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AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Case Studies in Environmental Medicine

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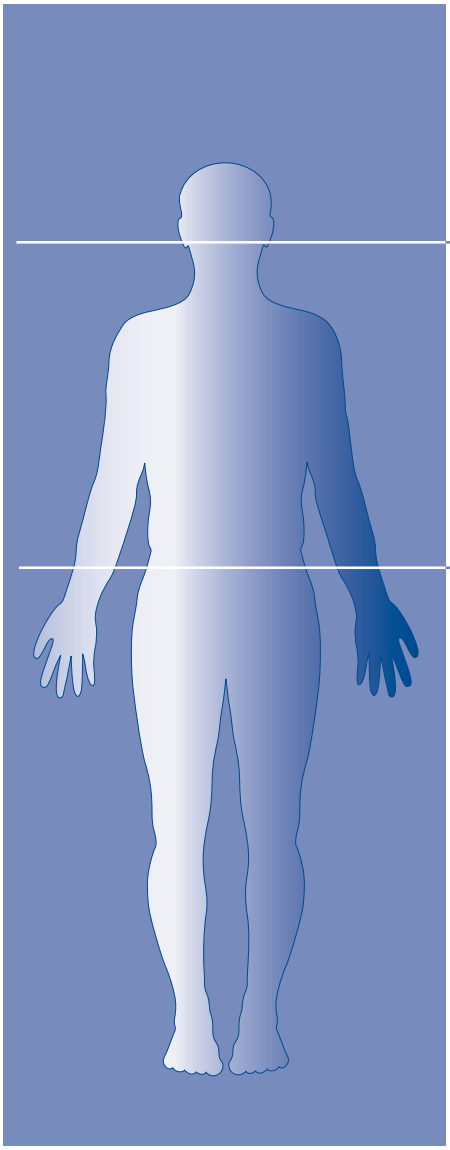

BENZENE TOXICITY

Environmental Alert

- Benzene is an important commercial commodity that, because of its frequent use, has become widespread in the environment 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.

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. This course is also available on the ATSDR Web site, www.atsdr.cdc.gov/HEC/CSEM/. See page 3 for more information about continuing medical education credits, continuing nursing education units, and continuing education units.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine

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Disclaimer

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, ATSDR has made 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. The document must be interpreted in light of specific information regarding the patient and in conjunction with other sources of authority.

Use of trade names and commercial sources is for identification only and does not impy endorsement by the Agency for Toxic Substances and Disease Registry or the U.S. Department of Health and Human Services.

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Each content expert for this case study indicated no conflict of interest to disclose with the case study subject matter.

ATSDR Publication No.: ATSDR-HE-CS-2001-0003

Case Studies in Environmental Medicine (CSEM): Benzene Toxicity

Goals and Objectives

The goal of the CSEM is to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients.

After completion of this educational activity, the reader should be able to discuss the major exposure route for benzene, describe two potential environmental and occupational sources of benzene exposure, give two reasons why benzene is a health hazard, describe three factors contributing to benzene poisoning, identify evaluation and treatment protocols for persons exposed to benzene, and list two sources of information on benzene.

Accreditation

Continuing Medical Education (CME)

The Centers for Disease Control and Prevention (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 1.5 hours in category 1 credit toward the American Medical Association (AMA) Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Continuing Nursing Education (CNE)

This activity for 1.5 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

Continuing Education Units (CEU)

CDC has been approved as an Authorized Provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.1 continuing education units (CEUs).

Instructions

See page 4

The response form must be completed and returned electronically, by fax, or by mail for eligibility to receive continuing education credit.

Instructions for Completing CSEM Online

1. Read this CSEM, *Benzene Toxicity*; all answers are in the text.
2. Link to the MMWR/ATSDR Continuing Education General Information page (www.cdc.gov/atsdr/index.html).
3. Once you access this page, select the Continuing Education Opportunities link.
4. Once you access the MMWR/ATSDR site online system, select the electronic file and/or register and test for a particular ATSDR course.
   a. Under the heading "Register and Take Exam," click on the test type desired.
   b. If you have registered in this system before, please use the same login and password. This will ensure an accurate transcript.
   c. If you have not previously registered in this system, please provide the registration information requested. This allows accurate tracking for credit purposes. Please review the CDC Privacy Notice (www.cdc.gov/privacy.htm).
   d. Once you have logged in/registered, select the test and take the posttest.
5. Answer the questions presented. To receive continuing education credit, you must answer all of the questions. Some questions have more than one answer. Questions with more than one answer will instruct you to "indicate all that are true."
6. Complete the course evaluation and posttest no later than **June 29, 2006**.
7. You will be able to immediately print your continuing education certificate from your personal transcript.

