87% of exposures were below an 8-hour time-weighted average (TWA) of 1 ppm and 98% were below 10 ppm.

In 1980, an estimated 37 million people in this country were exposed to benzene vapors at self-service gasoline stations. During gasoline pumping, atmospheric benzene levels up to 6.6 ppm have been measured, with a 6-hour TWA of 0.1 ppm. This risk has been lowered by installing vapor recapture

Exposure Pathways

Benzene is commonly used as a solvent and as a raw material in chemical syntheses.

Benzene is added to unleaded motor fuels for its anti-knock characteristics.

Because benzene plays such a vital role in many industrial processes and is a component of gasoline, it is widespread in the environment.

Benzene (C_6H_6) is the first member of a series of aromatic hydrocarbons recovered from refinery streams during catalytic reformation and other petroleum processes. It is a clear, colorless, highly flammable liquid at room temperature. Its vapor is heavier than air and can travel to a source of ignition and flash back. It has a pleasant odor detectable at concentrations greater than 4 parts per million (ppm). (The workplace permissible exposure level [PEL] is 1 ppm). Common synonyms for benzene include benzol, cyclohexatriene, phenyl hydride, and coal tar naphtha.

Benzene is one of the world's major commodity chemicals. Its primary use (85% of production) is as an intermediate in the production of other chemicals, predominantly styrene (for styrofoam and other plastics), cumene (for various resins), and cyclohexane (for nylon and other synthetic fibers). Benzene is an important raw material for the manufacture of synthetic rubbers, gums, lubricants, dyes, pharmaceuticals, and agricultural chemicals.

Benzene is a natural component of crude and refined petroleum. The mandatory decrease of lead alkyls in gasoline has led to an increase in the aromatic hydrocarbon content of gasoline to maintain high octane levels and antiknock properties. In the United States, gasoline typically contains less than 2% benzene by volume, but in other countries the benzene concentration may be as high as 5%.

Because of its lipophilic nature, benzene is an excellent solvent. Its use in paints, thinners, inks, adhesives, and rubbers, however, is decreasing and now accounts for less than 2% of current benzene production. Benzene was also an important component of many industrial cleaning and degreasing formulations but now is replaced mostly by toluene, chlorinated solvents, or mineral spirits. Although benzene is no longer added in significant quantities to most commercial products, traces of it may still be present as a contaminant.

Because of its many uses, benzene is widespread in the environment. It is a component of both indoor and outdoor air pollution. Benzene levels measured in ambient air have ranged from less than 0.001 ppm in pristine rural areas to more than 0.1 ppm in urban areas. Sources of benzene in air are usually associated with chemical manufacturing or gasoline, including gasoline bulk-loading and discharging facilities and combustion engines (such as in automobiles, lawn mowers, and snow blowers). In almost all cases, benzene levels inside residences or offices are higher than levels outside. Benzene levels are also usually higher in homes with attached garages and those occupied by smokers. In the fall and winter when buildings are less-well ventilated, benzene levels are even higher. The Environmental Protection Agency (EPA) classifies benzene as a Group A* carcinogen and has estimated that a lifetime exposure to 0.004 ppm benzene in air will result in, at most, 1 additional case of leukemia in 10,000 people exposed. (EPA risk estimates assume there is no threshold for benzene's carcinogenic effects.)

Leakage from underground storage tanks and seepage from landfills or improper disposal of hazardous wastes has resulted in benzene contamination of groundwater used for drinking. Effluent from industries is also a source of ground-water contamination. EPA's Office of Drinking Water has estimated that lifetime exposure to a benzene concentration of 68 parts per billion (ppb) in drinking

Case Study

A 50-year-old diesel mechanic with recurring nosebleeds, fatigue, and weight loss

A 50-year-old man is prompted to visit your office because of a nosebleed that has been recurring for 2 days. He says that this is the third episode of nosebleeds in the last 6 months. He expresses concern that he becomes easily fatigued at work, and 2 months ago he began noticing bruises on his arms and legs, although he does not recall the causes. He has lost more than 12 pounds in the last 2 years, which he attributes to loss of appetite.

History of previous illness includes a fractured arm in childhood. He has had three bad colds in the past 2 years that lasted for more than a week and included coughing and breathing difficulty. The patient occasionally drinks beer; he quit smoking cigarettes 4 years ago. He does not have allergies and is taking no medications at this time.

On examination, you find a muscular man with somewhat pale and dry skin. Conjunctivae are pale. Numerous ecchymoses and petechiae are noted on arms and legs. Many seem to be old with incomplete healing. BP is 138/84; HR is 94. Temperature is normal. His throat is moderately inflamed, and prominent cervical nodes are palpable. Examination is otherwise within normal limits.

On further questioning, you learn that the patient is a diesel mechanic and has worked on trucks for the same employer for the previous 12 years. He and his wife divorced 8 years ago; his wife became nervous and withdrawn after two miscarriages, which led to marital stress. He has lived in his home for the past 16 years. He has a daughter, age 16, who lives with his ex-wife.

Laboratory studies reveal the following: glucose, BUN, and bilirubin within normal limits; Hgb 10.2 g/dL (normal 14.0-18.0); Hct 32.6% (44.8-52.0); RBC 3.32 mil/mm^3 (4.3-6.0); MCV 98 fl (80-100); MCH 31 pg (26-31); MCHC 31% (31-36); WBC 1500 mm^3 (5000-10,000); segs 60% (40-60); bands 1% (0-5); lymphs 31% (20-40); monos 8% (4-8); platelets 50,000/mm^3 (150,000-400,000). A chest X ray is negative except for some suggestion of hyperlucency; ECG is normal.

$$p_{\mathrm{retest}}$$

(a) What is the problem list for this patient? What is the differential diagnosis?

_____

(b) What additional testing would you recommend?

_____

(c) What measures would you take to manage the case and treat this patient?

_____

Answers to the Pretest can be found in Challenge answers (3) through (7) later in this document.

How to use this issue . . .

This issue begins with a composite case 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 benzene is to help you:

- **Explain why benzene may be an acute and chronic health hazard**
- **Describe the factors that may contribute to benzene poisoning**
- **Identify potential environmental and occupational sources of benzene exposure**
- **Identify evaluation and treatment protocols for persons exposed to benzene**
- **List sources of information on benzene**

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 Clinical Toxicology (AACT), 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.

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Case Studies in Environmental Medicine

Benzene Toxicity

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Environmental ALERT . . .

Benzene is an important commercial commodity and has become widespread in the environments of developed countries.

In the United States, gasoline contains up to 2% benzene by volume; in other countries, the benzene concentration in gasoline may be as high as 5%.

Benzene in the workplace has been associated with aplastic anemia and leukemia and may also cause nonhematologic cancers.

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..

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Agency for Toxic Substances and Disease Registry

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Case Studies in Environmental Medicine

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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:

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