ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

Case Studies in Environmental Medicine

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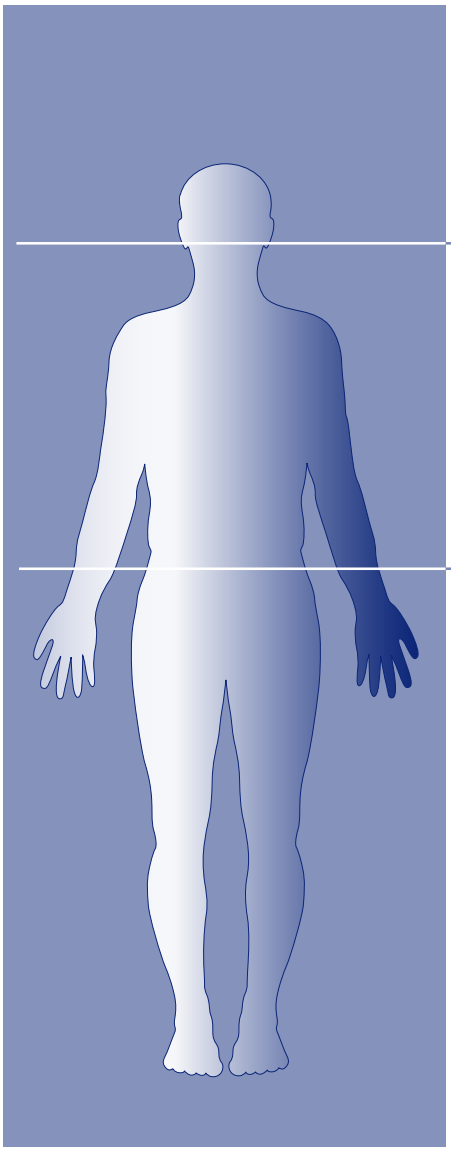

TOLUENE TOXICITY

Environmental Alert

- Use of toluene is increasing, in part because of its popularity as a solvent replacement for benzene.
- Gasoline contains 5% to 7% toluene by weight, making toluene a common airborne contaminant in industrialized countries.
- Many organic solvents have great addictive potential; toluene is the most commonly abused hydrocarbon solvent, primarily through "glue sniffing."

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 pediatrics and environmental health. This monograph is intended as a resource for pediatricians and other child health care providers 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 imply 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-2002-0008

Case Studies in Environmental Medicine (CSEM): Toluene Toxicity

Goals and Objectives

The goals of this CSEM are to increase the knowledge of health care providers, especially pediatricians, of the special susceptibilities of children to hazardous substances in the environment and to aid in their evaluation of potentially exposed patients.

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

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 1.25 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 1.4 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 questionnaire and posttest 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, *Toluene 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 **February 28, 2007**.
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, *Toluene 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 **January 28, 2007,** to CDC by mail or fax:

Mail
Continuing Education Coordinator
Division of Toxicology and
Environmental Medicine, ATSDR
1600 Clifton Road, NE (MS F-32)
Atlanta, GA 30333

or

Fax
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 pregnant 28-year-old has cough and dyspnea

A 28-year-old pregnant female comes to your office in the late afternoon with complaints of coughing spasms, chest tightness, and a sensation of being unable to breathe. These symptoms began about 6 hours earlier, while she was repainting a disassembled bicycle with an acrylic lacquer spray paint in a small, poorly ventilated basement area. The painting took about 2 hours to complete.

The patient also experienced nausea, headache, dizziness, and lightheadedness, which cleared within an hour after leaving the basement area. The chest and respiratory complaints, however, have persisted, prompting the office visit. She is concerned that her symptoms are related to the paint spraying and might affect her pregnancy.

Vital signs include blood pressure 116/80, heart rate 90/minute at rest, respiratory rate 22/minute, and temperature 98.8°F. There are no orthostatic changes in pulse or blood pressure. The head, eyes, ears, nose, and throat (HEENT) examination is negative except for very mild scleral injection. There are mild expiratory wheezes throughout both lung fields, but no rales and no abnormal findings on percussion. Spirometry shows a forced expiratory volume in 1 second (FEV_1) of 72% of predicted value and a moderately decreased peak expiratory flow rate of 275 liters (L)/minute. The FEV_1/forced vital capacity is 75%. There is no cyanosis. Cardiovascular and neurologic examinations are normal. The abdomen is soft and nontender, and a bimanual pelvic examination reveals a 16-week gravid uterus. There is no vaginal bleeding, and no adnexal masses are present. On questioning the patient further, you discover that 2 years ago she was exposed to fumes of toluene diisocyanate (TDI) from an accidental spill during her work as a bookkeeper at an industrial research laboratory. The patient had only eye and upper airway irritation at the time of the accident but developed severe shortness of breath and coughing 4 hours later. She was hospitalized for several days but recovered.

Pretest

(a) What further information and history would you attempt to elicit?

(b) One of the ingredients in the spray paint is toluene. Could this be responsible for the patient's symptoms?