Instructions for Completing CSEM on Paper

1. Read this CSEM, *Benzene Toxicity*; all answers are in the text.
2. Complete the evaluation questionnaire and posttest, including your name, mailing address, phone number, and e-mail address, if available.
3. Circle your answers to the questions. To receive your continuing education credit, you must answer all of the questions.
4. Sign and date the posttest.
5. Return the evaluation questionnaire and posttest, no later than **June 1, 2006,** to ATSDR by mail or fax:

Mail	**or**	**Fax**
Continuing Education Coordinator Division of Toxicology and Environmental Medicine Agency for Toxic Substances and Disease Registry 4770 Buford Hwy, NE (Mail Stop F-32) Atlanta, GA 30341-3717		770-488-4178 ATTN: Continuing Education Coordinator

6. You will receive an award certificate within 90 days of submitting your credit forms. No fees are charged for participating in this continuing education activity.

Case Study

A 50-year-old diesel mechanic has 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. In the past 2 years he has had three bad colds 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. Review of systems: patient admits to fatigue, headache, dizziness, nausea and loss of appetite, loss of weight, and weakness.

On examination, blood pressure is 138/84; heart rate is 94 and regular; respiratory rate is 20, temperature 98.9°; skin exam reveals pale and dry skin. A head, ear, nose, and throat exam shows a hyperemic inflamed pharynx, bleeding gums, and pale conjunctivae. The lung exam is clear to auscultation and the cardiovascular exam shows a regular rate and rhythm. The abdominal exam indicates no hepatosplenomegaly; the genitourinary exam is unremarkable; and the neurologic exam shows a normal gait, Glasgow coma scale 15. The extremity exam finds numerous ecchymoses and petechiae in variable stages of healing on the upper and lower extremities, although the extremities have good range of movement. The lymph node exam reveals prominent, palpable cervical nodes, and the rectal exam stool guaiac is negative.

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. There was 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, blood urea nitrogen, and bilirubin within normal limits; hemoglobin (Hgb) 10.2 grams/deciliter (normal 14.0–18.0); hematocrit (Hct) 32.6% (44.8–52.0); red blood cell count 3.32 million per millimeter cubed (mm^3) (4.3–6.0); mean corpuscular volume (MCV) 98 femtoliters (80–100); mean corpuscular hemoglobin (MCH) 31 picograms (26–31); mean corpuscular hemoglobin concentration (MCHC) 31% (31–36); white blood cell count 1,500/mm^3 (5,000–10,000); segmented cells 60% (40–60); bands 1% (0–5); lymphocytes 31% (20–40); monocytes 8% (4–8); platelets 50,000/mm^3 (150,000–400,000). A chest radiograph is remarkable for hyperlucency. There are no infiltrates, effusions, or other abnormalities noted; electrocardiogram is within normal limits. Urine was negative for blood.

Pretest

(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?

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 enzymes may potentiate those effects of benzene that depend on metabolism. Although benzene-induced central nervous system (CNS) depression is probably not dependent on metabolism, alcohol and other CNS depressants might act cumulatively.

Workers employed in industries using or producing benzene (i.e., petrochemical companies; petroleum refining and coke and coal chemical manufacturing; rubber tire manufacturing; and companies involved in the storage or transport of benzene and petroleum products containing benzene) have the greatest likelihood of exposure. The Occupational Safety and Health Administration (OSHA) estimates that approximately 238,000 workers in the United States may be exposed to benzene during refining operations; gasoline storage, shipment, and retail operations; chemical manufacturing; and plastics and rubber manufacturing. Of these workers, only 10,000 (4%) were above an 8-hour time-weighted average (TWA) of 1 ppm and only 0.2% were above 10 ppm. Other workers who may be exposed to benzene because of their occupations include steel workers, printers, rubber workers, shoe makers, laboratory technicians, and gas station employees.

Atmospheric benzene levels of up to 6.6 ppm and 6-hour TWAs of 0.1 ppm have been measured during gasoline pumping. This risk has been lowered by installing vapor recapture devices on delivery hoses. These devices, 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 (MFOs) in the liver and bone marrow. MFO-inducing drugs (e.g., phenobarbital and ethanol) and certain chemicals (e.g., chlordane and parathion) may increase the rate at which toxic metabolites of benzene are formed. It also seems likely that persons who have bone marrow that is metabolically hyperactive (e.g., fetuses, infants and children, and those persons with hemolytic anemia) are at increased risk of benzene toxicity because the cells are rapidly dividing. Persons with compromised hemoglobin, such as those with B-thalassemia or viral hepatitis, may be at increased risk for benzene-induced aplastic anemia. Exposure to benzene may also stimulate specific CYP (or P450) enzymes, which are responsible for oxygenation of benzene and have a propensity to generate oxygen radicals. These radicals are a major cause of benzene toxicity.

