Agency for Toxic Substances and Disease Registry
Case Studies in Environmental Medicine (CSEM)
Trichloroethylene Toxicity

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Table of Contents

Key Concepts	• Trichloroethylene (TCE) is a common industrial solvent and contaminant of hazardous waste sites, groundwater, and drinking water. • TCE is a CNS depressant and a suspected hepatotoxin in humans. • TCE is reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals.
About This and Other Case Studies in Environmental Medicine	This educational case study document 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 promote the adoption of medical practices that aid in the evaluation *and care of* potentially exposed patients. The complete series of *Case Studies in Environmental Medicine* is located on the ATSDR Web site at www.atsdr.cdc.gov/csem/**.** In addition, the downloadable PDF version of this educational series and other environmental medicine materials provides content in an electronic, printable format, especially for those who may lack adequate Internet service.
How to Apply for and Receive Continuing Education Credit	See Internet address www2.cdc.gov/atsdrce/ for more information about continuing medical education credits, continuing nursing education credits, and other continuing education units.

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ATSDR Authors: Dianyi Yu, MD.

ATSDR Planners: Frank Bove, ScD; Valerie J. Curry, MS; John Doyle, MPA; Bruce J. Fowler, Ph.D.; Kimberly Gehle, MD; Sharon L. Hall, Ph.D.; Michael Hatcher, DrPH; Kimberly Jenkins, BA; Ronald T. Jolly; Daphne Moffett, Ph.D.; Delene Roberts, MSA; Oscar Tarrago, MD; Brian Tencza, MS; Dianyi Yu, MD.

ATSDR Commenters: Frank Bove, Sc.D.; Daphne Moffett, Ph.D; Bruce J. Fowler, Ph.D.; Kimberly Gehle, MD.

Contributors:

Peer Reviewers: Thomas H. Milby, MD.; Robert Geller, MD.

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
Environmental Medicine and Educational Services Branch

How to Use This Course

Introduction	The goal of *Case Studies in Environmental Medicine* (CSEM) is to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. This CSEM focuses on trichloroethylene toxicity.
Available Versions	Two versions of the Trichloroethylene Toxicity CSEM are available: • the HTML version http://www.atsdr.cdc.gov/csem/tce/ provides content through the Internet; • the downloadable PDF version provides content in an electronic, printable format, especially for those who may lack adequate Internet service. The HTML version offers interactive exercises and prescriptive feedback to the user.
Instructions	To make the most effective use of this course, we recommend that you: • take the initial check to assess your current knowledge about trichloroethylene toxicity, • read the title, learning objectives, text, and key points in each section, • complete the progress check exercises at the end of each section and check your answers, and • complete and submit your assessment and posttest responses online if you wish to obtain continuing education credit. Continuing education certificates can be printed immediately upon completion.
Instructional Format	This course is designed to help you learn efficiently. Topics are clearly labeled so that you can skip sections or quickly scan sections you are already familiar with. This labeling will also allow you to use this training material as a handy reference. To help you identify and absorb important content quickly, each section is structured as follows

Section Element	Purpose
Title	Serves as a "focus question" that you should be able to answer after completing the section
Learning Objectives	Describes specific content addressed in each section and focuses your attention on important points
Text	Provides the information you need to answer the focus question(s) and achieve the learning objectives
Key Points	Highlights important issues and helps you review
Progress Check exercises	Enables you to test yourself to determine whether you have mastered the learning objectives
Progress Check answers	Provides feedback to ensure you understand the content and can locate information in the text

Learning Objectives

Upon completion of the Trichloroethylene Toxicity CSEM, you should be able to:

- explain what trichloroethylene (TCE) is,
- identify sources of trichloroethylene exposure,
- identify the primary route of exposure to trichloroethylene,
- identify the populations most heavily exposed to trichloroethylene,
- identify who is at risk of exposure to trichloroethylene,
- identify the OSHA permissible exposure limit (PEL) for trichloroethylene,
- identify EPA's maximum contaminant level (MCL) for trichloroethylene in drinking water,
- explain the characteristics of the absorption, distribution, metabolism and elimination of TCE in the body,
- describe the physiological effects associated with trichloroethylene exposure,
- identify the primary focuses of the exposure history,
- describe the characteristic finding on patient examination,
- describe characteristic clinical presentations of patients with acute or chronic trichloroethylene exposure,
- identify direct and indirect measurements that can assist with diagnosis of trichloroethylene exposure,
- describe the principal treatment strategy for managing trichloroethylene poisoning,
- describe advice on self care and follow-up care normally provided to patients exposed to trichloroethylene.

Initial Check

Instructions	This Initial Check will help you assess your current knowledge about trichloroethylene toxicity. To take the Initial Check, read the case below and then answer the questions that follow.
Case Study	***Concerns of a young family exposed to TCE-contaminated drinking water***

Your practice is in a suburban community with a number of high-technology industries. A couple for whom you have been the family physician asks for an appointment to discuss their daughter's illnesses and a matter of concern to them.

During the initial consultation, the mother reports that they are living in an area supplied by municipal well water. They have recently received a notice from the municipal water district stating that their drinking water contains 100 parts per billion (ppb) trichloroethylene (TCE), and as a precaution, they are being supplied with bottled drinking water until an alternative well can be put into service. The notice indicates that the well water is suitable for bathing and laundering. The father interjects that he is familiar with TCE; it is used in the electronics plant where he works.

The daughter, aged four has had a number of ear infections during her first two years, culminating in a myringotomy at age three. Follow-up by an Ear, Nose, and Throat (ENT) specialist has shown normal hearing. Although there have been no further infections, the mother stresses that her daughter seems to have a greater number of colds than her classmates and "has not seemed as healthy as she should be." However, the daughter's chart does not reflect an unusual number of office visits or calls. The mother also notes that the child's day-care center is next to "some kind of machine shop" where a chemical odor has been noticed recently. Several of the children and one of the teachers have complained of eye and throat irritation in association with the odor.

The mother, who is 33 years old, then reveals that she might be pregnant and she has had mild nausea for one week. It has been eight weeks since her last menstrual period. Both parents are concerned about the possibility that the TCE in the drinking water might have affected the fetus. Although this pregnancy was planned, they might consider terminating the pregnancy if the fetus was likely to be "damaged." They are also concerned that the entire family might suffer from cancer or other diseases in the future.

Before receiving bottled water, the family drank tap water when thirsty and made coffee with tap water. Tap water also was used for cooking and brushing teeth, and is still used for bathing. They have never noticed discoloration or an off-taste to the tap water. They encourage their child to drink water instead of sodas during the summer and estimate the amount of water each of them drinks is two to three glasses a day.

You schedule each parent and the child for an individual office visit.

Initial Check Questions

1. What would you include in the mother's and daughter's problem list?
2. What additional information would you seek before seeing the family again?
3. What reassurances might you provide at the end of this initial visit?
4. What are the possible sources of exposure to TCE for the family described in the case study?
5. Which members of the family described in the case study are at increased risk for adverse effects from TCE? Explain.
6. On the next visit to your office, the mother states that some families in their neighborhood are being seen by another practitioner, who has sent specimens to a laboratory for measurement of indicators of TCE exposure. What biologic indicators of TCE exposure are likely being measured?
7. If biologic measurements are performed, what considerations should be taken into account to properly interpret the results?
8. The father says that he has felt increasingly tired and easily fatigued for the past few months. Results of his physical examination are entirely within normal limits. What tests, if any, would you order?
9. The mother's obstetrician calls one month later. Examination, including sonogram, is normal for her stage of pregnancy. The obstetrician asks you about the potential fetotoxicity of TCE and whether a more invasive evaluation (amniocentesis or chorionic villus biopsy) is indicated. What is your response?
10. You evaluate the 4-year-old child. A review of her history reveals three to four episodes of otitis media, which were treated with ampicillin, in each of the last three years. The child was placed on continuous prophylactic antibiotics during the last two cold seasons. Last year, the child developed additional infections despite the antibiotic regimen, and you referred her to an otolaryngologist, who performed a myringotomy and tympanostomy without incident. The mother estimates the child has had four episodes of coryza or mild influenza last year, with about seven days of illness that merited staying home from day care.

    Does this pattern reflect compromise of the child's immune system?

11. The mother asks about immune system tests. A health care practitioner evaluating other families has performed such tests. Is the assessment of immunocompetence appropriate in this case?
12. TCE has been identified as the irritant at the day-care center. The mother described in the case study is concerned and wishes to take action to get the level reduced. What can you recommend to her?

Initial Check Answers

1. The mother's problem list includes pregnancy and anxiety; the child's, frequent otitis media (status post myringotomy and tympanostomy tube placement) and frequent upper respiratory infections.

2. You will need information on TCE toxicity, including reproductive and developmental effects; information on TCE contamination of the family's drinking water, including duration and level of contamination; copies of information provided to the family by the municipal water company; and responses, if any, from local and state health agencies.

   More information for this answer can be found in the sections "How Are People Exposed to Trichloroethylene?" and "What Are the Physiologic Effects of Trichloroethylene?"

3. None of the symptoms described in the case indicate serious illness. However, you should reassure the family that you will perform a complete physical examination with appropriate testing at the next visit. In response to concern about the child's infections, you should indicate that you will collect information about possible TCE effects on the immune system. Explain to the parents that tests of immune function are often difficult to interpret and might not be appropriate. You might indicate that you will consult sources of information on TCE's effects on pregnancy. It is important to maintain a balance between reassurance that the unborn child is probably not affected by the water contamination and concern for the possible risk to the fetus. Reassurance should not, however, appear to trivialize the family's fears. It would also be appropriate to discuss that no evaluation, however thorough, can totally exclude the possibility that a person might develop an illness, including cancer.

   More information for this answer can be found in the section "What Are the Physiologic Effects of Trichloroethylene?"

4. Possible sources of the family's TCE exposure include home drinking water (ingestion and dermal and inhalation exposure during bathing), the father's workplace (inhalation), and the daughter's day-care center (inhalation). Other sources would be washing dishes, laundry, or any other use of hot water in the home; the use of TCE-containing consumer products such as correction fluid, spot removers, and so forth.

   More information for this answer can be found in the section "How Are People Exposed to Trichloroethylene?"

5. All members of the family described in the case study are at increased risk for adverse effects from TCE exposure.

   More information for this answer can be found in the section "How Are People Exposed to Trichloroethylene?"

6. The most convenient biologic indicators of TCE exposure are the urinary metabolites, trichloroethanol and trichloroacetic acid. These metabolites are not specific to TCE, however, because they are also metabolites of tetrachloroethylene (perchloroethylene), 1,1,1-trichloroethane (methyl chloroform), and certain medications. TCE itself can be measured directly in blood or exhaled air, but because of the difficulty of obtaining samples, such measurements are not indicated here.

   More information for this answer can be found in the section "What Laboratory Tests Can Assist in the Evaluation of Patients Exposed to Trichloroethylene?"

