ATSDR

August 1993

Case Studies in Environmental Medicine

21

Toluene Toxicity

Environmental ALERT . . .

- ***Toluene's use is increasing partially 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. *See page 17 for more information about continuing medical education credits and continuing education units.*

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U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

ATSDR

How to use this issue...

This issue begins with a composite case study that describes a realistic encounter with a patient. This description is followed by a pretest. The case study is further developed through Challenge questions at the end of each section. To fully benefit from this monograph, readers are urged to answer each question when it is presented. (Answers to the Pretest and Challenge questions are found on pages 15-16.) The monograph ends with a posttest, which can be submitted to the Agency for Toxic Substances and Disease Registry (ATSDR) for continuing medical education (CME) credit or continuing education units (CEU). See page 17 for further instructions on how to receive these credits.

The objectives of this monograph on toluene are to help you:

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

Contents

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

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Case Study

A pregnant 28-year-old with 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 complaints, however, have persisted, prompting the office visit. She is concerned that her symptoms are related to the paint spraying and may 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 HEENT examination is negative except for very mild scleral injection. There are mild expiratory wheezes throughout both lung fields but no rales or no abnormal findings on percussion. Spirometry shows an FEV1 of 72% of predicted value and a moderately decreased peak expiratory flow rate of 275 L/minute. The FEV1/FVC is 75%. 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 employment 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.

(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?

Answers can be found on page 15.

Exposure Pathways

- **Use of toluene as a benzene replacement is increasing.**

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 160 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.

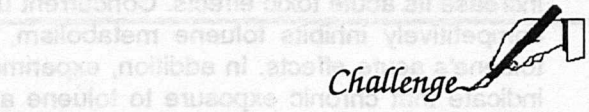
- **Common household products and cigarette smoke contribute to toluene in indoor air.**

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 up to 50%.

Industrial use of toluene as a solvent replacement for the more toxic benzene is increasing. In addition to the products mentioned above, 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.



Additional information for the case study: 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 spirits 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.

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

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. Automobile mechanics; gasoline manufacturers, shippers, and retailers; dye and ink makers; and painters are at greatest risk. Other workers who are potentially exposed to toluene include, but are not limited to, the following:

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

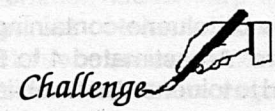
Many organic solvents, including toluene, have an addictive potential equal to that of alcohol or opiates. The adolescent population is most likely to intentionally abuse solvents, although the prevalence of this abuse is unknown. Solvent inhalation techniques are referred to as "bagging" or "huffing." Studies indicate that volatile-solvent sniffers are typically boys between the ages of 10 and 15 years of age who 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 are known to abuse organic solvents.

- **Chronic, intentional toluene abuse may lead to serious adverse effects and death.**
- **Concurrent use of alcohol or salicylates increases the risk of adverse effects from toluene exposure.**
- **Persons with cardiovascular, respiratory, and liver disease are at increased risk of toluene's adverse effects.**

Because toluene is metabolized in the liver, liver disease may increase its acute toxic effects. Concurrent use of alcohol, which competitively inhibits toluene metabolism, may 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 may have added risk due to their inability to detoxify alcohol. Because salicylates can also competitively inhibit toluene metabolism, concurrent use of salicylates may reduce the clearance of both toluene and salicylates.

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), may experience bronchospasm on exposure to any irritant, including toluene.

Because toluene accumulates in adipose tissues, obese persons tend to retain more toluene than persons of normal weight, but the clinical significance of this is unknown.



Additional information for the case study: 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.

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

Biologic Fate

Inhalation is the primary route of toluene exposure, but significant amounts 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 distributed to highly perfused and fatty tissues.**

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 one hour in fatty tissue. Toluene's affinity for the lipid-rich structures of nervous tissue results in central nervous system toxic effects within minutes.

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

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.

(3) Is there any clinical benefit in 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 central nervous system 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 this data to relatively low-level exposure in the environmental setting, however, is unknown.

Toluene's anesthetic action can result in rapid central nervous system (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 may have added neurotoxic effects.

At low concentrations, toluene produces disturbances in basal ganglia dopaminergic mechanisms in experimental animals. Human exposure to 100 parts per million (ppm) of toluene (the permissible exposure level in the workplace) caused 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 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 may 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.