Challenge

(1) 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?

Exposure Pathways

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, aromatic odor detectable at concentrations of 1.5 to 4.7 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 an important raw material in chemical syntheses and is a historically important solvent.

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%.

- Benzene is added to unleaded motor fuels to increase fuel performance.

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 has been 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.

- Benzene is widespread in the environment because of its use in many industrial processes and its presence in gasoline.

Benzene is widespread in the environment. Airborne benzene is usually produced by processes associated with chemical manufacturing or the gasoline industry, including gasoline bulk-loading and discharging facilities and combustion engines (e.g., automobiles, lawn mowers, and snow blowers). Benzene is a component of both indoor and outdoor air pollution. Benzene levels measured in ambient outdoor air have a global average of 6 micrograms per cubic meter ($\mu g/m^3$) (range 2–9 $\mu g/m^3$). In almost all cases, benzene levels inside residences or offices are higher than levels outside and still higher in homes with attached garages and those occupied by smokers. Seasonal variations also affect benzene levels, with higher levels found in the fall and winter when buildings are less well ventilated. People

living around hazardous waste sites, petroleum-refining operations, petrochemical manufacturing sites, or gas stations may be exposed to higher levels of benzene in air. In addition to being inhaled, airborne benzene is absorbed across intact skin in experimental animals. For most people, the level of exposure to benzene through food, beverages, or drinking water is not as high as their exposure through air.

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 groundwater contamination. In addition to being ingested, benzene in water can also be absorbed through wet skin and inhaled as it volatilizes during showering, laundering, or cooking. Typical drinking water contains less than 0.1 parts per billion (ppb) benzene. Benzene has been detected in bottled water, liquor, and food.

Cigarette smoke is another common source of personal and environmental benzene exposure, representing about half of the benzene to which the general population is exposed. Persons who smoke one pack of cigarettes a day inhale a daily dose of approximately 1 milligram (mg) of benzene, about 3 to 4% of the amount inhaled daily by a worker exposed at the current occupational PEL. Nonsmokers who live with smokers and who are passively exposed to environmental tobacco smoke typically experience 50% greater exposure to benzene than do nonsmokers who live in a smoke-free environment.

Challenge

(2) 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 near his property until 9 years ago, when the company moved. 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 questions will you ask to gauge the extent of the patient's exposure to benzene?

Biologic Fate

Benzene is rapidly and extensively absorbed by inhalation and ingestion. Absorption through the skin is rapid but not extensive, as most of it

evaporates quickly. In humans, approximately 50% of inhaled benzene is absorbed after a 4-hour exposure to approximately 50 ppm benzene in air. An in vivo study on human volunteers indicated that approximately 0.05% of a benzene dose applied to the skin was absorbed, whereas in an in vitro study of human skin, the absorption of benzene was consistently 0.2% after exposure to doses ranging from 0.01 to 520 microliters per square centimeter. Oral absorption has not been studied in humans. In animals, at least 90% of benzene was absorbed following oral ingestion of a dose of 340 to 500 milligrams per kilogram per day (mg/kg/day).

- Benzene is absorbed rapidly and extensively after inhalation or ingestion.

After exposure, benzene is found throughout the body, but it preferentially distributes into the bone marrow and tissues with either high perfusion rates or high lipid content. Thus, autopsies of people who died after acute exposure showed that lipid-rich tissues, such as the brain and fat, and well-perfused tissues, such as the kidney and the liver, have higher levels of benzene than other tissues.

Once absorbed, benzene is initially metabolized in the liver and later in the bone marrow. Although the total quantity of metabolites is greater in blood than marrow, the concentrations of those metabolites in the marrow can be 400 times greater than in blood. Benzene metabolism in the liver involves oxidation, with phenol as the major metabolite. Further metabolic products are formed in liver and in bone marrow by the enzymatic addition of hydroxyl groups to the benzene ring. Such metabolites include hydroquinone, catechol, and 1,2,4-trihydroxybenzene, which are further conjugated and excreted in the urine. These hydroxylated metabolites can be further oxidized to their corresponding quinones or semiquinones. Benzene oxide may also be metabolized via glutathione conjugation to form S-phenyl mercapturic acid. Additionally, 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 chronic benzene toxicity. One or more benzene metabolite is suspected to be responsible for the hematogenous toxicity, although the identity of the ultimate toxicant is unknown. In the marrow, the metabolites may bind covalently to cellular macromolecules (e.g., proteins, DNA, and RNA), causing disruption of cell growth and replication.

- Benzene is metabolized in the liver and bone marrow.