(c) The patient is concerned about possible effects on the fetus. What advice would you offer?

(d) How will you treat this patient?

Who's At Risk

Workers who manufacture or use toluene or toluene-containing products are at increased risk of exposure. An estimated 4 to 5 million workers are occupationally exposed to toluene. Workers at greatest risk for exposure include automobile mechanics; gasoline manufacturers, shippers, and retailers; dye and ink makers; and painters. Other workers who are potentially exposed to toluene include, but are not limited to, the following:

- adhesives and coatings manufacturers and applicators,
- audio equipment product workers,
- chemical industry workers,
- coke-oven workers,
- fabric manufacturers (fabric coating),
- hazardous waste site personnel,
- linoleum manufacturers,
- pharmaceutical manufacturers,
- printing workers,
- shoe manufacturers, and
- styrene producers.

- Chronic, intentional toluene abuse can lead to serious adverse effects and death.

Many organic solvents, including toluene, have an addictive potential. Alcohol or opiates demonstrate a physiologic or biochemical addiction. Toluene is psychologically addictive. The adolescent population is most likely to intentionally abuse solvents, although the prevalence of this abuse is unknown. Solvent inhalation techniques are referred to as "bagging" or "huffing." Studies indicate that volatile-solvent sniffers are typically boys between the ages of 10 and 15 years of age who might concurrently use or later develop an alcohol, marijuana, or opiate habit. In general, solvent abuse tends to decrease with increasing age, but adults of both sexes might also abuse organic solvents.

- Concurrent use of alcohol or salicylates increases the risk of adverse effects from toluene exposure.

Because toluene is metabolized in the liver, liver disease can increase its acute toxic effects. Concurrent use of alcohol, which competitively inhibits toluene metabolism, can also increase toluene's acute effects. In addition, experimental animal studies indicate that chronic exposure to toluene augments alcohol-induced fatty liver disease; thus, workers exposed to toluene who are chronic alcohol drinkers can have added risk due to their inability to detoxify alcohol.

Concurrent use of medication with toluene exposure can have an influence on toluene toxicity. Salicylates can competitively inhibit toluene metabolism; concurrent use of salicylates can reduce the clearance of both toluene and salicylates. Studies in humans indicate that the common analgesics, acetaminophen and aspirin, might inhibit toluene metabolism and influence toluene toxicity. CYP2E1 is involved in the initial step of the principal metabolic pathway for toluene and acetaminophen, and represents a potential site for a competitive metabolic interaction. Aspirin and one of the principal downstream metabolites of toluene, benzoyl coenzyme A, are conjugated with glycine. When glycine pools are depleted by competition for glycine by aspirin metabolism, toluene metabolism might be inhibited. In volunteers exposed for 4 hours to 300 mg/m^3 toluene (80 parts per million [ppm]) with or without doses (1,000 mg/70 kg=14.3 mg/kg) of acetaminophen (paracetamol) or acetyl salicylic acid (aspirin), co-exposures with these analgesics increased the concentration of toluene in the blood compared with exposure to toluene alone. Acetaminophen co-exposure also significantly increased the area under the blood concentration versus time curve and the apparent blood clearance of toluene, consistent with an inhibition of toluene metabolism. These results are consistent with the hypothesis that high doses of aspirin might potentiate toluene effects on hearing by inhibiting toluene metabolism. This mechanism can be particularly important in workers exposed to toluene.

Like many organic solvents, toluene is a respiratory tract irritant, particularly at high airborne concentrations. Persons with underlying respiratory tract disorders, such as asthma and chronic obstructive pulmonary disease (COPD) or reactive airways dysfunction syndrome (RADS), can experience bronchospasm on exposure to any irritant, including toluene. Because toluene accumulates in adipose tissues, persons who are obese tend to retain more toluene than persons of normal weight, but the clinical significance of this is unknown.

- Persons with cardiovascular, respiratory, and liver disease are at increased risk for toluene's adverse effects.

Challenge

The patient's history is negative for asthma, chronic bronchitis, and allergic conditions. She has not been employed in any position entailing chemical exposure since the toluene diisocyanate exposure 2 years ago, but she has noticed mild, transient chest tightness and difficulty breathing when using self-service gasoline filling stations and when exposed to tobacco smoke.

(1) Could the patient's current problem be related to the spray paint? Explain.

Exposure Pathways

Toluene is a clear, colorless liquid with an aromatic odor. It is a natural constituent of crude oil and is produced from petroleum refining and coke-oven operations. At room temperature, toluene is both volatile and flammable. The odor threshold for toluene in air is low—about 80 parts per billion (ppb), which is about 500 times lower than the level permitted in the workplace. In water, it can be tasted and smelled at a level of 40 ppb. These levels are well below the concentrations at which adverse effects have been observed for short-term exposure. Because toluene is lipid soluble, it has a moderate tendency to bioaccumulate in the food chain. Synonyms for toluene include toluol, methylbenzene, phenylmethane, and methacide.