Respiratory Effects

- **Toluene is a respiratory-tract irritant.**

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 may occur during altered consciousness can lead to chemical pneumonitis.

Cardiac Effects

Toluene appears to lower the threshold of myocardial susceptibility to the dysrhythmic 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 dysrythmias. In cases of severe poisoning, cardiac dysrythmias may also occur secondary to hypoxia and acidosis caused by CNS-mediated hypoventilation.

- **Cardiac dysrhythmias are postulated as 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 with 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 usually have been reversible. Accumulation of hippuric acid and other organic acid byproducts 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 may 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 solvents, including toluene.**

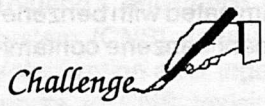
Toluene has been implicated in adverse developmental effects that have occurred in offspring of chronic toluene abusers. Children chronically exposed in utero from high-dose maternal solvent abuse throughout pregnancy have demonstrated microcephaly, CNS dysfunction, attention deficits and hyperactivity, 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 all 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.

- **The role of toluene in developmental toxicity is uncertain.**

- **Toluene is not considered a human carcinogen.**

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, there is no evidence 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.



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

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_____

(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 and duration of exposure, assessment of a patient with suspected toluene exposure begins with defining the route(s) of exposure and determining if the exposure was acute or chronic and at what concentrations. The temporal relationship of symptom onset to possible exposure should be explored. In addition, the following information may be helpful: occupational history; recent hobbies and household remodeling projects, particularly painting and furniture refinishing; 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 may 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 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 may also occur in hobbyists and do-it-yourself workers in confined spaces. Acute exposure results in CNS depression with headache, dizziness, lightheadedness, and euphoria and can lead to cardiopulmonary collapse, coma, and death.

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

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 X ray do not require further hospital observation.

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

Chronic Exposure

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

Repeated high-dose exposures associated with solvent abuse may 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 Tests

If toluene exposure is suspected, baseline studies should include the following:

electrolytes
BUN and creatinine
liver enzymes
urinalysis
electrocardiogram with rhythm monitoring

Repeat baseline tests in 3 to 6 months to detect delayed hepatic, renal, or neuropsychiatric effects. Patients with substantial chronic exposures should have annual assessments. Referral for detailed neuropsychologic assessment is indicated only if the patient's abnormal mental status or behavioral changes persist after exposure ceases.

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 a 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

Urinary hippuric acid levels should be interpreted with caution.

Hippuric acid, a metabolite of toluene, may 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 higher than 2.5 grams per gram (g/g) creatinine suggest toluene exposure.

Treatment and Management

Acute Exposure

There is no antidote 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. Patients with inhalation exposure may require low-flow oxygen (approximately 40%) and hydration. More severe cases may require assisted ventilation. Contaminated clothes 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.

- **There is no antidote for toluene toxicity.**

In cases of toluene ingestion, do not induce emesis 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 (greater than 5 milliter [mL]) 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) of toluene may be treated by administering activated charcoal orally without emptying the gut.

- **Therapy for toluene overexposure consists of supportive care.**

Epinephrine and other catecholamines should be used cautiously because of risk of cardiac dysrhythmias. In substantial intoxications, fluid and electrolytes should be monitored. Intravenous potassium and sodium bicarbonate may be required to correct hypokalemia and acidemia, respectively. Hypocalcemia may 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 neuropsychiatric status and referral for substance-abuse treatment when appropriate. Environmental conditions that may have led to unintentional exposures should be corrected.

Chronic Exposure

There is no specific clinical treatment 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 to encourage abstinence.

- **There is no clinical treatment for chronic toluene exposure.**

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 100 ppm and a short-term exposure limit (STEL) of 150 ppm. The National Institute for Occupational Safety and Health (NIOSH) recommends a TWA of 100 ppm and a STEL of 150 ppm. NIOSH has established the level of 2000 ppm as immediately dangerous to life or health (IDLH). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) identical to the OSHA standards (Table 1).

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 Environmental Protection Agency (EPA) has instituted a maximum contaminant level (MCL) 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.