Approximately 17% of absorbed benzene is excreted unchanged via the lungs after a 4-hour exposure to 52 to 62 ppm benzene. Respiratory elimination is triphasic, with approximate half-lives of 1, 3, and greater than 15 hours. Urinary excretion of phenol conjugates is biphasic, with half lives of 5.7 and 28 hours. Approximately 33% of absorbed benzene is excreted in urine, primarily as phenol conjugates, muconic acid, and S-phenyl-*N*-acetyl cysteine.

- Benzene is excreted via the lungs and urine.

Physiologic Effects

- Benzene primarily affects the CNS and the hematopoietic system.

Benzene exposure affects the 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. These effects are believed to be caused by benzene itself rather than its metabolites, because the onset of CNS effects at extremely high doses is too rapid for metabolism to have occurred.

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.

Benzene can cause dangerous hematologic toxicity such as anemia, leukopenia, thrombocytopenia, or pancytopenia after chronic exposure. These effects are believed to be caused by the metabolites of benzene, which most likely damage the DNA of the pluripotential stem cells. All of the blood's components (i.e., erythrocytes, leukocytes, and thrombocytes [platelets]) may be affected to varying degrees. The accelerated destruction or reduction in the number of all three major types of blood cells is termed pancytopenia. Potentially fatal infections can develop if granulocytopenia is present, and hemorrhage can occur as a result of thrombocytopenia. Paroxysmal nocturnal hemoglobinuria, a disorder in which the breakdown of the red blood cells is accelerated and results in bleeding into the urine during sleep when the condition is active, 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.

Aplastic anemia is caused by bone marrow failure, resulting in hypoplasia with an inadequate number of all cell lines. Severe aplastic anemia typically has a poor prognosis and can progress to leukemia, whereas pancytopenia may be reversible. Benzene-induced aplastic anemia is generally caused by chronic exposure at relatively high doses. Fatal aplastic anemia following benzene exposure was first reported in workers in the nineteenth century.

Leukemia

Several agencies (e.g., the U.S. Department of Health and Human Services, the U.S. Environmental Protection Agency [EPA], and the International Agency for Research on Cancer) classify benzene as a confirmed human carcinogen. EPA estimates that a lifetime exposure to 4 ppb benzene in air will result in, at most, 1 additional case of leukemia in 10,000 people exposed. EPA has also estimated that lifetime exposure to a benzene concentration of 100 ppb in drinking water would correspond to, at most, 1 additional cancer case in 10,000 people exposed.

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

Cohort studies of benzene-exposed workers in several industries (e.g., sheet-rubber manufacturing, shoe manufacturing, and rotogravure [a special printing process]) have demonstrated significantly elevated risk of leukemia—predominantly acute myelogenous leukemia, but also erythroleukemia and acute myelomonocytic leukemia. The latency period for benzene-induced leukemia is typically 5 to 15 years after first exposure. Patients with benzene-induced aplastic anemia 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 occupational exposures to low levels of benzene (less than approximately 1 ppm) 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 recent case-control studies, 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 were the controls.

Other Effects

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

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

Information on the reproductive toxicity of benzene in humans is meager. Some effects on the testes have been noted in animals exposed via inhalation. Benzene has not been proven teratogenic in humans. In animals, high levels of benzene have resulted in decreased fetal weights and minor skeletal variants.

- Benzene has not been shown to be teratogenic in humans.

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 are a detailed family history of blood dyscrasias including hematologic neoplasms, genetic hemoglobin abnormalities, bleeding abnormalities, and abnormal 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.

- Acute benzene toxicity is characterized by CNS 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.
- Ventricular fibrillation can occur due to myocardial sensitization.

Signs and Symptoms

Acute Exposure

"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 was reported to produce staggering gait, vomiting, tachycardia, pneumonitis, somnolence, delirium, seizures, coma, and death. Other symptoms include bronchial and laryngeal irritation after inhalation. Pulmonary edema has been reported. Ingestion may cause substernal pain; cough; hoarseness; and burning of the mouth, pharynx, and esophagus shortly after ingestion. It may also cause stomach pain, nausea, and vomiting.

Chronic Exposure

- Symptoms of chronic benzene exposure may be nonspecific, such as fever, bleeding, 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 significantly affected. 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; fatigue; and anorexia.

The clinical picture of patients chronically exposed to benzene was well described 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. Followup of the workers a year after cessation of exposure suggested that the effects of

benzene can persist or can evolve over time. However, most patients recover after exposure ceases.

Laboratory Evaluation

The laboratory evaluation of benzene-exposed persons should include the following: complete blood count with differential, Hct, Hgb, erythrocyte count, erythrocyte indices (i.e., MCV, MCH, and MCHC), and platelet count. Plasma folate and vitamin B12 levels may be used to rule out megaloblastic anemia if the MCV is elevated. These 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.