- Gasoline, which contains 5% to 7% toluene, is the largest source of toluene release to the atmosphere.

The principal source of toluene exposure for the general population is gasoline, which contains 5% to 7% toluene by weight. Toluene is released to the atmosphere during the production, transport, and combustion of gasoline. Not surprisingly, toluene concentrations are highest in areas of heavy traffic, near gasoline filling stations, and near refineries. Toluene is short-lived in ambient air because of its reactivity with other air pollutants.

- Common household products and cigarette smoke contribute to toluene in indoor air.

Common household products and cigarette smoke are the principal sources of toluene indoors. Indoor air is often several times higher in toluene concentration than outside air. Cigarette smokers absorb about 80 to 100 micrograms (µg) of toluene per cigarette. Toluene-containing consumer products include household aerosols, paints, paint thinners, varnishes, shellac, rust inhibitors, adhesives and adhesive products, and solvent-based cleaning and sanitizing agents. Toluene is used as a solvent in cosmetic nail polishes at concentrations of up to 50%.

- Use of toluene as a benzene replacement is increasing.

Industrial use of toluene as a solvent replacement for the more toxic benzene is increasing. In addition to the products mentioned previously, toluene is commonly used in some printing operations, leather tanning, and chemical processes.

Intentional inhalation of toluene makes it one of the most abused hydrocarbon solvents. Glues, paints, and solvent mixtures are the most commonly abused products.

Although most environmental toluene is released directly to the atmosphere, it is occasionally detected in drinking water supplies. Water contamination occurs because toluene is a common chemical in hazardous waste and sludge disposal sites, industrial effluents, and

petroleum wastes. Nonetheless, drinking water levels of toluene are usually low relative to those of other volatile organic chemicals.

Challenge

The patient brings you the spray paint can, which lists the following ingredients on the label: paint (pigment), petroleum distillates, and a minor amount of methanol. A call to the regional poison control center reveals that the petroleum distillates in this brand of paint are mostly toluene, with minor amounts of xylene. The patient asks you if this toluene is the same chemical that caused her hospitalization 2 years ago.

(2) How will you answer the patient's question?

Biologic Fate

Inhalation is the primary route of toluene exposure; however, toluene can be absorbed through ingestion and dermal contact. Peak blood concentrations occur 15 to 30 minutes after inhalation. The amount of toluene absorbed by inhalation depends on the respiratory minute volume; thus, exercise affects the absorption rate of toluene. At rest, the lungs absorb about 50% of an inhaled dose.

- Systemic absorption of inhaled toluene is rapid.

The rate of absorption after oral intake is slower than after inhalation. Nevertheless, gastrointestinal absorption is nearly complete, and blood toluene levels peak 1 to 2 hours after ingestion. Percutaneous absorption is slow through intact skin and rarely produces toxicity.

Toluene is lipophilic and has little water solubility. It is distributed quickly to highly perfused tissues such as brain, liver, and kidney. It passes readily through cellular membranes and accumulates primarily in adipose and other tissues with high fat content. In the body, the half-life of toluene ranges from several minutes in highly vascular organs to slightly over 1 hour in fatty tissue. Toluene's affinity for the lipid-rich structures of nervous tissue results in CNS toxic effects within minutes.

- Toluene is distributed to highly perfused and fatty tissues.

About 80% of absorbed toluene is oxidized in the liver to benzoic acid, which is then conjugated with glycine to form hippuric acid or with glucuronic acid to form benzoyl glucuronate. A small amount of toluene undergoes aromatic ring oxidation to form ortho- and para-cresols. Most inhaled or ingested toluene is eliminated in urine within 12 hours after exposure; a small amount (up to 20%) is eliminated as free toluene in expired air. Less than 2% of total toluene metabolites are excreted in the bile.

- The major toluene metabolite is hippuric acid, which is excreted in the urine.

Challenge

(3) Is there any clinical benefit for measuring blood toluene levels or levels of urinary toluene metabolites in this patient?

Physiologic Effects

Central Nervous System Effects

- The principal effect of toluene exposure is CNS depression.

Toluene produces reversible effects on the liver, kidneys, and nervous system; the nervous system appears to be most sensitive to its effects. The physiologic effects of toluene depend on the concentration and length of exposure. Most data concerning toluene's effects on human health come from studies of workers with chronic exposure to toluene or from intentional solvent abusers who inhale high levels of toluene for self-intoxication. The applicability of these data to relatively low-level exposure in the environmental setting, however, is unknown.

Toluene's anesthetic action can result in rapid CNS depression and narcosis at high concentrations. Volatilization after ingestion and hypoxia after aspiration can contribute to CNS toxicity, and aromatic impurities in commercial toluene-containing products can have added neurotoxic effects.