Table 1. Standards and regulations for toluene

Agency*	Focus	Level	Comments
ACGIH	Air-workplace	100 ppm (375 mg/m³) 150 ppm (560 mg/m³)	Advisory; TLV-TWA† STEL§
NIOSH	Air-workplace	100 ppm (375 mg/m³) 150 ppm (560 mg/m³)	Advisory; TWA STEL
OSHA	Air-workplace	100 ppm (375 mg/m³) 150 ppm (560 mg/m³)	Regulation;PEL¶as TWA STEL
EPA	Drinking Water	1 ppm (1.0 mg/L)	Regulation; MCL**
			Health Advisories
		21.5 ppm (21.5 mg/L) 3.46 ppm (3.46 mg/L)	1 day 10 day
			Longer term
		3.46 ppm (3.46 mg/L) 2.42 ppm (2.42 mg/L)	Child Lifetime

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

†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.

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 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 not for comparison in cases of acute exposure.

Suggested Reading List

Cunningham SR, Dalzell GWN, McGirr P, et al. Myocardial infarction and primary ventricular fibrillation after glue sniffing (letter). Br Med J 1987;294:739-40.

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Press E, Done AK. Solvent sniffing. Physiological effects and community control measures for the intoxication from the intentional inhalation of organic solvents. I and II, Pediatrics 1967;39:451 and 611.

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

Will AM, McLaren EH. Reversible renal damage due to glue sniffing. Br Med J 1981;283:525-6.

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

Government Documents

Agency for Toxic Substances and Disease Registry. Toxicological profile for toluene (update draft). Atlanta: US Department of Health and Human Services, Public Health Service, 1992.

US Department of Commerce. Health assessment of toluene in California drinking water. Washington, DC: US Department of Commerce, March 8, 1989.

Sources of Information

More information on the adverse effects of toluene and 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 in a series. For other publications in this series, please use the order form on the inside back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Answers to Pretest and Challenge Questions

Pretest questions are found on page 1. Challenge questions begin on page 3.

Pretest

(a) The ingredients of the spray paint should be identified. Obtaining the original container and inspecting the label may be sufficient. If the ingredients are not listed on the label, the information may be obtained by contacting the distributor or manufacturer, or the information may 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 exposure has ceased both indicate that an intercurrent disorder may 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 then exposure to irritating substances continues to provoke symptoms similar to asthma. This history suggests reactive airways dysfunction syndrome, or RADS. (See below for criteria used to diagnose RADS.) 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
- a single, specific exposure in an accident or incident involving high concentrations of an irritant fume, gas, or vapor that was associated with the initial symptoms
- symptoms onset occurred within 24 hours of the initial exposure and persisted for at least 3 months
- pulmonary function tests usually indicate airflow obstruction challenge testing is positive
- 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, and concomitant abuse of ethanol occurred so that 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, (416) 598-5781.

(d) Treatment for RADS is essentially the same as treatment for asthma: ß-agonist inhalants (e.g., albuterol or terbutaline sulfate), cromolyn sodium, and corticosteroids. Of the various ß-agonist inhalants, terbutaline sulfate is not teratogenic in experimental animals and may represent the best choice for this patient. Consider cromolyn sodium if prophylactic treatment is deemed necessary. The usual precautions for use of corticosteroids apply. The patient should be counseled to avoid exposure to all pulmonary irritants.

Challenge

(1) You could explain to the patient that toluene diisocyanate (TDI) is not the same chemical as the chemical in the spray paint. Both toluene and toluene diisocyanate 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 (less than 100 ppm) it normally causes few symptoms. On the other hand, TDI is very irritating to the eyes and respiratory tract and may cause bronchospasm at levels less than 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 (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 (c) above.

(5) There are few data to suggest that toluene is carcinogenic. Earlier incidents of cancer occurring after chronic toluene exposure were caused by toluene's significant contamination with benzene, which is a known carcinogen. (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 (d) above.

Posttest and Credits

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

The Centers for Disease Control and Prevention (CDC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor continuing medical education for physicians, and by the International Association for Continuing Education and Training (IACET) to sponsor continuing education units for other health professionals.

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

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

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

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

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

The **American Association of Occupational Health Nurses (AAOHN)**. AAOHN has approved this program for 1.0 contact hours. Applicant will receive the assigned code number in the award letter.

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

To receive continuing education credit (CME or CEU), complete the Posttest on page 18 in the manner shown in the sample question below. **Circle all correct answers.**

Which of the following is known to precipitate migraine headaches?