- Hematologic abnormalities are the primary concern in benzene exposure.

Direct Biologic Indicators

Measurement of benzene in breath and blood can be useful in certain occupational settings. Because of benzene's relatively short biologic half-life, blood benzene levels reflect exposure during the preceding hours, not cumulative body burden. A less invasive measurement of workplace exposure is benzene concentration in end-expired air. A study has shown that workers exposed to benzene at levels between 0.2 and 4.1 ppm had measurable benzene vapor in their breath 16 hours after exposure and showed a progressive buildup of benzene in their expired air during the workweek.

- Benzene measurements in blood and breath are generally not clinically useful in nonoccupational settings.

Urinary phenol concentrations generally correlate well with benzene exposure to concentrations above 10 ppm. Workplace exposure to 10 ppm for 8 hours typically produces a postshift urinary phenol level of 45 to 50 mg/liter (mg/L), but excretion of phenol from dietary and other background sources (e.g., Pepto-Bismol) can obscure the contribution to urinary phenol of exposure air levels below 10 ppm. Under circumstances of such low-level exposure, urinary phenol levels are unreliable. Unexposed persons rarely have urinary phenol levels greater than 20 mg/L. Other benzene metabolites, such as muconic acid and phenyl mercapturic acid, are also used as indicators of exposure to benzene. Analysis of urinary muconic acid appears to be a better indicator than phenol for chronic, low-level benzene exposure. However, it is not specific for benzene exposure. Phenylmercapturic acid concentrations in the urine are highly specific parameters, although data concerning a dose-response relationship between phenylmercapturic acid production and benzene uptake in workers are not yet available.

- Because of the contributions of background exposure, urinary phenol concentrations may not accurately reflect low occupational benzene exposures (e.g., <10 ppm).

Indirect Biologic Indicators

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

An increase in MCV, a decrease in total lymphocytes, and decreases in red blood cells and white blood cells 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.

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

If aplastic anemia is suspected, a bone marrow aspiration and biopsy should be performed. Aspiration of the marrow space often produces no sample (i.e., dry tap) in patients with aplastic anemia. However, a dry tap is not diagnostic of aplastic anemia; therefore, a biopsy specimen also should be obtained and examined for architecture and cellularity. In aplastic anemia, only the empty reticular meshwork of the marrow is evident; fat cells replace 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 myelodysplasia are seen on cytogenetic analysis.

Challenge

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

(4) 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.

There is no antidote for benzene poisoning; therefore, treatment for persons acutely exposed to benzene is generally supportive and symptomatic. Immediate removal of the patient from exposure, administration of oxygen, and monitoring and treatment of cardiopulmonary status are the first considerations. 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 liquid benzene has contacted the skin or eyes, 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, do not induce emesis. Care must be taken to avoid aspiration of stomach contents during vomiting because benzene can produce a severe chemical pneumonitis. Ensure that the patient's airway is properly controlled and maintained before initiating orogastric tube lavage. Gastric lavage is indicated if large amounts of benzene have been ingested or if the patient is seen more than 1 hour after ingestion. Activated charcoal

may be used; it decreases benzene absorption in experimental animals, and the benefits are likely to be similar in humans. Monitor the cardiac status of the patient: benzene is one of several solvents that may increase the susceptibility of the myocardium to the dysrhythmogenic effects of catecholamines.

Epinephrine should be used only in the setting of cardiac arrest or severe refractory reactive airway disease because its use may lead to ventricular fibrillation secondary to the irritability of the myocardium.

Chronic Exposure

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.

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

Challenge

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

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

Standards and Regulations

Workplace

Air

In 1987, OSHA instituted a PEL for benzene of 1 ppm, measured as an 8-hour 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 lifetime has been estimated as 5 excess leukemia deaths per 1,000 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 current PEL for benzene is 1 ppm.

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. In 1997, the American Conference of Governmental Industrial Hygienists lowered its TWA-threshold limit value to 0.5 ppm to reflect the change in cancer classification to A1 (i.e., confirmed human carcinogen).