7. To properly interpret any of the tests mentioned in answer 6, knowledge of the time lapse between exposure and collection is necessary. To prevent contamination or sample loss (evaporation or adsorption), the proper collection, handling, storage, and transportation procedures must be followed. It is likely that members of this family would have elevated levels of TCE or its metabolites, above background levels, for a few hours after exposure, for instance, after they shower. However, there are no appropriate reference values currently available for a health risk assessment.

   More information for this answer can be found in the section "What Laboratory Tests Can Assist in the Evaluation of Patients Exposed to Trichloroethylene?"

8. No further studies are indicated for TCE exposure. A workup for fatigue can indicate additional tests.

9. Evidence from animal and epidemiologic studies suggests that several reproductive and developmental toxicity end points may be associated with TCE exposure, including infertility in males and females, impaired fetal growth, and cardiac teratogenesis. Invasive procedures are therefore justified in this case.

   More information for this answer can be found in the section "What Are the Physiologic Effects of Trichloroethylene?"

10. No. A survey of infections in children under three years of age over a September-to-March period found an average of 2.5 total infections and more than one episode of otitis media per child (1.4 episodes per child for those in day care). More than 3% of the children in day care were hospitalized for tympanostomies (Bell, Gleiber *et al.* 1989). The child described in the case study appears to have an above-average rate of infections, but they are not frequent enough to suggest immunologic impairment.

11. No. Immunocompetence tests are not appropriate because no evidence of immune function abnormalities has been found in this case. It is uncertain about TCE drinking water exposures and immune system abnormalities given the lack of quality studies on this question.

Primary immunodeficiency is suspected in an infant who has repeated upper respiratory tract or other infections. It is also suspected if repeated infection occurs in a child who has had little exposure to infectious agents, or any child with unusual infections, incomplete clearing of infections, growth failure, hepatosplenomegaly, or features associated with specific immunodeficiency disorders, such as ataxia or telangiectasia. The child described in the case study has none of these indications.

More information for this answer can be found in the section "What Are the Physiologic Effects of Trichloroethylene?"

12. Although EPA has not issued an emission standard for TCE, New York State has set a guideline for TCE air emission of 5 µg/m³.

Assuming discussions with the owner or operator of the shop adjacent to the day-care center have not been effective in reducing the level of ambient TCE, the community's air pollution control center should be notified. States might allow this control under the jurisdiction of local air pollution control districts, county health departments, or other local agencies. The agency responsible for enforcement of air standards should be contacted to investigate possible release of TCE onto the day-care center property.

More information for this answer can be found in the section "What Are the U.S. Standards for Trichloroethylene Exposure?"

What is Trichloroethylene?

Learning Objectives	Upon completion of this section, you should be able to: • explain what TCE is.
Definition	TCE ($Cl_2C=CHCl$) is a clear, colorless, nonflammable liquid possessing a sweet, fruity odor characteristic of chloroform. The odor threshold is approximately 100 parts per million (ppm) (Agency for Toxic Substances and Disease Registry 1997).
Uses	Estimated use patterns suggest that 80% of TCE is used for vapor degreasing of fabricated metal parts in the automotive and metal industries. Consumer products that contain TCE include: • adhesives, • spot removers, • cleaning fluids for rugs, • paint removers/strippers, and • typewriter correction fluids
Other Uses	Before its ban for certain applications in 1977, TCE was also used as a general (mostly obstetric) anesthetic, grain fumigant, disinfectant, pet food additive, and extractant of spices in foods and caffeine in coffee (Candura and Faustman 1991)
Synonyms	Trichloroethylene is also known as • acetylene trichloride, • ethylene trichloride, • TCE, • Tri, and • trichloroethene Trade names for trichloroethylene include: • Benzinol, • Circosolve, • Flock Fli, • Narcogen, • Perm-A-Chlor, • Tri-clene, and • Vestrol
Key Points	• TCE is used mainly for vapor degreasing of fabricated metal parts in the automotive and metal industries.

Progress Check

1. Trichloroethylene is:

   A. a clear, colorless, nonflammable liquid
   B. used for vapor degreasing of fabricated metal parts in the automotive and metal industries
   C. no longer used as a general anesthetic, grain fumigant, disinfectant, or pet food additive since 1977
   D. all of the above.

   To review relevant content, see "Definition," "Uses," and "Other Uses" in this section.

Where is Trichloroethylene Found?

Learning Objectives

Upon completion of this section, you should be able to:

- identify sources of TCE exposure.

Introduction

TCE does not occur naturally; therefore, its presence indicates manufacture, use, or storage. Production of TCE has increased from just over 260,000 lbs in 1981 to 320 million lbs in 1991. The U.S. International Trade Commission (USITC) has not published more recent production statistics because there are only two U.S. manufacturers (Agency for Toxic Substances and Disease Registry 1997; HSDB April 2006).

Vapor degreasing of fabricated metal parts and some textiles accounts for 80% of its use. 5% is used as an intermediate in the production of organic chemicals and pharmaceuticals. Miscellaneous uses (5%) include solvents for dry cleaning, extraction and as a refrigerant/heat exchange liquid. An estimated 10% is exported.

Occupational Exposures

Occupational exposures may occur in chemical industries that manufacture:

- other polychlorinated aliphatic hydrocarbons, flame retardant chemicals, and insecticides where TCE is a chemical intermediate,
- pentachloroethane, or
- polyvinyl chloride.

Other potential exposures occur in the manufacturing processes of:

- disinfectants,
- dyes,
- perfumes,
- pharmaceuticals, and
- soaps.

The following occupations also have increased likelihood of exposure:

- dry cleaners,
- mechanics,
- oil processors,
- printers,
- resin workers,
- rubber cementers,
- shoemakers,
- textile and fabric cleaners,
- varnish workers, and
- workers reducing nicotine in tobacco.

Although some dry cleaners used TCE in the past, most dry cleaners now use tetrachloroethylene (perchloroethylene) or 1,1,1-trichloroethane.

In the workplace, TCE is seldom present as a pure substance. Industrial grade TCE contains small amounts of stabilizers in the form of antioxidants or acid receptors; total chemical impurities usually do not exceed 0.1% by weight. Decomposition of TCE into dichloroacetylene (a neurotoxic compound) and phosgene (a serious pulmonary irritant) occurs in the presence of alkali at temperatures above 60°C for the unstabilized compound and above 130°C for the stabilized compound.

Environmental Exposures

Because of its widespread use, TCE has become a common environmental contaminant. Contamination results from:

- discharge to surface waters and groundwater by industry commerce, and individual consumers,
- evaporative losses during use,
- incidental addition of TCE during food production, or
- leaching from hazardous waste landfills leaching into groundwater

In the atmosphere, TCE is destroyed by photooxidation, with a half-life of 3-8 days during the summer months and approximately 2 weeks in cold climates during the winter. This relatively short half-life significantly limits the transport of TCE in air; however, the continual volatilization of TCE from emission sources or contaminated surface waters ensures its persistence in air.

The average TCE level detected in samples collected from ambient air in the Norwegian Arctic between 1982 and 1983 was 0.007 ppb. This compares to mean TCE concentrations of 0.03 ppb in rural or remote areas, 0.46 ppb in urban and suburban areas, and up to 1.2 ppb in areas near emission sources of TCE. Indoor air concentrations have ranged from 0.14 ppb in a school to 5 ppb in an office building (Agency for Toxic Substances and Disease Registry 1997).

TCE is now a common contaminant at Superfund sites and many Department of Defense facilities. TCE has been identified in at least 861 of the 1,428 sites proposed for inclusion on the U.S. EPA National Priorities List (Agency for Toxic Substances and Disease Registry 1997). According to U.S. EPA Toxic Release Inventory (Wu and Schaum 2000; U.S. EPA 2003). TCE releases into the environment have ranged from 55.6 million pounds in 1987 down to 7.2 million pounds in 2003.

TCE in drinking water is a result of its rapid leaching from landfills and its discharge from industrial wastewaters. TCE volatilizes quickly from water at a rate that depends on temperature, water movement, and aeration. The biodegradation of TCE under anaerobic conditions is slow, making TCE relatively persistent in subsurface waters. An EPA national groundwater survey (US Environmental Protection Agency 1985) detected TCE in approximately 10% of the wells tested. It is the most frequently detected organic solvent in groundwater supplies, and is estimated to be in up to 34% of the nation's drinking water supplies (Agency for Toxic Substances and Disease Registry 1997).

Because of TCE's volatility, household activities such as bathing, laundering, and cooking with contaminated water may produce TCE air concentrations above ambient levels.

	Both natural and processed foods may contain TCE because of direct uptake through the environment, contamination of water used in food processing, and contamination by solvents used in cleaning food processing equipment. Most processed foods examined contain levels of a few parts per billion. Studies indicate that TCE has a low tendency to bioaccumulate in the food chain (Agency for Toxic Substances and Disease Registry 1997).
Exposures from Consumer Products	TCE is found as an ingredient in a number of consumer products such as • adhesives, • cleaning fluids for rugs, • paint removers/strippers, • spot removers, spot removers, and • typewriter correction fluids.
Key Points	• Workplace is a major source of TCE exposure. • The most common sources of non-occupational exposure to TCE are ambient air and drinking water.
Progress Check	2. TCE is a common environmental contaminant. What sources does contamination result from? A. evaporative losses during use B. discharge to surface waters and groundwater by industry, commerce, and individual consumers C. leaching from hazardous waste landfills into groundwater D. all of the above. *To review relevant content, see "Environmental Exposures" in this section.*

How Are People Exposed to Trichloroethylene?

Learning Objectives

Upon completion of this section, you should be able to

- identify the primary route of exposure to TCE.

Introduction

Occupational exposure to trichloroethylene may occur through inhalation and dermal contact at workplaces where TCE is produced or used.

The general population may be exposed to TCE via inhalation of ambient air and ingestion of food and drinking water.

Inhalation

The air pathway is the most common route of exposure to TCE, and the route that most commonly leads to illness. Exposure scenarios include inhalation of contaminated air:

- because of vapors formed during bathing and laundering from using contaminated water at home,
- due to accidental spills, and use of products in small, enclosed spaces,
- due to deliberate abuse because TCE inhalation can cause euphoria,
- during work in the same space as others working with TCE,
- during work with TCE,
- in areas where TCE is released to air and water by evaporation or fugitive emissions from industrial and from landfills, and
- on worker's skin and clothing.

Ingestion

Ingestion—a minor pathway of exposure—occurs through

- incidental addition of TCE during food production and
- swallowing food or drinking water contaminated with TCE

Skin

Dermal contact is a common route of TCE exposure in workplace and among the general public. However, dermal contact is less important since it is not likely to cause toxic effects under normal conditions.

Key Points

- The main route of occupational exposure to TCE is by inhalation.

Progress Check

3. The primary route of exposure to trichloroethylene is:

   A. ingestion
   B. inhalation
   C. dermal contact
   D. all are equally important

To review relevant content, see "Inhalation" in this section.

Who Is at Risk of Trichloroethylene Exposure?