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

After you have finished the Posttest, please transfer your answers to the answer sheet on the inside back cover and complete the evaluation on the lower half of that page. Fold, staple, and mail the inside back cover to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, Atlanta, GA 30333. Your confidential test score will be returned with an indication of where the correct answers can be found in the text. Validation of earned CME credit and CEU will also be forwarded to participants, and their names, if requested, will be placed on the mailing list to receive other issues in the *Case Studies in Environmental Medicine* series.

POSTTEST: TOLUENE

Circle all correct answers, and record your answers on page 19.

1. 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

2. 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

3. Which of the following statements about toluene are true?
   a. Toluene can be detected in blood within one 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.

4. The common physiologic effects of toluene may 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

5. 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

6. 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

7. Clinical effects associated with toluene exposure include
   a. double vision
   b. coronary artery disease
   c. bladder cancer
   d. headache
   e. lightheadedness

8. Which of the following might be used to treat patients with an inhalation overexposure to toluene?
   a. 100% oxygen
   b. methylene blue
   c. amyl nitrite
   d. bronchodilators
   e. soluble iron compounds

CASE STUDIES IN ENVIRONMENTAL MEDICINE: TOLUENE TOXICITY

If you wish CME credits or CEU, please indicate your answers to the Posttest questions on page 18 by circling the letters below for the correct answers. Complete the evaluation questionnaire and fill in the information requested on the reverse side. Tear off this last page, fold, staple, and mail to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, Atlanta, GA 30333.

1. a b c d e
2. a b c d e
3. a b c d e
4. a b c d e
5. a b c d e
6. a b c d e
7. a b c d e
8. a b c d e

Evaluation Questionnaire

Please complete the following evaluation by putting a check in the appropriate box.

	Yes	No	Undecided
1. As a result of completing this monograph, I will be able to:			
Explain why toluene may be an acute and chronic health hazard.	☐	☐	☐
Describe the known factors contributing to toluene poisoning.	☐	☐	☐
Identify potential environmental and occupational sources of exposure to toluene.	☐	☐	☐
Identify evaluation and treatment protocols for persons exposed to toluene.	☐	☐	☐
List sources of information on toluene.	☐	☐	☐
2. I am more likely to ask patients questions regarding possible environmental exposures as a result of reading this issue.	☐	☐	☐
3. I would recommend this issue to my colleagues.	☐	☐	☐
4. I will keep this issue as a reference.	☐	☐	☐

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☐ CEU ☐ Contact Hours - AAOHN ☐ CM - ABIH

Specialty _____

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Please send me the following *Case Studies in Environmental Medicine.*

- ☐ Arsenic
- ☐ Asbestos
- ☐ Benzene
- ☐ Beryllium
- ☐ Cadmium
- ☐ Carbon Tetrachloride
- ☐ Chlordane
- ☐ Cholinesterase Inhibitors
- ☐ Chromium
- ☐ Cyanide
- ☐ Dioxins
- ☐ Ethylene/Propylene Glycols
- ☐ Gasoline
- ☐ Jet Fuels 4 and 7
- ☐ Lead
- ☐ Mercury
- ☐ Methanol
- ☐ Methylene Chloride
- ☐ Multiple Chemical Sensitivity
- ☐ Nitrates/Nitrites
- ☐ Phenols
- ☐ Polyaromatic Hydrocarbons (PAHs)
- ☐ Polychlorinated Biphenyls (PCBs)
- ☐ Radiation
- ☐ Radon
- ☐ Skin Lesions
- ☐ Stoddard Solvent
- ☐ Tetrachloroethylene
- ☐ 1,1,1-Trichloroethane
- ☐ Trichloroethylene
- ☐ Toluene
- ☐ Vinyl Chloride
- ☐ Exposure History
- ☐ Risk Communication
- ☐ Reproductive Effects of Hazardous Substances

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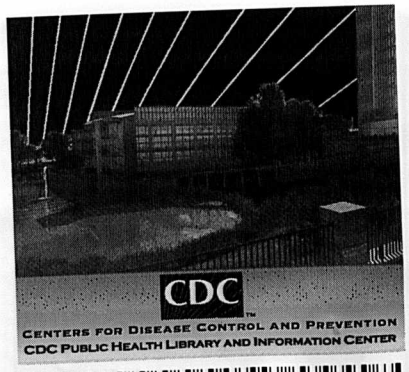

The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and is often uncertain. In this monograph, the Agency for Toxic Substances and Disease Registry (ATSDR) has made diligent effort to ensure the accuracy and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

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