Table 1. Summary of Standards and Regulations for Benzene

Agency	Focus	Level*	Comments
American Conference of Governmental Industrial Hygienists	Air (workplace)	0.5 ppm 2.5 ppm	Advisory; TWA†; confirmed human carcinogen STEL (15-minute ceiling limit)
National Institute for Occupational Safety and Health	Air (workplace)	0.1 ppm 1.0 ppm	Advisory; 10-hour TWA 15-minute ceiling limit
Occupational Safety and Health Administration	Air (workplace)	1 ppm 5 ppm 0.5 ppm	Regulation; TWA 15-minute STEL‡ Action level TWA
U.S. Environmental Protection Agency	Water (drinking)	5 ppb	Regulation; maximum contaminant level
Food and Drug Administration	Food	NA	Regulation; may be used only as a component of packaging adhesives

*ppb: parts per million; ppb: parts per billion.
†TWA (time-weighted average): concentration for a normal 8-hour workday or 40-hour workweek to which nearly all workers may be repeatedly exposed.
‡STEL (short-term exposure limit): a 15-minute TWA exposure that should not be exceeded at any time during the workday.

Environment

Air

- EPA restricts benzene emissions from specific point sources.

Under section 112 of the Clean Air Act, benzene is a hazardous air pollutant. 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, 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. Under the Clean Air Act Amendments of 1990, the use of clean ("oxygenated") fuels was mandated as a means of reducing motor vehicle emission-related air pollutants. EPA predicts that this clean fuels program will decrease ambient benzene levels by 33%.

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, 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

Effective April 1988, FDA mandated that benzene can only be an indirect food additive in adhesives used for food packaging.

- The Food and Drug Administration (FDA) prohibits the use of benzene in foods.

Challenge

(7) 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

Graber MA, Beaty L. 1999. Otolaryngology: nose. In: University of Iowa Family Practice Handbook. 3rd ed. Chapter 19. Ames (IA): University of Iowa.

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Yin S-N, Hayes RB, Linet MS, et al. 1996. A cohort study of cancer among benzene-exposed workers in China: overall results. Am J Ind Med 29:227–35.

Risk Assessment

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Crump KS. 1994. Risk of benzene-induced leukemia: a sensitivity analysis of the Pliofilm cohort with additional follow-up and new exposure estimates. J Toxicol Environ Health 42(2):219–42.

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Paxton MB, Chinchilli VM, Breet SM, et al. 1994. Leukemia risk associated with benzene exposure in the Pliofilm cohort. II: Risk estimates. Risk Anal 14(2):155–61.

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

Voytek PE, Thorslund TW. 1991. Benzene risk assessment: status of quantifying the leukemogenic risk associated with the low-dose inhalation of benzene. Risk Anal 11(3):355–7.

Related Publications

Agency for Toxic Substances and Disease Registry. 1997. Toxicological profile for benzene (update). Atlanta: US Department of Health and Human Services.

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US Environmental Protection Agency. 1985. Drinking water criteria document on benzene. Final draft. Washington (DC): US Environmental Protection Agency, Office of Drinking Water. Report No. PB86-118122.

Answers to Pretest and Challenge Questions

Pretest

(a) The patient's problem list includes epistaxis, fatigue, ecchymoses and petechiae, and anorexia with concomitant weight loss. The differential diagnosis includes nose picking, external trauma, dry nasal mucosa with vascular fragility, foreign bodies, blood dyscrasias, neoplasms, infections, vitamin deficiencies, toxic metal exposures, septal deformities, telangiectasias, angiofibromas, and aneurysm ruptures.

(b) Additional testing for the patient might include coagulation factors, blood smear evaluation for infectious agents, and assessment of nutrient status. Evaluation of the bone marrow should include a search for malignant cells.

(c) 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 levels of benzene below health screening values. Work exposure to toxic chemicals must be carefully evaluated. Adequate nutrients (e.g., vitamins and protein sources) in his diet should be assured. Care to prevent injury and bleeding must be exercised until proper blood coagulation (i.e., 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.

Challenge

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

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

(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 and alcohol); conditions include those causing rapid synthesis of bone marrow. Because the patient only occasionally drinks beer and did not take medications before his illness, 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 there are no data to quantify the risk; persons who have lived, worked, or visited for a prolonged time 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). Take-home exposures could also put other persons at risk of exposure to benzene, especially if work clothes are laundered at home and showers are taken after leaving the work site.

(3) The patient's problem list includes epistaxis, fatigue, ecchymoses and petechiae, and anorexia with concomitant weight loss. The differential diagnosis includes nose picking, external trauma, dry nasal mucosa with vascular fragility, foreign bodies, blood dyscrasias, neoplasms, infections, vitamin deficiencies, toxic metal exposures, septal deformities, telangiectasias, angiofibromas, and aneurysm ruptures.

(4) Additional testing for the patient might include coagulation factors, blood smear evaluation for infectious agents, and assessment of nutrient status. Evaluation of the bone marrow should include a search for malignant cells.

(5) 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 levels of benzene below health screening values. Work exposure to toxic chemicals must be carefully evaluated. Adequate nutrients (e.g., vitamins and protein sources) in his diet should be assured. Care to prevent injury and bleeding must be exercised until proper blood coagulation (i.e., 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.