Learning Objective	Upon completion of this section, you should be able to: • identify the populations most heavily exposed to TCE and • identify who is at risk of exposure to TCE.
Introduction	Most significant exposures to TCE occur in the workplace. Occupational exposure to TCE in the U.S. has been identified in various degreasing operations, silk screening, taxidermy, and electronic cleaning.
Worker Exposure	The National Institute for Occupational Safety and Health (NIOSH) conducted a survey of various industries from 1981 to 1983 and estimated that approximately 401,000 U.S. employees in 23,225 plants are potentially exposed to TCE. Time-weighted average concentrations from personal monitoring ranged from 1.2 to 5.1 ppm at individual industrial sites where TCE was used (Agency for Toxic Substances and Disease Registry 1997; Wu and Schaum 2000). Deaths have occurred in workers who were accidentally exposed to high levels (up to 8,000 ppm) of TCE, and in solvent abusers deliberately sniffing typewriter correction fluid (King, Smialek *et al.* 1985). Some of these deaths were due to asphyxia, whereas others were attributed to either ventricular fibrillation or asystole. Although no human studies have directly assessed potential dysrhythmogenic effects of TCE, no evidence exists to show that persons exposed to TCE at background environmental concentrations or at allowable workplace levels are at increased risk of developing cardiac dysrhythmias (Candura and Faustman 1991). Increased potential for exposure may be encountered by the following workers: • dry cleaners, • mechanics, • oil processors, • printers, • resin workers, • rubber cementers, • shoe makers, • textile and fabric cleaners, • tobacco denicotinizers, and • varnish workers
TCE Inhalant Abuse	Inhalants - particularly volatile solvents, gases, and aerosols - are often among the first drugs that young children use. One national survey indicates that about 3.0 percent of U.S. children have tried inhalants by the time they reach fourth grade. About 17% of US youth has ever tried to get 'high' from inhaled solvents, including TCE. National surveys indicate that more than 22.9 million Americans have abused inhalants at least once in their lives (NIDA 2005). Inhalant abuse can become chronic and extend into adulthood. Sudden death due to TCE abuse has been reported (Miller, Mycyk *et al.* 2002).

Banned Uses	Until 1977, when certain uses were banned, TCE was employed as an inexpensive, nonflammable, and self-administered obstetrical anesthetic (Tri-lene). It was discovered that alkali in rebreathing systems could lead to the production of dichloroacetylene, which produces cranial nerve injuries. Workers in environments containing this TCE-decomposition product could also be at risk of developing injury to trigeminal, optic, or facial nerve (Lawrence and Partyka 1981).
Degreaser's Flush	Alcohol potentiates TCE's effects on the central nervous system (CNS). Concurrent alcohol consumption and exposure to TCE can result in "degreaser's flush," (Stewart, Hake *et al.* 1974) a temporary redness and itching of the back, neck, and face. Liver dysfunction or disulfiram (Antabuse) treatment could reduce the metabolism of TCE thereby increasing its CNS depressant effects.
Use of Groundwater	TCE is one of the volatile organic contaminants most frequently found in groundwater. There have been a number of studies reported that examined the health of persons who ingested TCE-contaminated groundwater over varying period of time. The results of these studies have been inconsistent. A link between ingestion of TCE and incidence of cancer in humans is controversial, but has not been excluded.
Maternal Transmission	TCE rapidly crosses the placenta in both humans and animals, and can accumulate in the fetus (Agency for Toxic Substances and Disease Registry 1997). To gather information on the health effects of ingesting TCE-contaminated water, the ATSDR, in cooperation with the states, has established a national registry. This registry is discussed in Sources of Information section.
Key Points	• Workers in metal-fabricating and cleaning operations have the greatest likelihood of exposure to high concentrations of TCE. • Persons using groundwater contaminated with trichloroethylene can be exposed by inhalation as well as ingestion. • Trichloroethylene crosses the placenta and can accumulate in the fetus. • Ingestion of alcohol may potentiate the central nervous system depressant effects of TCE.
Progress Check	4. Occupations that entail exposure to trichloroethylene include which of the following? A. workers in metal-fabricating and cleaning operations B. workers in dry cleaners C. shoemakers D. all of the above. *To review relevant content, see "Worker Exposure" in this section.* 5. Who is most likely to be at risk of trichloroethylene exposure? A. the newborns of nursing mothers who are employed at a chemical industry. B. residents who use well water for food preparation, bathing, and laundry. C. consumers who use spot remover. D. mechanics who degrease fabricated metal parts in the automotive industries. *To review relevant content, see "Worker Exposure" in this section.*

What Are the U.S. Standards for Trichloroethylene Exposure?

Learning Objectives

Upon completion of this section, you should be able to:

- identify the OSHA permissible exposure limit (PEL) for TCE and
- identify the EPA's maximum contaminant level (MCL) for TCE in drinking water.

Introduction

The government has developed regulations and guidelines for TCE. These standards are designed to protect the public from potential adverse health effects.

Workplace Standards

The OSHA permissible exposure limit (PEL) is a time-weighted average (TWA) of 100 ppm, with 300 ppm TCE as a 5-minute maximum peak allowable in any 2-hour period (OSHA 1993).

The National Institute for Occupational Safety and Health (NIOSH) considers TCE a potential occupational carcinogen and recommends an exposure limit of 2 ppm (as a 60-minute ceiling) during the usage of TCE as an anesthetic agent (TCE is no longer used as an anesthetic agent) and 25 ppm as a 10-hour TWA during all other exposures.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends an 8-hour TWA of 50 ppm and a short-term exposure limit (STEL) of 100 ppm (American Conference of Governmental Industrial Hygienists. 2003).

Biologic exposure indices (BEIs) recommended by ACGIH that might involve either direct or indirect measures of individual worker exposure.

- The TCE metabolite, free trichloroethanol, can be measured in the blood. However, a number of other compounds affect the level of trichloroethanol found in the blood, thereby clouding the clinical significance of this metabolite as an indicator of TCE exposure. Thus, if higher-than-expected blood levels of trichloroethanol are detected, the clinician must consider alternate explanations for the elevated levels (Agency for Toxic Substances and Disease Registry 1997).
- Alternatively, a concentration of 100 milligrams (mg) of trichloroacetic acid per gram of creatinine in urine at the end of the work week reflects the upper biologic limit for TCE exposure. Urinary trichloroacetic acid levels can be increased by the same compounds that affect blood trichloroethanol levels (Agency for Toxic Substances and Disease Registry 1997). Because of large individual variations, a urinary trichloroacetic acid level of 100 mg per gram of creatinine should be used only as a "warning" level or mean for a group of workers (American Conference of Governmental Industrial Hygienists. 2003; Meditext 2004).

Table 1 summarizes current standards and regulations for TCE exposure.

Table 1. Standards and Regulations for Trichloroethylene.

Agency*	Focus	Level	Comments
American Conference of Governmental Industrial Hygienists	Air: workplace	50 ppm 100 ppm	Advisory; TLV/TWA† Advisory; STEL‡;
National Institute for Occupational Safety and Health	Air: workplace	25 ppm	Recommendation; 10-hour TWA§; potential carcinogen
Occupational Safety and Health Administration	Air: workplace	100 ppm 300 ppm	Regulation; PEL¶ over 8-hour workday Regulation; 5-minute maximum peak in any 2 hour period
Environmental Protection Agency	Air: environment	Not available	Not available
	Drinking water	5 ppb	Regulation

* ppm: parts per million; ppb: parts per billion.

†TLV/TWA (threshold limit value/time-weighted average): time-weighted average concentration for a normal 8-hour workday or 40-hour work week to which nearly all workers may be repeatedly exposed.

‡STEL(short-term exposure limit): concentration at which workers can be exposed continuously for a short period of time (usually 15 minutes) without suffering irritation, chronic irreversible tissue damage, or narcosis.

§TWA (time-weighted average): concentration for a normal 8-hour workday and 40-hour work week is set at a level at which nearly all workers may be repeatedly exposed without adverse effects.

¶PEL (permissible exposure limit): highest level averaged over an 8-hour workday to which a worker may be exposed. Note: A PEL of 50 ppm was enacted by Occupational Safety and Health Administration in 1989, but that level along with 375 others, was vacated for procedural reasons by the 11th Circuit Federal Court in 1993.

Environmental Standards

Environmental exposures to TCE are generally low and are decreasing because limitations have been imposed on its use as an anesthetic, solvent extractant, fumigant, and dry-cleaning agent.

Air

TCE has a short atmospheric half-life (less than seven days) and is not likely to bioaccumulate in the food chain.

Water

The World Health Organization recommended drinking water limit is 30µg TCE/liter (L) of water (30 ppb). EPA has set a maximum contaminant level (MCL) of 5µg/L (5 ppb) in drinking water (US Environmental Protection Agency 1985).

Although there is no incontrovertible evidence of human health effects associated with exposures to environmental levels of TCE (Brown, Farrar *et al.* 1990), the issue is not entirely settled. More reliable information is necessary for a final assessment.

Key Points

- OSHA's current permissible exposure limit is 100 ppm.
- EPA has established a drinking water MCL for TCE of 5 ppb.

Progress Check

6. OSHA's PEL for TCE in the workplace is which of the following?

   A. 50 ppm (8-hour TWA)
   B. 100 ppm (8-hour TWA)
   C. 25 ppm (8-hour TWA)
   D. none of the above.

   To review relevant content, see "Table 1" in this section.

7. EPA's MCL for TCE in drinking water is which of the following?

   A. 5 ppm
   B. 5 ppb
   C. 10 ppb
   D. none of the above.

   To review relevant content, see "Table 1" in this section.

What Is the Biological Fate of Trichloroethylene in the Body?

Learning Objectives

Upon completion of this section, you should be able to:

- explain the characteristics of the absorption, distribution, metabolism and elimination of TCE in the body.

Introduction

TCE is readily absorbed following both inhalation and oral exposures. Once absorbed, TCE diffuses readily across biological membranes and is widely distributed to tissues and organs via the circulatory system. Studies in animals and humans have found TCE or its metabolites in most major organs and tissues. TCE metabolism occurs primarily in the liver and eliminated either unchanged in expired air or by metabolic transformation with subsequent excretion primarily in urine.

Absorption and distribution

In humans, TCE is rapidly and extensively absorbed by the lungs and into the alveolar capillaries(Sato, Nakajima *et al.* 1977; Monster, Boersma *et al.* 1979; Clewell, Gentry *et al.* 1995).

Case reports of human poisoning after ingestion of TCE indicate that gastrointestinal absorption is also substantial (Kleinfeld and Tabershaw 1954; Defalque 1961; Bruning, Vamvakas *et al.* 1998).

Because of its lipid solubility, TCE accumulation occurs in organs containing high levels of adipose tissue, such as, the lungs, liver, kidneys and central nervous system. Consequently, slow release of TCE from adipose stores might act as an internal source of exposure, ultimately resulting in longer residence times and bioavailability of TCE(Fernandez, Droz *et al.* 1977; Dallas, Gallo *et al.* 1991; Fisher, Gargas *et al.* 1991; WHO 2005).

Age-dependent factors may influence TCE distribution in humans, suggesting greater susceptibility to TCE in children than in adults(Pastino, Yap *et al.* 2000; WHO 2005).