At low concentrations, toluene produces disturbances in basal ganglia dopaminergic mechanisms in experimental animals. Human exposure to 100 ppm of toluene (the permissible exposure level in the workplace) causes substantial complaints about poor air quality, altered temperature and noise perception, increased irritation of the nose and lower airways, and feelings of intoxication. Chronically exposed workers have scored lower on some tests of cognitive performance than did unexposed controls.

Several studies have examined the neuropsychiatric effects of acute exposure to toluene vapors. Cerebellar and CNS integrative dysfunction predominate. In addition, peripheral nerve dysfunction has been reported, but the peripheral neuropathies might have been due to impurities, such as n-hexane, in the toluene. Long-term toluene abuse has led to neuropsychiatric and neurobehavioral disorders, which in many cases, but not all, were reversible. Some chronic toluene abusers have developed structural CNS damage. Magnetic-resonance imaging (MRI) and brainstem auditory-evoked response evaluation of the brains of chronic toluene abusers show permanent changes in brain structure that correlated with the degree of brain dysfunction. MRI results revealed loss of gray-white matter contrast, diffuse supratentorial white

matter high-signal lesions, and low signal in the basal ganglia and midbrain. in the brains of neuropsychologically impaired toluene abusers.

Respiratory Effects

Toluene acts initially as a respiratory tract irritant. Several mechanisms precede respiratory decompensation: replacement of alveolar air by vaporized hydrocarbon, ventilation-perfusion dysfunction caused by bronchospasm, formation of a hyaline membrane, and solubilization of the lipid surfactant layer. As severity of exposure increases, respiratory depression leading to death can result. Pulmonary aspiration of gastric contents that might occur during altered consciousness can lead to chemical pneumonitis.

- Toluene is a respiratory tract irritant.

Cardiac Effects

Toluene appears to lower the threshold of myocardial susceptibility to the dysrhythmogenic effects of catecholamines. Sudden death among volatile-solvent abusers has often been preceded by strenuous physical activity and is believed to result from lethal, nonperfusing cardiac dysrhythmias. In cases of severe poisoning, cardiac dysrhythmias can also occur secondary to hypoxia and acidosis caused by CNS-mediated hypoventilation.

- Cardiac dysrhythmias are postulated to be a leading cause of death after intentional toluene abuse.

Hematopoietic Effects

Toluene does not cause the hematopoietic effects noted with chronic benzene exposure. Early studies suggesting such effects were performed using toluene that was contaminated with benzene. Modern distillation methods prevent significant benzene contamination of toluene.

- Toluene does not cause the severe blood dyscrasias associated with benzene exposure.

Other Effects

Metabolic acidosis, hypokalemia, hematuria, proteinuria, distal renal-tubular acidosis, and pyuria have been reported in chronic volatile-solvent abusers, although these effects have usually been reversible. Accumulation of hippuric acid and other organic acid by-products of toluene metabolism is thought to be responsible for the elevated anion-gap metabolic acidosis that occurs with toluene abuse. Elevated urinary concentration of retinol-binding protein has been correlated with toluene exposure in a dose-dependent manner, which suggests that early renal-tubular effects might occur in abusers. Hepatotoxicity has been reported in glue sniffers, but studies in chronically exposed workers show no or minimal hepatic damage.

- Metabolic acidosis can occur in persons who abuse volatile organic solvents, including toluene.

Toluene has been implicated in adverse developmental effects that have occurred in offspring of chronic toluene abusers. Children chronically exposed in utero from high-dose maternal solvent abuse throughout

- The role of toluene in developmental toxicity is uncertain.

pregnancy have demonstrated microcephaly, CNS dysfunction, attention deficits and hyperactivity, developmental delay, minor craniofacial and limb anomalies, and variable growth deficiency. Severe neonatal acidosis has also been noted, possibly secondary to maternal renal-tubular acidosis. However, these case reports must be regarded with caution because most results to date have been confounded by probable exposure to alcohol or other organic solvents during pregnancy. In addition, the small number of exposed persons and the lack of precise exposure data limit the conclusions that can be drawn.

Although epidemiologic studies of workers exposed to multiple organic solvents have found greater risks of death from numerous cancers compared to the general nonexposed population, no evidence exists showing that toluene alone causes cancer. Animal studies have not suggested that toluene is carcinogenic.

In high concentrations, toluene exerts an irritant action on the eyes, skin, and mucous membranes. Direct dermal exposure defats the skin, leading to dryness, fissuring, and possible secondary infection. A few cases of contact urticaria have been described after occupational exposure to a solvent mixture containing toluene, but it is not clear that toluene was the responsible agent.

Challenge

(4) The patient expresses concern that her fetus might have been harmed by the exposure to toluene in the spray paint. What advice can you give her?

(5) Should the patient be concerned about future development of cancer from the spray paint exposure?