(6) 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.

(7) One step in your quest to establish a causal relationship between benzene-contaminated home water and the patient's condition would be to investigate competing causes of low blood counts for this patient (e.g., drugs, radiation exposure, and family history), keeping in mind that most cases of aplastic anemia are idiopathic. You 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 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 need to determine the amounts of benzene each source might have contributed to the patient's exposure.

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.

Additional 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 or for clinical inquiries, contact ATSDR, Division of Health Education and Promotion, Office of the Director, at 404-498-0101.

Electronic databases are also available on the Internet as well as on CD-ROMs. Some CD-ROMs such as TOMES Plus also contain environmental databases that can put current, peer-reviewed environmental data at the physician's fingertips. Most involve a charge, but updates are sent regularly after the initial purchase.

In addition to other resources, ATSDR has created a subregistry for benzene within the National Exposure Registry. This subregistry is mandated by the Comprehensive Environmental Response, Compensation, and Liability Act of 1980. 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 one-time, high-level

environmental exposures (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 subregistry, please contact ATSDR, Division of Health Studies, Office of the Director, at 404-498-0105.

Notes

Case Studies in Environmental Medicine:

Benzene Toxicity

Evaluation Questionnaire and Posttest, Course Number SS3039

Course Goal: To increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients.

Objectives

- Discuss the major exposure route for benzene.
- Describe two potential environmental and occupational sources of benzene exposure.
- State two reasons why benzene is a health hazard.
- Describe three factors that contribute to benzene poisoning.
- Identify evaluation and treatment protocols for persons exposed to benzene.
- List two sources of information on benzene.

Tell Us About Yourself

Please carefully read the questions. Provide answers on the answer sheet (page 29). Your credit will be awarded based on the type of credit you select.

1. **What type of continuing education credit do you wish to receive?**
   ****Nurses should request CNE, not CEU. See note on page 28.**
   A. CME (for physicians)
   B. CME (for non-attending)
   C. CNE (continuing nursing education)
   D. CEU (continuing education units)
   E. [Not used]
   F. [Not used]
   G. [Not used]
   H. None of the above

2. **Are you a...**
   A. Nurse
   B. Pharmacist
   C. Physician
   D. Veterinarian
   E. None of the above

3. **What is your highest level of education?**
   A. High school or equivalent
   B. Associate, 2-year degree
   C. Bachelor's degree
   D. Master's degree
   E. Doctorate
   F. Other

4. Each year, approximately how many patients with benzene exposure do you see?
A. None
B. 1–5
C. 6–10
D. 11–15
E. More than 15

5. Which of the following best describes your current occupation?
A. Environmental Health Professional
B. Epidemiologist
C. Health Educator
D. Laboratorian
E. Physician Assistant
F. Industrial Hygienist
G. Sanitarian
H. Toxicologist
I. Other patient care provider
J. Student
K. None of the above

6. Which of the following best describes your current work setting?
A. Academic (public and private)
B. Private health care organization
C. Public health organization
D. Environmental health organization
E. Non-profit organization
F. Other work setting

7. Which of the following best describes the organization in which you work?
A. Federal government
B. State government
C. County government
D. Local government
E. Non-governmental agency
F. Other type of organization

Tell Us About the Course

8. How did you obtain this course?
A. Downloaded or printed from Web site
B. Shared materials with colleague(s)
C. By mail from ATSDR
D. Not applicable

9. How did you first learn about this course?

A. State publication (or other state-sponsored communication)
B. *MMWR*
C. ATSDR Internet site or homepage
D. PHTN source (PHTN Web site, e-mail announcement)
E. Colleague
F. Other

10. What was the most important factor in your decision to obtain this course?

A. Content
B. Continuing education credit
C. Supervisor recommended
D. Previous participation in ATSDR training
E. Previous participation in CDC and PHTN training
F. Ability to take the course at my convenience
G. Other

11. How much time did you spend completing the course, evaluation, and posttest?

A. 1 to 1.5 hours
B. More than 1.5 hours but less than 2 hours
C. 2 to 2.5 hours
D. More than 2.5 hours but less than 3 hours
E. 3 hours or more

12. Please rate your level of knowledge before completing this course.

A. Great deal of knowledge about the content
B. Fair amount of knowledge about the content
C. Limited knowledge about the content
D. No prior knowledge about the content
E. No opinion

13. Please estimate your knowledge gain after completing this course.

A. Gained a great deal of knowledge about the content
B. Gained a fair amount of knowledge about the content
C. Gained a limited amount of knowledge about the content
D. Did not gain any knowledge about the content
E. No opinion

Please use the scale below to rate your level of agreement with the following statements (questions 14–25) about this course.