Metabolic Pathways

TCE undergoes metabolism by two major pathways (Lash, Fisher *et al.* 2000):

- oxidation by cytochrome P450 enzymes
- conjugation with glutathione (GSH) by glutathione-S-transferases (GSTs)

The oxidative metabolism of TCE take place primarily in the liver, although it may also occur in other tissues, such as the lung(Lash, Fisher *et al.* 2000).

The principal metabolites derived from oxidation pathway are:

- chloral hydrate, further metabolized to trichloroethanol (TCOH),
- trichloroacetic acid (TCA), and
- dichloroacetic acid (DCA)

The GSH conjugation also occurs mainly in the liver by GST, although several other tissues (kidney, biliary tract and intestines) are involved(Lash, Fisher *et al.* 2000).

The metabolites derived from the conjugation pathway are:

- S-(1,2-dichlorovinyl)glutathione (DCVG)
- S-(1,2-dichlorovinyl)cysteine (DCVC) (can be further converted to other reactive metabolites)

The mutagenic and carcinogenic potential of TCE is generally thought to be due to reactive intermediate biotransformation products rather than the parent molecule itself.

The oxidative metabolites are responsible for the effects on the liver (both cancer and non-cancer), whereas the conjugative metabolites may preferentially affect other organs (e.g., kidney) (Davidson and Beliles 1991; Lash, Fisher *et al.* 2000; WHO 2005). For examples, one of the issues of most concern with TCE is its conversion to DCA which is clearly carcinogenic in both mice and rats(Chen 2000; Bull, Orner *et al.* 2002; WHO 2005); Dichlorovinylcysteine (DCVC) is mutagenic and may cause DNA damage in mammalian cells in vitro and in vivo (NTP 2004). However, TCA or DCA is unlikely to be responsible for human liver cancer at environmental levels of exposure to TCE(DeAngelo, Daniel *et al.* 1997; WHO 2005).

One study (Lipscomb, Garrett *et al.* 1997) reported significant variability in TCE metabolism in a sample of 23 human hepatic microsomal samples. The results indicate that humans are not uniform in their capacity for cytochrome P450-dependent metabolism of TCE. An increased activity of this metabolic pathway may increase susceptibility to TCE induced toxicity in the human.

Elimination

Elimination pathways appear to be similar for ingestion and inhalation. A relatively small amount of absorbed TCE is exhaled unchanged; most of an absorbed dose is metabolized and excreted in the urine, as TCA, TCOH or DCV conjugates.

Studies in human volunteers have shown that after exposure to air concentrations between 50 and 380 ppm, approximately 58% of an absorbed dose appears in urine as metabolites (Monster, Boersma *et al.* 1976; Monster, Boersma *et al.* 1979). The time between TCE inhalation and urinary excretion of trichloroethanol is relatively short (biologic half-life approximately 10 hours) compared with the urinary excretion of trichloroacetic acid (biologic half-life approximately 52 hours). Trichloroacetic acid is theoretically detectable in urine for at least a week after TCE exposure (Sato, Nakajima *et al.* 1977; Monster, Boersma *et al.* 1979).

No studies have provided evidence of saturation of TCE metabolism in humans, at least for short-term inhalation exposure to high concentrations up to 315 ppm (Agency for Toxic Substances and Disease Registry 1997).

Species *vs.* Susceptibility	Although the pathways for metabolism of TCE in mice, rats, and humans appear to be qualitatively similar, quantitatively differences among species may substantially alter the effective dose of reactive metabolite(s) that is delivered to a target organ (Bruckner, Davis *et al.* 1989). It has been estimated that humans metabolize approximately 20 times less TCE on a body weight basis than rats at similar exposure levels. Consequently, humans metabolize approximately 60 times less TCE on a body weight basis than mice (Goeptar, Commandeur *et al.* 1995). Species differences in TCE metabolism might explain observed differences in susceptibility to specific TCE-related diseases. Liver cancer, for example, occurs mainly in strains of mice that generate high levels of trichloroacetic and dichloroacetic acids as TCE metabolites in liver cells. By contrast, rats that metabolize more TCE via glutathione conjugation are prone to renal cancer. Because of such species-specific effects, caution must be used when extrapolating adverse effects from experimental animals to humans (Kimbrough, Mitchell *et al.* 1985; Fan 1988; Goeptar, Commandeur *et al.* 1995; Kaneko, Wang *et al.* 1997; Lash, Fisher *et al.* 2000).
Key Points	• Pulmonary and gastrointestinal absorption of TCE is rapid. Because of its lipid solubility, TCE accumulation occurs in organs containing high levels of adipose tissue, such as, the lungs, liver, kidneys and central nervous system. • The mutagenic and carcinogenic potential of TCE is thought to be due to reactive intermediate biotransformation products rather than the parent molecule TCE itself. • Because of species difference in TCE metabolism, caution should be used in extrapolating adverse effects to humans.

Progress Check

8. Which of the following statements about metabolism of an absorbed dose of TCE is correct?

   A. a small amount is exhaled unchanged
   B. most of the dose is metabolized in the liver
   C. TCE is excreted in the urine as trichloroacetic acid and trichloroethanol
   D. all of the above.

   To review relevant content, see "Half Life" and "Key Points" in this section.

9. Which of the metabolic pathways of TCE is associated with hepatic toxicity?

   A. cytochrome P450-dependent oxidation
   B. glutathione (GSH) conjugation
   C. both cytochrome P450-dependent oxidation and glutathione (GSH) conjugation
   D. none of the above.

   To review relevant content, see "Metabolic Pathways" in this section.

What Are the Physiological Effects of Trichloroethylene?

Learning Objectives

Upon completion of this section, you should be able to

- describe the physiological effects associated with TCE exposure.

Introduction

Some occupational studies have shown that TCE produces

- CNS effects
- decreased appetite
- gastrointestinal irritation
- headaches
- mucous membrane
- skin irritation

Hepatotoxicity has been associated primarily with TCE inhalation and ingestion of very large amounts.

Renal failure has been reported in concert with confirmed hepatic damage.

Cardiac dysrhythmias may be induced by heavy TCE exposure.

Neurological Effects

TCE-induced CNS symptoms depend on both concentration and exposure duration.

Acute Exposure

In one study of human volunteers, exposure to TCE air levels of 27 ppm for one to four hours caused drowsiness and mucous membrane irritation, and at 81 ppm, headaches (Nomiyama and Nomiyama 1977).

In another study, an 8-hour exposure (two 4-hour exposures separated by 1.5 hours) to 110 ppm TCE for two 4-hr periods resulted in decreased performance on tests of perception, memory, reaction time, and dexterity (Salvini, Binaschi *et al.* 1971). However, a later attempt to replicate these results found no effects other than fatigue and drowsiness (Stewart RD 1974a).

The available data suggest that the threshold for CNS effects in humans is in the range 81-110 ppm TCE, although the effects observed at these exposure levels reflected only mild symptoms of CNS depression (Brown, Farrar *et al.* 1990).

Symptoms due to short-term exposures typically resolve within a few hours of exposure. However, one report demonstrated evidence of long-term residual oculomotor and ciliary reflex dysfunction as well as impaired neuropsychological performance as a result of acute TCE intoxication (Feldman, White *et al.* 1985).

Chronic Exposure

In a study of 73 workers employed from one month to 15 years in various industrial cleaning and degreasing operations using TCE, complaints due to chronic exposure included:

- a reduced number of word associations,
- ataxia,
- decreased appetite,
- headache,
- short-term memory loss,
- sleep disturbances, and
- vertigo

Greater frequency of symptoms was noted in workers exposed to higher (85 ppm) than lower (14 ppm) mean TCE concentrations (Grandjean, Munchinger *et al.* 1955).

Some of the observed neurological effects from long-term exposure to TCE indicate impaired trigeminal nerve function (e.g., blink reflex and masseter reflex) (Buxton and Hayward 1967; Agency for Toxic Substances and Disease Registry 1997). This is thought to be neurotoxicity induced dichloroacetylene, a breakdown product of TCE (Armstrong and Green 2004).

A study found neurobehavioral deficits from exposures to drinking water contaminated with to TCE (Reif, Burch *et al.* 2003).

Deliberate Abuse

Abuse of volatile chlorocarbon solvents is a risk factor for development of cerebellar damage and ataxia.

Animal Studies

Studies on the neurological effects of acute TCE inhalation in animals have produced results similar to human studies (Agency for Toxic Substances and Disease Registry 1997).

Gastrointestinal, Hepatic and Renal Effects

When swallowed, TCE causes gastrointestinal (GI) irritation, with possible inflammation of the GI tract, manifested as:

- abdominal pain
- diarrhea
- nausea
- vomiting

Hepatotoxicity has been associated primarily with intentional TCE inhalation abuse. In these cases, hepatic histological examination has revealed centrilobular necrosis with fatty infiltration (Joron, Cameron *et al.* 1955; Thiele, Eigenbrodt *et al.* 1982).

Chronic TCE exposures at concentrations currently permissible in the workplace or at those expected in ambient air are not likely to cause liver damage (Agency for Toxic Substances and Disease Registry 1997).

Studies that have examined exposure to TCE and development of kidney disease (Lash, Parker *et al.* 2000).

- One case report links acute renal failure with normal liver function in a male worker opening bins containing 7.5 L of a nearly pure solution of TCE (David, Wolman *et al.* 1989).
- One study reports that adverse kidney effects associated with occupational exposure to TCE are very mild (Nagaya, Ishikawa *et al.* 1989).
- Another study of a small group of male metal degreasers in Sweden observed no increase in *N*-acetyl-β-glucosamineidase (NAG) excretion into urine, and concluded that TCE was not nephrotoxic at low exposures levels (Selden, Hultberg *et al.* 1993).
- A retrospective study was performed on 39 workers who were exposed to high levels of TCE from 1956 to 1975. The study concluded that chronic exposure to high doses of TCE causes persistent changes to the proximal tubules (Bruning, Sundberg *et al.* 1999).
- In a recent cross-sectional study of 70 workers currently exposed to TCE, the mean exposure to TCE, estimated from urinary trichloroacetic acid concentrations, was 32 ppm (range 0.5 – 252 ppm) with average duration of exposure of 4.1 years (range 1-20 years). The results suggested that kidney damage could occur at exposure concentrations higher than 250 ppm (Green, Dow *et al.* 2004).
- A study reports on a 17-year-old male who ingested approximately 70 ml TCE in a suicide attempt. This study first demonstrated that a single, oral dose of TCE can produce nephrotoxicity in humans (Bruning, Vamvakas *et al.* 1998).

Cardiac Effects

A few case studies of persons who died following acute occupational exposure to TCE have revealed cardiac arrhythmias to be the apparent cause of death(Kleinfeld and Tabershaw 1954; Smith 1966).

When TCE was administered as an anesthetic agent, serious ventricular arrhythmias and cardiac arrests were rare and were nearly always associated with hypoxia(Norris and Stuart 1957).

Significant ventricular ectopy would not be expected from TCE exposure at background environmental levels or those currently allowed in the workplace (Candura and Faustman 1991).