Clinical Evaluation

History and Physical Examination

Because signs and symptoms of toluene intoxication typically depend on the intensity, duration, and frequency of exposure, assessment of a patient with suspected toluene exposure begins with defining the route or routes of exposure and determining if the exposure was acute or chronic and at what concentrations the exposure occurred. The temporal relationship of symptom onset to possible exposure should be explored. In addition, the following information might be helpful: history of chronic illness; chronic use of medications (e.g., aspirin); social history; tobacco use and exposure to tobacco smoke; alcohol or illicit drug use;

occupational history; recent hobbies and household remodeling projects, particularly painting and furniture refinishing; and use of consumer products such as nail polish, adhesives, aerosols, and solvent-based cleaners. Because many products containing toluene are mixtures, attempts should be made to ascertain the total composition. Proximity of residence to landfills and industrial facilities and the source of drinking water might provide clues to environmental exposures. (See *Case Studies in Environmental Medicine: Taking an Exposure History*.)

Clinical evaluation of a patient with acute exposure should focus on the organ systems most often affected by toluene: neuropsychiatric, renal, cardiovascular, and respiratory. In the case of chronic abusers, the hepatic system should also be evaluated. Possible volatile-solvent abuse and concomitant use of alcohol or other drugs of abuse should be considered when chemically induced CNS depression is present.

Signs and Symptoms

Acute Exposure

Substantial nonoccupational, acute exposures to toluene are most frequently the result of intentional inhalation of glue, paint, or solvent vapors. High-concentration exposures can also occur in hobbyists and do-it-yourself workers in confined spaces. Short-term exposure to high concentrations of toluene (e.g., 600 ppm) can produce fatigue, dizziness, headaches, loss of coordination, nausea, and stupor; 10,000 ppm can cause death from respiratory failure.

- Symptoms are unlikely to occur after exposure to airborne concentrations below the odor threshold.

Acute exposure results in CNS depression with headache, dizziness, lightheadedness, and euphoria, and can lead to cardiopulmonary collapse, coma, and death. In addition to CNS depression, acute ingestion can cause nausea, vomiting, possible hematemesis, and burning of the oropharynx and epigastrium. Aspiration can lead to hoarseness, coughing, and chemical pneumonitis.

If a large ingestion of toluene is suspected or if respiratory distress develops after acute inhalation exposure, hospital admission, chest radiography, spirometry, determination of arterial blood gases, and monitoring of vital signs are recommended. Acutely exposed patients who are asymptomatic and have a negative chest radiograph do not require further hospital observation.

Dermal exposure usually only causes skin irritation. When contact with the solvent is unusually extensive and prolonged, some systemic absorption can occur. Ocular exposure to liquid toluene can cause corneal burns.

- Chronic solvent abuse is associated with various neurobehavioral and neuropsychologic effects.

Chronic Exposure

Repeated high-dose exposures associated with solvent abuse can result in progressive memory loss, fatigue, poor concentration, irritability, persistent headaches, and signs and symptoms of cerebellar dysfunction. Although these effects generally are reversible if exposure ceases, some patients remain substantially impaired. Muscular weakness has been noted in patients who develop renal-tubular acidosis.

Laboratory Evaluation

In general, if toluene exposure is suspected, baseline studies should include the following:

- electrolytes with blood urea nitrogen and creatinine;
- complete blood count and smear;
- electrocardiogram with rhythm monitoring;
- liver enzymes;
- urinalysis;
- creatine kinase;
- neuropsychologic assessment (a referral for detailed neuropsychologic evaluation is indicated only if the patient's abnormal mental status or behavioral changes persist after exposure ceases); and
- chest radiograph, if symptomatic.

Baseline tests should be repeated in 3 to 6 months to detect delayed hepatic or renal abnormalities or both. A neuropsychologic follow-up evaluation should also be carried out at this time. Patients with substantial chronic exposures should have annual reassessments.

The patient in this case study should be hospitalized and connected to a cardiac and fetal monitor, with a pulse oximeter in place; vital signs should be monitored at short interval periods. An obstetrical and environmental medical consult should also be part of this patient's initial clinical assessment and followup.

Direct Biologic Indicators

- Toluene can be measured in blood, but the level has little clinical relevance.

Because excretion of toluene and its metabolites is rapid (essentially complete within 12 to 24 hours), biologic samples for analysis must be obtained soon after exposure. A venous blood sample taken within 1 day after exposure can be used to confirm toluene exposure (normal for unexposed populations is 0.1 milligrams/deciliter [mg/dL]); however,

the toluene level obtained will not correlate well to the degree of exposure or to symptoms. Analysis of exhaled air for toluene is experimental only.

Indirect Biologic Indicators

Hippuric acid, a metabolite of toluene, can also result from the metabolism of other chemicals, including common food additives, and is typically found in significant amounts in the urine from unexposed persons. Hippuric acid levels of >2.5 grams per gram (g/g) creatinine suggest toluene exposure.

- Urinary hippuric acid levels should be interpreted with caution.

Treatment and Management

Acute Exposure

No antidote exists for toluene intoxication; care is supportive. In cases of acute exposure, treatment consists of removal of patients from the contaminated environment, support of cardiopulmonary function, and prevention of further absorption.