A. Agree
B. No opinion
C. Disagree
D. Not applicable

14. The objectives are relevant to the goal.

15. The tables and figures are an effective learning resource.

16. The content in this course was appropriate for my training needs.

17. Participation in this course enhanced my professional effectiveness.

18. I will recommend this course to my colleagues.

19. Overall, this course enhanced my ability to understand the content.

20. I am confident I can discuss the major exposure route for benzene.

21. I am confident I can describe two potential environmental and occupational sources of benzene exposure.

22. I am confident I can state two reasons why benzene is a health hazard.

23. I am confident I can describe three factors that contribute to benzene poisoning.

24. I am confident I can identify evaluation and treatment protocols for persons exposed to benzene.

25. I am confident I can list two sources of information on benzene.

Posttest

If you wish to receive continuing education credit for this program, you must complete this posttest. Each question below contains four suggested answers, of which one or more is correct. Choose the answer:

A if 1, 2, and 3 are correct
B if 1 and 3 are correct
C if 2 and 4 are correct
D if 4 is correct
E if 1, 2, 3, and 4 are correct

26. Which of the following statements about benzene exposure are true?

(1) Benzene vapor may emanate from products in the home.
(2) Possible routes of benzene exposure include dermal absorption.
(3) Benzene in the water supply could expose persons by ingestion, inhalation, and dermal absorption.
(4) In the United States, benzene is no longer found in commercial gasoline.

27. Smokers may be at increased risk of benzene exposure because

(1) carbon monoxide potentiates the effects of benzene
(2) cigarette smoke contains toluene, which is metabolized to benzene
(3) smokers drink less alcohol as they smoke
(4) inhaled cigarette smoke contains benzene

28. An appropriate biologic measure of high-dose benzene exposure may be

(1) blood benzene concentration
(2) benzene levels in end-expired air
(3) urinary phenol level
(4) thyroid function tests and tissue benzene concentration

29. Hematologic abnormalities associated with benzene toxicity may include all except

(1) leukopenia
(2) myelogenous leukemia
(3) aplastic anemia
(4) thrombocytopenia

30. Which of the following statements about benzene metabolism are true?

(1) The metabolic fate of absorbed benzene depends on the route of exposure.
(2) Benzene's hematotoxicity is probably due to the effects of active metabolites.
(3) Only the liver can metabolize benzene.
(4) Benzene's metabolites may bind covalently to cellular macromolecules.

31. Which of the following statements are true for benzene?

(1) Benzene is used as a solvent.
(2) Benzene is used is artisan work, shoe manufacturing, and chemical industries.
(3) Benzene can be inhaled from tobacco smoke and while pumping of handling gasoline.
(4) Benzene may cause leukemia, pancytopenia, or aplastic anemia.

32. Treatment of acute benzene toxicity would include

(1) immediate removal of the patient from the source of exposure
(2) administration of large doses of catecholamines
(3) symptomatic and supportive measures
(4) administration of hyperbaric oxygen, intravenous fluids and large doses of catecholamines

33. Benzene exposures have been reported to occur during

(1) shoe manufacturing
(2) manufacturing of certain synthetic polymers
(3) gasoline transfer
(4) rocket fuel formulating or blueprint drawing

Note to Nurses

CDC is accredited by the American Nurses Credentialing Center's (ANCC) Commission on Accreditation. ANCC credit is accepted by most State Boards of Nursing.

California nurses should write in "ANCC - Self-Study" for this course when applying for relicensure. A provider number is **not** needed.

Iowa nurses must be granted special approval from the Iowa Board of Nursing. Call 515-281-4823 or e-mail marmago@bon.state.ia.us to obtain the necessary application.

Case Studies in Environmental Medicine:

Benzene Toxicity

Answer Sheet, Course Number SS3039

Instructions for submitting hard-copy answer sheet: Circle your answers. To receive your certificate, you must answer **all** questions. Mail or fax your completed answer sheet to

Fax: 770-488-4178, ATTN: Continuing Education Coordinator

Mail: Agency for Toxic Substances and Disease Registry
ATTN: Continuing Education Coordinator
Division of Toxicology and Environmental Medicine
4770 Buford Hwy, NE (Mail Stop F-32)
Atlanta, GA 30341-3717

Remember, you can access the case studies online at www.atsdr.cdc.gov/HEC/CSEM/ and complete the evaluation questionnaire and posttest online at www2.cdc.gov/atsdrce/.

Online access allows you to receive your certificate as soon as you complete the posttest.

Be sure to fill in your name and address on the back of this form.

1. A B C D E F G H
2. A B C D E
3. A B C D E F
4. A B C D E
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6. A B C D E F
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33. A B C D E

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