The underlying mechanism of these cardiac effects of TCE exposure might be due to changed sensitization of the heart to catecholamines (Agency for Toxic Substances and Disease Registry 1997).

Reproductive and Developmental Effects	Adverse effects were noted in residents of several communities where TCE was found to be present in drinking water (Bove, Shim *et al.* 2002). The Tucson study (1990) (Goldberg, Lebowitz *et al.* 1990) reported a higher risk of congenital cardiac defects associated with exposure to TCE-contaminated drinking water. The New Jersey study (1995) (Bove, Fulcomer *et al.* 1995) reported a strong association between exposure to TCE-contaminated drinking water and oral clefts as well as neural tube defects (NTDs). The Woburn study (1996) (Massachusetts Department of Public Health 1996) found associations between exposures to TCE-contaminated well water and small for gestational age (SGA), fetal deaths, eye defects, choanal atresia, NTDs, cleft lip, and hypospadias. The Camp LeJeune study (1998) also found increased risk of SGA associated with TCE (Bove, Shim *et al.* 2002). One retrospective occupational study suggested an increased risk of spontaneous abortion in women exposed to TCE, but the result was not statistically significant, and the effect disappeared when odds ratios were adjusted for potential confounders (Windham, Shusterman *et al.* 1991). In animals, some abnormalities (decreased fetal body weight, ossification anomalies, and cardiac defects) have been reported infrequently (Agency for Toxic Substances and Disease Registry 1997).
Carcinogenic Effects	Evidence for the carcinogenicity of TCE in humans comes from several cohort studies where specific TCE exposures were well characterized for individual study subjects. A meta-analysis of these cohort studies found that occupational exposure to TCE was associated with excess incidences of liver cancer, kidney cancer, non-Hodgkin's lymphoma, prostate cancer, and multiple myeloma, with the strongest evidence for the first three cancers (Wartenberg, Reyner *et al.* 2000; NTP 2004). It is important to note that the conclusions drawn in these studies were based on a relatively small number of exposed workers and were confounded by exposure to other solvents and other risk factors. Other studies did not reveal any excess cancer mortality from low exposures to TCE (Axelson, Andersson *et al.* 1978; Tola, Vilhunen *et al.* 1980; Shindell and Ulrich 1985; Spirtas, Stewart *et al.* 1991; Axelson, Selden *et al.* 1994). A study (Massachusetts Department of Public Health 1996) performed in Woburn, Massachusetts by the Massachusetts Department of Health (1996) found an elevated risk of childhood leukemia in a group exposed to TCE in uterus. The New Jersey study (Bove, Fulcomer *et al.* 1995) found associations with childhood leukemia among females and with non-Hodgkin's lymphoma. A review on mutagenicity of TCE and its metabolites indicated that TCE and its metabolites are not potent genotoxic agents and require high doses to induce a response (Moore and Harrington-Brock 2000). The full tumor development is likely to require promotional stimuli under high

(suggested: >500 ppm peak exposures) and long-term (several years) exposure to TCE (Bolt, Lammert *et al.* 2004).

A cohort study of 169 male workers having been exposed to unusually high levels of TCE in Germany between 1956 and 1975 supported a nephrocarcinogenic effect of TCE in humans. A further case-control study confirmed the results of the previous cohort study, supporting the concept of involvement of prolonged and high-dose TCE exposures in the development of renal cell cancer (Bruning and Bolt 2000). The finding of a TCE-specific mutation of the von Hippel-Landau (VHL) tumor suppressor gene, a gene associated with kidney tumors, provides strong evidence that TCE causes kidney cancer (Brauch, Weirich *et al.* 1999).

A study of three Michigan communities exposed to chlorinated solvents, including TCE in drinking water, showed no significant increase in cancers, including leukemia, among the exposed population. However, the cohort size in the study was only 223 (Agency for Toxic Substances and Disease Registry 1997). A study of 4,280 people exposed to TCE and other contaminants in drinking water in three states reported an increase in respiratory tract cancer in males. The study authors concluded that, based on the incidence of smoking in the population, "it would be inappropriate to relate this excess solely to TCE exposure" (Agency for Toxic Substances and Disease Registry 1997).

The findings in humans are supported by evidence of carcinogenicity in experimental animals, in which tumors occurred at several of the same sites as in humans. Inhalation or oral exposure to high doses of TCE produces liver and lung tumors in mice (Maltoni, Lefemine *et al.* 1988), and renal adenocarcinomas, testicular tumors, and possibly leukemia in rats (Maltoni, Lefemine *et al.* 1988).

However, it is important to understand interspecies differences in TCE metabolism and pharmacokinetics in order to reduce uncertainties inherent in species-to-species extrapolations (Bruckner, Davis *et al.* 1989).

Many studies reviewed by the International Agency for Research on Cancer (IARC) examined the relationship between TCE exposure and kidney and liver cancer mortality or incidence. Most of studies were of occupational exposures (Bull 2000; Lash, Parker *et al.* 2000).

In conclusion, TCE is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals, and information suggesting TCE acts through mechanisms that indicate it would likely cause cancer in humans (NTP 2004).

Other Effects

Respiratory

TCE produces minimal irritation of the respiratory tract at concentrations that do not exceed current workplace standards (Waters, Gerstner *et al.* 1977).

TCE is not a sensitizing agent, and bronchospasm is unlikely to occur except after exposure to high concentrations (Agency for Toxic Substances and Disease Registry 1997). Reactive Airway Dysfunction Syndrome (RADS) or Irritant Induced Asthma (IIA) has been attributed to exposure to very high concentrations of solvents (Rosenman, Reilly *et al.* 2003).

In a study conducted with human volunteers, 200 ppm TCE was inhaled simultaneously with ethanol ingestion, an increase in both heart rate and breathing rate was observed. However, when 200 ppm TCE was inhaled in the absence of ethanol ingestion, these TCE-related effects did not occur (Agency for Toxic Substances and Disease Registry 1997).

TCE is both acutely toxic and carcinogenic to the mouse lung following exposure by inhalation. Toxicity to the mouse lung is confined almost exclusively to the nonciliated Clara cell (Forkert, Sylvestre *et al.* 1985).

Comparisons between species suggest that the ability of the human lung to metabolize TCE is approximately 600-fold less than that in the mouse.

In addition, the human lung differs markedly from the mouse lung in the number and morphology of its Clara cells. Thus, risks from TCE exposure to human lung damage are minimal (Green 2000).

Skin

Like other organic solvents, TCE may produce contact dermatitis, rashes, and burns. The defatting dermatitis resulting from prolonged contact may reduce resistance to skin infections. An irritant reaction resembling an exfoliative dermatitis or scarlatiniform reaction can occur from dermal contact with contaminated clothing (Waters, Gerstner *et al.* 1977; Agency for Toxic Substances and Disease Registry 1997).

A syndrome called degreaser's flush (Stewart, Hake *et al.* 1974) has been associated with the interaction of ingested ethanol and inhaled TCE. Typically, erythema resulting from vasodilation develops around the face, back, and shoulders within 30 minutes of exposure and resolves in about an hour.

Immune System

The immunotoxic effects of TCE were evaluated in an animal study. The investigators concluded that, although the effects observed were not remarkable, the immune system does appear to be sensitive to the chemical (Sanders, Tucker *et al.* 1982). A few reports have been found on human immunological abnormalities related to usage of TCE contaminated well water(Byers, Levin *et al.* 1988; Kilburn, Warshaw *et al.* 1992; Waller, Clauw *et al.* 1994). A recent study of TCE exposed workers has found immune abnormalities (Iavicoli, Marinaccio *et al.* 2005).

Key Points

- CNS depression is the most prominent effect of acute TCE exposure.
- Chronic occupational TCE exposure has been associated with neurological abnormalities.
- Case reports associate liver damage with inhalation of high levels of TCE.
- Renal toxicity has been described in the literature but would not be expected from ambient air exposure.
- Significant cardiac effects would not be expected from TCE exposure at background environmental levels or those currently allowed in the workplace.
- Several studies have reported reproductive or developmental abnormalities thought to be associated with exposure to TCE in drinking water.
- TCE is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals, and information suggesting TCE acts through mechanisms that indicate it would likely cause cancer in humans (NTP 2004).
- TCE is a mild respiratory tract irritant and can produce contact dermatitis.

Progress Check

10. Trichloroethylene has been associated with all of the following types of cancer in humans except for

    A. liver cancer
    B. brain cancer
    C. Non-Hodgkin's lymphoma
    D. kidney cancer.

    To review relevant content, see "Carcinogenic Effects" in this section.

11. The reported cranial neuropathic effects of TCE exposure include

    A. sensorineural hearing loss
    B. trigeminal functional losses
    C. Bells Palsy
    D. color vision loss.

    To review relevant content, see "Neurological Effects" in this section.

12. Which of following statements is correct?

    A. Comparisons between species suggest that the ability of the human lung to metabolize TCE is much greater than that in the mouse.
    B. Inhalation or oral exposure to high doses of TCE for a prolonged period is likely to induce liver and lung tumors in both animals and humans.
    C. TCE and its metabolites are potent genotoxic agents.
    D. none of the above.

    To review relevant content, see "Carcinogenic Effects" in this section.

How Should Patients Exposed to Trichloroethylene Be Evaluated?

Learning Objectives

Upon completion of this section, you should be able to:

- identify the primary focuses of the exposure history,
- describe the characteristic finding on patient examination, and
- describe characteristic clinical presentations of patients with acute or chronic TCE exposure.

Introduction

When considering the human health effects of TCE, it is important to make a distinction between occupational exposures to relatively high levels by inhalation and general environmental exposures to low levels in drinking water and ambient air.

Patient History

An occupational history should be routinely obtained. It should include items such as:

- company name and location
- job title
- description of chemical processes encountered
- known toxic agents used
- workplace investigations
- complaints of co-workers

An environmental history should also be obtained, including:

- location and duration of residence
- proximity to industry
- diet
- daily activities
- type of water supply
- use of consumer products that contain TCE

If a temporal association between symptoms and exposure to certain products is suspected, an attempt should be made to identify the specific chemical ingredients involved. In the situation involving occupational or consumer product exposure, if the product label does not list the chemical ingredients, the regional poison control center may maintain a list of ingredients in consumer and proprietary products. In the U.S.: call 1-800-222-1222, or check http://www.aapcc.org/ for an updated list of U.S. Poison Control Centers. The World Health Organization and the International Program on Chemical Safety maintain an international list of poison control centers:

http://www.who.int/ipcs/poisons/centre/directory/en/index.html

In occupational exposures in the U.S., the employer or manufacturer is required by law to provide a material safety data sheet (MSDS), which lists the chemical ingredients and describes their potential toxicity.

Physical Examination

The patient's complaints should be identified in terms of onset, duration, and intensity. Complaints should be investigated by focusing first on major organ systems that are likely to be affected by exposure to TCE (CNS, hepatic, integumentary, cardiovascular, renal), and then on systems unlikely to be affected (respiratory, gastrointestinal, endocrine, skeletal).