- No antidote exists for toluene toxicity.
- Therapy for toluene overexposure consists of supportive care.

Patients with inhalation exposure might require low-flow oxygen (approximately 40%) and hydration. More severe cases might require assisted ventilation. Contaminated clothing should be removed and isolated, decontaminated, or disposed of safely. Exposed skin should be washed thoroughly with soap and water. Treatment of ocular exposure should begin with irrigation for at least 15 minutes.

In cases of toluene ingestion, induction of emesis is contraindicated because of the risk of CNS depression and subsequent pulmonary aspiration from vomiting. Standard regimes for administering a cathartic and activated charcoal should be followed. If the patient has ingested a large amount (>5 milliliters [mL] or greater than 1 teaspoon) of toluene and is examined within 30 minutes of ingestion, the benefits of gastric lavage should be weighed against the risk of pulmonary aspiration. Ingestion of a small amount (<5 mL or less than 1 teaspoon) of toluene can be treated by administering activated charcoal orally without emptying the gut. Activated charcoal should be used cautiously because in some cases it can cause vomiting, which may be hazardous to a patient who has ingested a volatile hydrocarbon or has a diminished level of consciousness. Children have important toxicokinetic and physiologic differences that make their responses to environmental exposures different from those of adults. The behaviors and activities of children can introduce greater opportunities for exposure to contaminants in air, water, and soil, compared with those of adults living in the same environment. Children differ from adults in their exposures and can differ

in their susceptibility to hazardous chemicals: the same amount might have a significantly different effect.

Epinephrine and other catecholamines should also be used cautiously, because of risk of cardiac dysrhythmias. In substantial intoxications, fluid and electrolytes should be monitored. Metabolic acidosis is usually accompanied by severe hypokalemia; therefore, administration of bicarbonate should be avoided because bicarbonate can worsen hypokalemia by causing intracellular shifting of potassium. Hypocalcemia can occur after electrolyte replenishment; it should be corrected with intravenous calcium. Use appropriate supportive treatment to correct acute renal failure if it occurs.

Discharge planning should include follow up of hepatic, renal, and neuropsychologic status and referral for substance-abuse treatment when appropriate. In the clinical case presented, a developmental pediatric evaluation should take place to closely monitor the offspring for toluene embryopathy syndrome.

Environmental conditions that might have led to unintentional exposures should be corrected.

Chronic Exposure

- No clinical treatment exists for chronic toluene exposure.

No specific clinical treatment exists for patients who have been chronically exposed to toluene. Sources of exposure must be identified and minimized. Intentional volatile-solvent abusers should be referred to appropriate treatment programs.

Challenge

(6) How will you treat the patient in the case study?

Standards and Regulations

Workplace

Air

The workplace air standards mandated by the Occupational Safety and Health Administration (OSHA) include an 8-hour time-weighted average (TWA) of 200 ppm. The National Institute for Occupational Safety and Health (NIOSH) recommends a TWA of 100 ppm and a STEL of 150 ppm. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a 8 hour TWA threshold limit value of 50 ppm.

Environment

Air

The federal government has not established specific standards for toluene in ambient air. At least 10 states have guidelines or standards for acceptable ambient air concentrations of toluene.

Water

As of July 30, 1992, the U.S. Environmental Protection Agency (EPA) instituted a maximum contaminant level of 1 ppm (1.0 milligrams per liter [mg/L]) for toluene in drinking water. Approximately 10 states have drinking water standards or guidelines for toluene ranging from 0.1 to 2 ppm.

Biologic Standards

Biological exposure indices (BEI) are reference values established by ACGIH that are intended as guidelines for evaluating potential exposure hazards in the workplace. The BEI for the urinary metabolite of toluene (hippuric acid) is 2.5 g/g creatinine; the sample is collected at the end of the work shift. Hippuric acid is also a metabolite of other aromatic

Table 1. Standards and Regulations for Toluene

Agency	Focus	Level*	Comments
American Conference of Governmental Industrial Hygienists	Air: workplace	50 ppm (375 mg/m^3)	Advisory; TLV-TWA†
National Institute for Occupational Safety and Health	Air: workplace	100 ppm (375 mg/m^3) 150 ppm (560 mg/m^3)	 Advisory; TWA STEL‡
Occupational Safety and Health Administration	Air: workplace	200 ppm (375 mg/m^3)	Regulation; PEL§ as TWA
U.S. Environmental Protection Agency	Drinking water	1 ppm (mg/L) 20 ppm (mg/L) 2 ppm (mg/L) 2 ppm (mg/L) 7 ppm (mg/L) 1 ppm (mg/L)	Regulation; MCL¶ Health advisories 1 day (10-kg child) 10 day (10-kg child) Longer term Child Adult Lifetime Adult

*ppm: parts per million; mg/m^3: milligrams per cubic meter; mg/L: milligrams per liter.
†TLV-TWA (threshold limit value 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): maximum level allowed in any 15-minute sampling period.
§PEL (permissible exposure limit): highest level in air to which a worker may be exposed, averaged over an 8-hour workday.
¶MCL (maximum contaminant level): enforceable level for drinking water.

solvents and certain endogenous agents; therefore, it is not specific to toluene. The BEI for toluene in venous blood, collected at the end of the work shift, is 1.0 mg/L, whereas the toluene index in end-exhaled air (the residual air in the lungs after the person has exhaled normally), measured during the work shift, is 20 ppm. These biologic standards are useful as confirmatory tests for the effectiveness of workplace industrial hygiene practices, but are not useful for comparison purposes in cases of acute exposure.