Vital signs should be recorded, especially abnormalities of heart rate or rhythm. Eyes, nose, throat, and skin should be examined carefully for inflammation or irritation. The conjunctiva may be injected, and nasal mucosa may be injected and swollen. Repeated inhalation exposures to trichloroethylene can cause defatting of nasal mucosa, leading to a friable condition with drying, cracking, or bleeding. Skin contact may cause dermatitis by irritation and defatting.

The patient's abdomen should be palpated for hepatomegaly and right upper quadrant tenderness.

Patients should receive a complete neurological examination, including a mental status exam and evaluation of the cranial nerves, to detect either peripheral or central nervous system involvement. Cranial neuropathies in patients with a history of TCE exposure are uncommon.

Signs and Symptoms

No unique pattern of symptoms characterizes TCE-induced illness.

Acute Exposure

With inhalation of high concentrations, TCE causes initial CNS excitation followed by CNS depression. Depending on the duration and intensity of exposure, symptoms (Meditext 2004) can include:

- ataxia,
- bronchial irritation,
- confusion,
- dizziness,
- drowsiness,
- dyspnea,
- euphoria,
- fatal cardiac dysrhythmias,
- fatigue,
- headache,
- lethargy,
- light-headedness,
- pulmonary edema,
- renal and hepatic damage,
- respiratory depression,
- seizures,
- stupor, and
- visual disturbances

Coma and respiratory depression may occur with prolonged, high-level exposure (*i.e.*, above 2,000 ppm). Serious ventricular arrhythmias can develop up to 24 hours after large TCE ingestions (Agency for Toxic Substances and Disease Registry 1997).

Effects from ingestion include:

- abdominal pain,
- circulatory collapse,
- diarrhea,
- dizziness,
- dysphagia,
- dysrhythmias,
- hallucinations or distorted perceptions,
- headache,
- incoordination,
- jaundice,
- nausea,
- paresthesia,
- partial paralysis,
- somnolence, and
- vomiting

The main systemic response is CNS depression (Meditext 2004).

TCE is a skin irritant and may cause defatting dermatitis of the skin. Scleroderma has been linked with TCE exposure. Dermal absorption is not likely to be significant if dermatitis is prevented. Vasodilation and malaise ('degreasers flush') recur in workers who drink ethanol after exposure to TCE (Meditext 2004).

After any type of acute exposure, the clinician should keep in mind that:

- because respiratory depression is the most common serious sequela of acute TCE exposure, the adequacy of ventilation should be carefully assessed,
- because of possible arrhythmias, patients with preexisting cardiovascular disease should be monitored by continuous electrocardiogram and frequent evaluation of vital signs, and
- because hepatic injury may occur, liver function tests should be performed.

Chronic Exposure

The symptoms seen in humans in cases of long-term exposure were similar to those seen in acute exposure, but occurred in more extreme and persistent forms (Kleinfeld and Tabershaw 1954; Fan 1988).

Reported neurological effects associated with chronic workplace exposure to TCE have included nonspecific symptoms such as:

- ataxia,
- decreased appetite,
- dizziness,
- emotional instability,
- fatigue,
- headache,
- impaired judgment,
- memory loss,
- sleep disturbances, and
- weakness

WHO (1985) noted that chronic effects such as disturbance of the nervous system can occur following prolonged exposure to TCE concentrations of about 100 ppm (WHO 1985).

Although some CNS symptoms may disappear within several weeks after cessation of exposure, other CNS adverse health effects such as memory loss and mood swings may persist in persons who have been exposed to TCE for long periods (Agency for Toxic Substances and Disease Registry 1997).

Persistent neurological symptoms suggest the possibility of psychiatric disorders and also prompt a search for exposure to neurotoxicants, such as alcohol and other drugs of abuse.

Key Points

- TCE exposure produces no unique clinical clues.
- Respiratory depression can result from acute, high-dose TCE exposure.
- At permissible workplace levels, CNS symptoms of TCE exposure are usually nonspecific and transient.

Progress Check

13. A temporal association between symptoms and exposure to certain products is one of the focuses of patient history because:

    A. it helps evaluate general health
    B. it helps find out patient history on alcohol and drug use
    C. it helps provide important clues on the cause
    D. all of the above

    To review relevant content, see "Patient History" in this section.

14. On patient examination, short-term memory loss, if associated with TCE exposure, is generally:

    A. irreversible
    B. reversible
    C. similar to the forms of dementia
    D. the initial symptom of acute exposure

To review relevant content, see "Signs and Symptoms" in this section.

15. Symptoms associated with inhalation of high-level TCE may include all of the following except:

    A. dyspnea
    B. euphoria
    C. stupor
    D. diarrhea

    To review relevant content, see "Signs and Symptoms" and "Acute Exposure" in this section.

What Laboratory Tests Can Assist in the Evaluation of Patients Exposed to Trichloroethylene?

Learning Objective

Upon completion of this section, you should be able to:

- identify direct and indirect measurements that can assist with diagnosis of TCE exposure.

Introduction

TCE may be measured to confirm TCE exposure. Significant exposure to TCE may result in elevated values of routine laboratory tests, including renal and liver function tests.

Direct Biologic Indicators

TCE

Directly testing for TCE in the blood can be used for either immediate exposure or chronic exposure. However there are multiple factors that influence these results, including time when the sample was taken, total body fat, activity level, and enzyme activity of aldehyde and alcohol dehydrogenase (Waksman and Phillips 2004). Detectable plasma levels of TCE in persons without occupational exposure are approximately 0.01 to 0.13 micrograms per deciliter (µg/dL).

TCE Metabolites

Although TCE disappears rapidly from the blood, metabolites (e.g., trichloroacetic acid) can persist in the blood for several weeks and in urine up to three weeks after heavy exposure (Sato, Nakajima *et al.* 1977; Monster, Boersma *et al.* 1979). Immediate exposure is best measured by trichloroethanol levels in the blood. Chronic exposure is best measured by urinary trichloroacetic acid (Waksman and Phillips 2004).

Caution

The presence of TCE metabolites should be interpreted with caution because some medications (chloral hydrate and disulfiram) and other chlorinated hydrocarbons (1,1,1-trichloroethane and tetrachloroethylene) are also metabolized to trichloroacetic acid and excreted in the urine (Agency for Toxic Substances and Disease Registry 1997).

Indirect Biologic Indicators

Kidney

Urinary excretion of glutathione-S-transferase alpha (Bruning, Sundberg *et al.* 1999), α1-microglobulin (Bolt, Lammert *et al.* 2004), β2-microglobulin (Nagaya, Ishikawa *et al.* 1989) and N-acetyl-β-D-glucosaminidase (Brogren, Christensen *et al.* 1986; Selden, Hultberg *et al.* 1993) are used to indicate kidney damage, but neither marker is specific to TCE-induced damage; a number of short-chain halogenated hydrocarbons can produce similar effects (Agency for Toxic Substances and Disease Registry 1997).

Liver

Biochemical abnormalities are uncommon after acute TCE exposures. Rarely have elevations of serum hepatic transaminases (serum glutamic-oxaloacetic transaminase (SGOT) or aspartate aminotransferase (AST), serum glutamic-pyruvic transaminase (SGPT) or alanine aminotransferase (ALT)), bilirubin, and creatinine resulted from acute TCE exposure; (Rasmussen, Brogren *et al.* 1993; Agency for Toxic Substances and Disease Registry 1997) nevertheless, liver and kidney function and serum creatinine tests should be performed to establish baselines.

Heart

Electrocardiogram and continuous cardiac monitoring should be considered for heavily exposed persons.

Gastrointestinal

Ingestion of large amounts of TCE, which can cause profuse diarrhea, can produce an electrolyte imbalance.

Nervous System

Because the trigeminal, optic, and facial nerves can be impaired by exposure to dichloroacetylene, changes in the visual fields and trigeminal nerve potentials can be noted (Szlatenyi and Wang 1996).

Immune System

Two studies that may be of value are Kahn and Letz (1989) and American College of Physicians (1989).

If it had been indicated, laboratory evaluation of immunologic host-defense defects would consist of three phases.

The preliminary screening is a complete blood count with differential smear and quantitative immunoglobulin levels. These tests, together with history and physical examination, will identify more than 95% of patients with primary immunodeficiencies.

The second testing phase consists of readily available studies including B-cell function (such as antibodies and response to immunization), T-cell function (skin tests and contact sensitization), and complement levels.

The first two phases combined will detect most immunodeficiencies amenable to conventional treatment with gamma globulin or plasma.

The third phase (in-depth investigation) consists of testing induction of B-lymphocyte differentiation *in vitro*, stimulated by pokeweed mitogen

	and histological and immunofluorescent examination of biopsy specimens; T-cell surface markers; assays of T-cell helper or killer cell functions; and functional assays using appropriate target cells. It is inappropriate to perform the latter tests on environmentally exposed patients except for epidemiologic research. If the patient's concerns include an increased risk of autoimmune illnesses, general evaluation for autoimmune diseases might include • C-reactive protein (CRP), • evaluation of the antinuclear antibody (ANA), and • the erythrocyte sedimentation rate (ESR). If a specific autoimmune disease is suspected, appropriate serologic markers should be assessed, where available.
Key Points	• TCE can be detected in the breath and urine up to 16 hours after exposure; metabolites can persist for a week or more. • Urinary metabolites are trichloroethanol and trichloroacetic acid. • Urinary proteins, liver function tests, a serum creatinine test, and continuous cardiac monitoring should be considered for persons acutely exposed to high levels of TCE.
Progress Check	16. To confirm TCE exposure, which of the following measurements is the most reliable testing? A. trichloroacetic acid in blood and urine B. TCE in breath, blood, or urine C. elevated values of renal and liver function tests D. elevated values of routine laboratory tests. *To review relevant content, see "Direct Biologic Indicators" in this section.*

How Should Patients Exposed to Trichloroethylene Be Treated and Managed?

Learning Objectives	Upon completion of this section, you should be able to: • describe the principal treatment strategy for treating and managing TCE poisoning.
Introduction	There is no antidote for TCE poisoning. Treatment consists of support of respiratory and cardiovascular functions.
Acute Exposure	In the case of dermal contact with liquid TCE, contaminated clothes should be removed and the affected areas washed with copious amounts of soap and water. Direct eye splashes require irrigation for at least 15 minutes. Corneal epithelium damage usually resolves spontaneously after irrigation. Patients should be removed from the contaminated environment as soon as possible; begin artificial ventilation, if needed. Those with altered mental status or apparent respiratory insufficiency should receive supplemental oxygen. If the patient's pulse is absent, cardiopulmonary resuscitation should be initiated. Gut decontamination (emesis, lavage, or saline cathartic) is recommended if it can be initiated within two to three hours after the ingestion of more than a swallow of TCE. However, the effects of these measures have not been clinically evaluated. If emesis is considered, administer the emetic only to patients who are fully conscious and have an intact gag reflex. Activated charcoal has not been proven to absorb TCE, but, in general, it effectively decreases absorption of most ingested toxic agents. • No data are available on the ability of hemodialysis or hemoperfusion to increase TCE elimination. • No specific antidotes exist (Meditext 2004). • Patients with serious TCE toxicity should be monitored for the possible development of arrhythmias. • When diarrhea is present, monitor for the development of electrolyte abnormalities and screen for the possible development of hepatorenal dysfunction (Meditext 2004). • Sequelae are unusual in acute exposures but reported (Lawrence and Partyka 1981; Feldman, White *et al.* 1985; Szlatenyi and Wang 1996).
Chronic Exposure	No known treatment for chronic exposure to TCE exists. Potentially involved organ systems should be independently evaluated, and supportive measures should be initiated.
Key Points	• Removal from the source and supportive care is the recommended treatment for acute TCE exposure. • Symptomatic treatment is recommended for chronic TCE exposure.