Suggested Reading List

Agency for Toxic Substances and Disease Registry. 2002. Case studies in environmental medicine: pediatric environmental health. Atlanta: US Department of Health and Human Services. Available from URL: www.atsdr.cdc.gov/HEC/CSEM.

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Wallen M. 1986. Toxicokinetics of toluene in occupationally exposed volunteers. Scand J Work Environ Health 12:588–93.

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Wilkins-Haug L, Gabow PA. 1991. Toluene abuse during pregnancy: obstetrics complications and perinatal outcome. Obstet Gynecol 77:505–9.

Wiseman M, Banim S. 1987. "Glue sniffer's" heart? Br Med J 294:739.

US Department of Commerce. Health assessment of toluene in California drinking water. Washington: US Department of Commerce; 1989 Mar 8.

Sources of Information

More information on the adverse effects of toluene and on treating and managing cases of exposure to toluene can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Toluene Toxicity* is one monograph in a series. For other publications in this series, use the order form on page 30. For clinical inquiries, contact ATSDR, Division of Toxicology and Environmental Medicine at 770-488-3490; the Association of Occupational and Environmental Clinics (AOEC) (1010 Vermont Avenue NW, Suite 513, Washington, DC 20005, telephone: 202-347-4976, fax: 202-247-9450, e-mail: aoec@aoec.org, Web page: www.aoec.org); or the Pediatric Environmental Health Specialty Units (PEHSU) through AOEC.

Answers to Pretest and Challenge Questions

Pretest

(a) The ingredients of the spray paint should be identified. Obtaining the original container and inspecting the label might be sufficient. If the ingredients are not listed on the label, the information can be obtained by contacting the distributor or manufacturer, or the information might be available from the regional poison control center.

Further history should include questions regarding previous bouts of asthma, chronic bronchitis, allergic conditions, and prior episodes of chest complaints after chemical exposure.

(b) Yes. The patient's transient nausea, headache, dizziness, and lightheadedness are consistent with exposure to toluene (but not with exposure to toluene diisocyanate). Although toluene can be irritating to the airways, the degree of wheezing and dyspnea experienced by this patient and the persistence for several hours after cessation of exposure both indicate that an intercurrent disorder might be present.

The patient has no history of chronic respiratory disease, yet pulmonary function testing suggests airway obstruction. She has had a previous significant exposure to a strong respiratory-tract irritant (toluene diisocyanate), which caused severe respiratory symptoms within 24 hours; she reports that since this episode, exposure to irritating substances continues to provoke symptoms similar to asthma. This history suggests RADS. Criteria used to diagnose RADS are listed below. Using the spray paint in a poorly ventilated room could readily create a toluene concentration irritating enough to provoke bronchospasm in a patient with RADS.

The diagnostic criteria for RADS include the following:

- no history of respiratory system complaints prior to exposure;
- a single, specific exposure involving high concentrations of an irritant fume, gas, or vapor that was associated with the initial symptoms;
- onset of symptoms occurred within 24 hours of the initial exposure and persisted for at least 3 months;
- pulmonary function tests usually indicate airflow obstruction;
- methacholine challenge test is positive (e.g., <8 mg/mL); and
- other types of pulmonary disease have been ruled out.

(c) Toluene has caused fetal malformations in chronically exposed experimental animals. Cases have been reported of congenital malformations and severe neonatal acidosis in infants of women who chronically abused toluene throughout pregnancy. In most of those cases, the toluene doses were very high, but concomitant abuse of ethanol occurred, so fetal alcohol syndrome cannot be excluded. Given the mild, brief exposure that this patient incurred, it is unlikely that the fetus was harmed. Should the patient desire further counseling, you could refer her to a teratology consulting service such as the Motherisk Program at the Hospital for Sick Children in Toronto.

(d) Treatment for RADS is essentially the same as treatment for asthma: beta-agonist inhalants (e.g., albuterol or terbutaline sulfate), cromolyn sodium, and corticosteroids should be administered. Of the various beta-agonist inhalants, terbutaline sulfate is nonteratogenic in experimental animals and might be the best choice for this patient. Consider cromolyn sodium if prophylactic treatment is deemed necessary. Cromolyn sodium prevents both antibody-mediated and nonantibody-mediated mast cell degranulation and mediator release. The usual precautions for use of corticosteroids apply. The patient should be advised to avoid exposure to all pulmonary irritants.