Progress Check

17. The primary strategy for managing TCE poisoning patients includes

    A. supportive measures
    B. ventilation therapy
    C. reduction or elimination of exposure
    D. all of the above.

To review relevant content, see "Introduction" and "Acute Exposure" in this section.

18. All of following statements are correct except:

    A. Symptoms related to chronic exposure tend to worsen during exposure and improve when exposure ceases.
    B. CNS symptoms due to acute TCE inhalation exposure are transient but may linger for hours after exposure ceases.
    C. Supportive care directed to adequate ventilation and circulation should be provided.
    D. There is a specific antidote for TCE poisoning.

To review relevant content, see "Chronic Exposure" in this section.

What Instructions Should Be Given to Patients?

Learning Objective

Upon completion of this section, you should be able to:

- describe advice on self care and follow-up care normally provided to patients who are exposed to TCE.

Introduction

All patients exposed to TCE need some basic guidance on:

- self care, so they can minimize further risks and avoid complications to the extent possible and
- clinical follow up, so they understand when and why to return for further medical attention.

ATSDR has developed a patient education sheet on TCE that you might find useful. It can be found at [add URL for patient education]

Self Care

Patients should be advised to avoid exposures and conditions that might further increase their risk of disease or worsen their existing condition.

At work

- Be sure to use personal protective equipment (PPE) - gloves, goggles, masks.
- Ask employer for the MSDS on products that you use.
- Be sure all containers are labeled for any chemical you use at work.
- Ask your employer for training on how to use chemicals at work.
- Your employer is required to provide labeling, MSDS and training as part of the OSHA Hazard Communication Standard. It's the law!

At home

- Search for safer alternatives to products with TCE.
- When using consumer products containing TCE, open all windows and use fans in your workspace.
- Use respirators or gloves.
- Use cold water to wash dishes, clothes, etc.
- Ventilate the bathroom when showering.

Clinical Follow Up

Since TCE has been implicated as a likely cause of cancer, periodic physical exams may be of value in detecting abnormalities at an early stage if they occur.

Patients should be advised to consult their physician if they develop:

- any sign or symptom of central nervous system or
- signs or symptoms of other health changes (especially those possibly related to heart, liver, and kidney problems)

ATSDR's patient education sheet on TCE includes a more detailed checklist that you can use to indicate which types of follow up are relevant for a given patient.

Key Points	• Patients should be advised to avoid exposures and conditions that might further increase their risk of disease or worsen their existing condition. • Patients should contact their physician if they develop neurological problems or other health changes.
Progress Check	19. Patients who have been exposed to TCE should A. speak to their employer about PPE (if exposures are occupational) B. learn how to avoid further exposure C. know when to call their doctor D. all of the above. *To review relevant content, see all content in this section.*

Where Can I Find More Information?

For More Information

Please refer to the following Web resources for more information on the adverse effects of TCE, the treatment of TCE poisoning, and management of persons exposed to TCE. You may also contact ATSDR (see URLs provided below), your state and local health departments, and university medical centers.

Association of Occupational and Environmental Clinics

http://www.aoec.org

American College of Occupational and Environmental Medicine

http://www.acoem.org

American College of Medical Toxicologists

http://www.acmt.net

American College of Preventive Medicine:

http://www.acpm.org

ATSDR Information Center

http://www.atsdr.cdc.gov/icbkmark.html

ATSDR Information Center Contact Information

http://www.atsdr.cdc.gov/contacts.html

Other CSEMs

Case Studies in Environmental Medicine: Trichloroethylene Toxicity is one monograph in a series. To view the *Taking an Exposure History* CSEM and other publications in this series, please go to

http://www.atsdr.cdc.gov/csem/exphistory/

Posttest

Introduction	ATSDR seeks feedback on this course so we can asses its usefulness and effectiveness. We ask you to complete the assessment questionnaire online for this purpose. You can receive continuing education credits as follows, if you complete the assessment and posttest online.

Accrediting Organization	Credits Offered
Accreditation Council for Continuing Medical Education (ACCME)	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 **3.75** *AMA PRA Category 1 Credit(s)*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
American Nurses Credentialing Center (ANCC), Commission on Accreditation	This activity for **3.75** contact hours is provided by the Centers for Disease Control and Prevention, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.
National Commission for Health Education Credentialing, Inc. (NCHEC)	CDC is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. The Centers for Disease Control and Prevention is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the Certified Health Education Specialist (CHES) to receive **3.5** Category I contact hours in health education, CDC provider number GA0082.
International Association for Continuing Education and Training (IACET)	The Centers for Disease Control and Prevention (CDC) has been reviewed and approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), Suite 800, McLean, VA 22102. CDC will award **0.35** of CEU's to participants who successfully complete this program.

Instructions	To complete the assessment and posttest, go to www2.cdc.gov/atsdrce/ and follow the instructions on that page. You can immediately print your continuing education certificate from your personal transcript online. No fees are charged.

Posttest

1. Which of the following products contain trichloroethylene?

   A. anesthetic
   B. grain fumigant
   C. spot remover
   D. disinfectant

2. People can be exposed to trichloroethylene from

   A. environmental sources
   B. consumer products
   C. occupational sources
   D. all of the above

3. The common sources of non-occupational exposure to TCE are

   A. discharge to surface waters and groundwater by industry
   B. leaching from hazardous water landfills into groundwater
   C. continual volatilization of TCE from emission sources
   D. all of the above

4. Which of the following persons have an increased likelihood of trichloroethylene exposure?

   A. race-car drivers
   B. fabric cleaners
   C. pharmacists
   D. tree sprayers

5. NIOSH considers trichloroethylene a potential occupational carcinogen and recommends exposure limit of which as a 10-hour TWA

   A. 25 ppm
   B. 100 ppm
   C. 50 ppm
   D. none of the above

6. Which of the following statements about trichloroethylene is true?

   A. A large amount of absorbed TCE is exhaled unchanged
   B. Once absorbed, TCE is slowly cleared from the blood.
   C. most of an absorbed dose is metabolized in the liver
   D. Trichloroacetic acid is only detectable within 72 hours after TCE exposure.

7. Which of the following statements is not correctly described with regards to TCE metabolism?

   A. TCE accumulation occurs in organs containing high levels of adipose tissue
   B. Humans are uniform in their capacity for metabolism of TCE
   C. The pathways for metabolism of TCE in humans, rats, and mice are qualitatively similar
   D. Humans metabolize much less TCE on a body weight basis than rats or mice at similar exposure levels

8. Common clinical effects associated with acute exposure to pure TCE at concentrations > 2,000 ppm include

   A. CNS depression
   B. nausea
   C. upper respiratory tract and eye irritation
   D. all of the above

9. Chronic exposure to TCE might

   A. cause headaches or drowsiness
   B. mildly alter liver function
   C. cause short-term memory deficits
   D. all of the above

10. The main systemic response to TCE exposure is

    A. respiratory depression
    B. CNS depression
    C. gastrointestinal irritation
    D. skin irritation

11. Laboratory tests to confirm TCE exposure include

    A. breath analysis for trichloroacetic acid
    B. cardiac isoenzymes
    C. blood analysis for trichloroethanol
    D. urinary creatinine

12. Treatment for acute inhalation of TCE might include

    A. oxygen
    B. hemodialysis
    C. emesis
    D. milk of magnesia

Relevant Content	To review content relevant to the posttest questions, see:
Question	**Location of Relevant Content**
1	What is trichloroethylene?
2	Where is trichloroethylene found?
3	How are people exposed to trichloroethylene?
4	Who's at risk of trichloroethylene exposure?
5	What are U.S. standards for trichloroethylene exposure?
6	What is the biologic fate of trichloroethylene in the body?
7	What is the biologic fate of trichloroethylene in the body?
8	What are the physiological effects of trichloroethylene?
9	What are the physiological effects of trichloroethylene?
10	How should patients exposed to trichloroethylene be evaluated?
11	What laboratory tests can assist in the evaluation of patients exposed to trichloroethylene?
12	How should patients exposed to trichloroethylene be treated and manage?

Literature Cited

References

Agency for Toxic Substances and Disease Registry (1997). "Toxicological Profile for Trichloroethylene." U.S. Department of Health & Human Services, Public Health Service. Atlanta.

American Conference of Governmental Industrial Hygienists. (2003). "TLVs & BEIs: Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices for 2003." Cincinnatti, OH.

Armstrong, S. R. and L. C. Green (2004). "Chlorinated hydrocarbon solvents." Clinics in Occupational & Environmental Medicine **4**(3): 481-96.

Axelson, O., K. Andersson, *et al.* (1978). "A cohort study on trichloroethylene exposure and cancer mortality." J Occup Med **20**(3): 194-6.

Axelson, O., A. Selden, *et al.* (1994). "Updated and expanded Swedish cohort study on trichloroethylene and cancer risk." Journal of Occupational Medicine **36**(5): 556-62.

Bell, D. M., D. W. Gleiber, *et al.* (1989). "Illness associated with child day care: a study of incidence and cost." American Journal of Public Health **79**(4): 479-84.

Bolt, H. M., M. Lammert, *et al.* (2004). "Urinary alpha1-microglobulin excretion as biomarker of renal toxicity in trichloroethylene-exposed persons." International Archives of Occupational & Environmental Health **77**(3): 186-90.

Bove, F., Y. Shim, *et al.* (2002). "Drinking water contaminants and adverse pregnancy outcomes: a review." Environmental Health Perspectives **110 Suppl 1**: 61-74.

Bove, F. J., M. C. Fulcomer, *et al.* (1995). "Public drinking water contamination and birth outcomes.[see comment]." American Journal of Epidemiology **141**(9): 850-62.

Brauch, H., G. Weirich, *et al.* (1999). "Trichloroethylene exposure and specific somatic mutations in patients with renal cell carcinoma." Journal of the National Cancer Institute **91**(10): 854-61.

Brogren, C. H., J. M. Christensen, *et al.* (1986). "Occupational exposure to chlorinated organic solvents and its effect on the renal excretion of N-acetyl-beta-D-glucosaminidase." Archives of Toxicology Supplement **9**: 460-4.

Brown, L. P., D. G. Farrar, *et al.* (1990). "Health risk assessment of environmental exposure to trichloroethylene." Regul Toxicol Pharmacol **11**(1): 24-41.

Bruckner, J. V., B. D. Davis, *et al.* (1989). "Metabolism, toxicity, and carcinogenicity of trichloroethylene." Crit Rev Toxicol **20**(1): 31-50.