Challenge

(1) You could explain to the patient that TDI is not the same chemical as the chemical in the spray paint. Both toluene and TDI are liquids, but their chemical structures are different, as are their toxicities. Toluene is a common solvent found in many household products; its toxicity is low, and at low doses (<100 ppm) it

normally causes few symptoms. On the other hand, TDI is very irritating to the eyes and respiratory tract and can cause bronchospasm at levels <1 ppm. Furthermore, TDI can sensitize exposed individuals and cause coughing spasms at even lower levels than the original exposure, and this does not occur with toluene.

(2) See answer (b) above.

(3) There is little clinical benefit in measuring blood toluene levels or levels of toluene metabolites such as hippuric acid in the urine. Treatment would not be altered regardless of the results. The only available comparison data are from either deliberate toluene abusers or asymptomatic workers with chronic exposure, and it is unclear how such data would apply to this patient.

(4) See answer (c) above.

(5) There are few data to suggest that toluene is carcinogenic. Earlier reports of cancer occurring after chronic toluene exposure were probably caused by toluene's significant contamination with benzene, which is a known carcinogen. (Because of modern distillation methods, benzene is no longer a contaminant of toluene.) The patient can be reassured that a single exposure to toluene is unlikely to cause or contribute to the development of cancer.

(6) See answer (d) above.

Notes

Case Studies in Environmental Medicine:

Toluene Toxicity

Evaluation Questionnaire and Posttest, Course Number SS3061

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 toluene.
- Describe two potential environmental and occupational sources of exposure to toluene.
- Give two reasons why toluene is a health hazard.
- Describe the factors that contribute to toluene toxicity.
- Identify evaluation and treatment protocols for persons exposed to toluene.
- List two sources of information on toluene.

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 toluene 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 toluene.

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

22. I am confident I can give two reasons why toluene is a health hazard.

23. I am confident I can describe the factors that contribute to toluene toxicity.

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

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

Posttest

If you wish to receive continuing education credit for this program, you must complete this posttest. Each question below contains five suggested answers, of which one or more is correct. **Circle all correct answers on the answer sheet.**

26. Which of the following puts a person at increased risk for toluene's adverse effects?

A. Asthma.
B. Diabetes mellitus.
C. Chronic obstructive pulmonary disease.
D. Chronic ethanol consumption.
E. Dieting.

27. Which of the following are important potential sources of toluene exposure?

A. Combustion of plastics.
B. Shallow domestic wells in rural areas.
C. Meat preservatives.
D. A variety of household products including paints and adhesives.
E. Ambient air, particularly in areas with heavy traffic.

28. Which of the following statements about toluene are true?

A. Toluene can be detected in blood within 1 hour after a significant inhalation exposure.
B. Dermal absorption of toluene is more rapid than absorption by inhalation.
C. Toluene accumulates in adipose tissue.
D. Hippuric acid is the major metabolite of toluene.
E. Some absorbed toluene is exhaled unchanged.

29. The common physiologic effects of toluene can include

A. profound and rapid depression of bone marrow.
B. central nervous system depression and narcosis.
C. coronary artery vasospasm.
D. irritation of the eyes, skin, and mucous membranes.
E. respiratory tract irritation.

30. Some less common physiologic effects reported in toluene abusers include

A. distal renal tubular acidosis.
B. hyperthyroidism.
C. elevation of fasting blood sugar.
D. cardiac dysrhythmias.
E. blepharospasm.

31. Which of the following tests can be used to document exposure to toluene?

A. Urinary hippuric acid.
B. Toluene in venous blood.
C. Hippuric acid in blood.
D. Fasting blood sugar.
E. Cytoplasmic phosphokinase.

32. Clinical effects associated with toluene exposure include

A. double vision.
B. coronary artery disease.
C. bladder cancer.
D. headache.
E. lightheadedness.

33. Which of the following might be used to treat patients with an inhalation overexposure to toluene?

A. One hundred percent oxygen.
B. Methylene blue.
C. Amyl nitrite.
D. Bronchodilators.
E. Soluble iron compounds.

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:

Toluene Toxicity

Answer Sheet, Course Number SS3061

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: Continuing Education Coordinator
Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road, NE (MS F-32)
Atlanta, GA 30333

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

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.

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
5. A B C D E F G H I J K
6. A B C D E F
7. A B C D E F
8. A B C D
9. A B C D E F
10. A B C D E F G
11. A B C D E
12. A B C D E
13. A B C D E
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27. A B C D E
28. A B C D E
29. A B C D E
30. A B C D E
31. A B C D E
32. A B C D E
33. A B C D E

Name: E-mail (not required):

Address:

Zip code:

○ Check here to be placed on the list to pilot test new case studies

fold here first

Place Stamp Here

Continuing Education Coordinator

Agency for Toxic Substances and Disease Registry

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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.

tape or staple here

**DEPARTMENT OF HEALTH
AND HUMAN SERVICES**
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