Bruning, T. and H. M. Bolt (2000). "Renal toxicity and carcinogenicity of trichloroethylene: key results, mechanisms, and controversies." Critical Reviews in Toxicology **30**(3): 253-85.

Bruning, T., A. G. Sundberg, *et al.* (1999). "Glutathione transferase alpha as a marker for tubular damage after trichloroethylene exposure." Archives of Toxicology **73**(4-5): 246-54.

Bruning, T., S. Vamvakas, *et al.* (1998). "Acute intoxication with trichloroethene: clinical symptoms, toxicokinetics, metabolism, and development of biochemical parameters for renal damage." Toxicological Sciences **41**(2): 157-65.

Bull, R. J. (2000). "Mode of action of liver tumor induction by trichloroethylene and its metabolites, trichloroacetate and dichloroacetate." Environmental Health Perspectives **108 Suppl 2**: 241-59.

Bull, R. J., G. A. Orner, *et al.* (2002). "Contribution of dichloroacetate and trichloroacetate to liver tumor induction in mice by trichloroethylene." Toxicology & Applied Pharmacology **182**(1): 55-65.

Buxton, P. H. and M. Hayward (1967). "Polyneuritis cranialis associated with industrial trichloroethylene poisoning." Journal of Neurology, Neurosurgery & Psychiatry **30**(6): 511-8.

Byers, V. S., A. S. Levin, *et al.* (1988). "Association between clinical symptoms and lymphocyte abnormalities in a population with chronic domestic exposure to industrial solvent-contaminated domestic water supply and a high incidence of leukaemia." Cancer Immunology, Immunotherapy **27**(1): 77-81.

Candura, S. M. and E. M. Faustman (1991). "Trichloroethylene: toxicology and health hazards." G Ital Med Lav **13**(1-6): 17-25.

Chen, C. W. (2000). "Biologically based dose-response model for liver tumors induced by trichloroethylene." Environmental Health Perspectives **108 Suppl 2**: 335-42.

Clewell, H. J., P. R. Gentry, *et al.* (1995). "Considering pharmacokinetic and mechanistic information in cancer risk assessments for environmental contaminants: examples with vinyl chloride and trichloroethylene." Chemosphere **31**(1): 2561-78.

Dallas, C. E., J. M. Gallo, *et al.* (1991). "Physiological pharmacokinetic modeling of inhaled trichloroethylene in rats." Toxicology & Applied Pharmacology **110**(2): 303-14.

Davidson, I. W. and R. P. Beliles (1991). "Consideration of the target organ toxicity of trichloroethylene in terms of metabolite toxicity and pharmacokinetics." Drug Metab Rev **23**(5-6): 493-599.

DeAngelo, A. B., F. B. Daniel, *et al.* (1997). "Failure of monochloroacetic acid and trichloroacetic acid administered in the drinking water to produce liver cancer in male F344/N rats." Journal of Toxicology & Environmental Health **52**(5): 425-45.

Defalque, R. J. (1961). Pharmacology and toxicology of trichloroethylene. A critical review of the literature, Clinical Pharmacology & Therapeutics. 2:665-88, 1961 Sep-Oct.

Fan, A. M. (1988). "Trichloroethylene: water contamination and health risk assessment." Reviews of Environmental Contamination & Toxicology **101**: 55-92.

Feldman, R. G., R. F. White, *et al.* (1985). "Long-term follow-up after single toxic exposure to trichloroethylene." American Journal of Industrial Medicine **8**(2): 119-26.

Fernandez, J. G., P. O. Droz, *et al.* (1977). "Trichloroethylene exposure. Simulation of uptake, excretion, and metabolism using a mathematical model." British Journal of Industrial Medicine **34**(1): 43-55.

Fisher, J. W., M. L. Gargas, *et al.* (1991). "Physiologically based pharmacokinetic modeling with trichloroethylene and its metabolite, trichloroacetic acid, in the rat and mouse." Toxicology & Applied Pharmacology **109**(2): 183-95.

Forkert, P. G., P. L. Sylvestre, *et al.* (1985). "Lung injury induced by trichloroethylene." Toxicology **35**(2): 143-60.

Goeptar, A. R., J. N. Commandeur, *et al.* (1995). "Metabolism and kinetics of trichloroethylene in relation to toxicity and carcinogenicity. Relevance of the mercapturic acid pathway." Chem Res Toxicol **8**(1): 3-21.

Goldberg, S. J., M. D. Lebowitz, *et al.* (1990). "An association of human congenital cardiac malformations and drinking water contaminants." Journal of the American College of Cardiology **16**(1): 155-64.

Grandjean, E., R. Munchinger, *et al.* (1955). Investigations into the effects of exposure to trichlorethylene in mechanical engineering, British Journal of Industrial Medicine. 12(2):131-42, 1955 Apr.

Green, T. (2000). "Pulmonary toxicity and carcinogenicity of trichloroethylene: species differences and modes of action." Environ Health Perspect **108 Suppl 2**: 261-4.

HSDB (April 2006). "Hazardous Substances Data Bank." National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

Iavicoli, I., A. Marinaccio, *et al.* (2005). "Effects of occupational trichloroethylene exposure on cytokine levels in workers." Journal of Occupational & Environmental Medicine **47**(5): 453-7.

Joron, G. E., D. G. Cameron, *et al.* (1955). Massive necrosis of the liver due to trichlorethylene, Canadian Medical Association Journal. 73(11):890-1, 1955 Dec 1.

Kaneko, T., P. Y. Wang, *et al.* (1997). "Assessment of the health effects of trichloroethylene." Ind Health **35**(3): 301-24.

Kilburn, K. H., R. H. Warshaw, *et al.* (1992). "Prevalence of symptoms of systemic lupus erythematosus (SLE) and of fluorescent antinuclear antibodies associated with chronic exposure to trichloroethylene and other chemicals in well water." Environmental Research **57**(1): 1-9.

Kimbrough, R. D., F. L. Mitchell, *et al.* (1985). "Trichloroethylene: an update." J Toxicol Environ Health **15**(3-4): 369-83.

King, G. S., J. E. Smialek, *et al.* (1985). "Sudden death in adolescents resulting from the inhalation of typewriter correction fluid." JAMA **253**(11): 1604-6.

Kleinfeld, M. and I. R. Tabershaw (1954). Trichloroethylene toxicity; report of five fatal cases, A. M. A. Archives of Industrial Hygiene & Occupational Medicine. 10(2):134-41, 1954 Aug.

Lash, L. H., J. W. Fisher, *et al.* (2000). "Metabolism of trichloroethylene." Environ Health Perspect **108 Suppl 2**: 177-200.

Lash, L. H., J. C. Parker, *et al.* (2000). "Modes of action of trichloroethylene for kidney tumorigenesis." Environmental Health Perspectives **108 Suppl 2**: 225-40.

Lawrence, W. H. and E. K. Partyka (1981). "Chronic dysphagia and trigeminal anesthesia after trichloroethylene exposure." Annals of Internal Medicine **95**(6): 710.

Lipscomb, J. C., C. M. Garrett, *et al.* (1997). "Cytochrome P450-dependent metabolism of trichloroethylene: interindividual differences in humans." Toxicol Appl Pharmacol **142**(2): 311-8.

Maltoni, C., G. Lefemine, *et al.* (1988). "Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice." Annals of the New York Academy of Sciences **534**: 316-42.

Massachusetts Department of Public Health, C. f. D. C. a. P., Massachusetts Health Research Institute, (1996). "Final Report of the Woburn Environmental and Birth Study." Cambridge, MA: Massachusetts Department of Public Health.

Meditext (2004). "Trichloroethylene." Denver, Micromedex, Inc.

Miller, P. W., M. B. Mycyk, *et al.* (2002). "An unusual presentation of inhalant abuse with dissociative amnesia." Veterinary & Human Toxicology **44**(1): 17-9.

Monster, A. C., G. Boersma, *et al.* (1976). "Pharmacokinetics of trichloroethylene in volunteers, influence of workload and exposure concentration." International Archives of Occupational & Environmental Health **38**(2): 87-102.

Monster, A. C., G. Boersma, *et al.* (1979). "Kinetics of trichloroethylene in repeated exposure of volunteers." International Archives of Occupational & Environmental Health **42**(3-4): 283-92.

Moore, M. M. and K. Harrington-Brock (2000). "Mutagenicity of trichloroethylene and its metabolites: implications for the risk assessment of trichloroethylene." Environmental Health Perspectives **108 Suppl 2**: 215-23.

Nagaya, T., N. Ishikawa, *et al.* (1989). "Urinary total protein and beta-2-microglobulin

in workers exposed to trichloroethylene." Environmental Research **50**(1): 86-92.

NIDA (2005). "Research Report Series: Inhalant abuse." NIH Publication Number 05-3818.

Nomiyama, K. and H. Nomiyama (1977). "Dose-response relationship for trichloroethylene in man." International Archives of Occupational & Environmental Health **39**(4): 237-48.

Norris, W. and P. Stuart (1957). Cardiac arrest during trichlorethylene anaesthesia, British Medical Journal. (5023):860-3, 1957 Apr 13.

NTP (2004). "Trichloroethylene CAS No. 79-01-6." Eleventh Report on Carcinogens. Research Triangle Park, NC. National Toxicology Program.

OSHA (1993). "Air contaminants final rule." Occupational Safety and Health Administration. Federal Register 58:35338-35351.

Pastino, G. M., W. Y. Yap, *et al.* (2000). "Human variability and susceptibility to trichloroethylene." Environmental Health Perspectives **108 Suppl 2**: 201-14.

Rasmussen, K., C. H. Brogren, *et al.* (1993). "Subclinical affection of liver and kidney function and solvent exposure." International Archives of Occupational & Environmental Health **64**(6): 445-8.

Reif, J. S., J. B. Burch, *et al.* (2003). "Neurobehavioral effects of exposure to trichloroethylene through a municipal water supply." Environ Res **93**(3): 248-58.

Rosenman, K. D., M. J. Reilly, *et al.* (2003). "Cleaning products and work-related asthma." Journal of Occupational & Environmental Medicine **45**(5): 556-63.

Salvini, M., S. Binaschi, *et al.* (1971). "Evaluation of the psychophysiological functions in humans exposed to trichloroethylene." British Journal of Industrial Medicine **28**(3): 293-5.

Sanders, V. M., A. N. Tucker, *et al.* (1982). "Humoral and cell-mediated immune status in mice exposed to trichloroethylene in the drinking water." Toxicology & Applied Pharmacology **62**(3): 358-68.

Sato, A., T. Nakajima, *et al.* (1977). "A pharmacokinetic model to study the excretion of trichloroethylene and its metabolites after an inhalation exposure." British Journal of Industrial Medicine **34**(1): 56-63.

Selden, A., B. Hultberg, *et al.* (1993). "Trichloroethylene exposure in vapour degreasing and the urinary excretion of N-acetyl-beta-D-glucosaminidase." Arch Toxicol **67**(3): 224-6.

Shindell, S. and S. Ulrich (1985). "A cohort study of employees of a manufacturing plant using trichlorethylene." Journal of Occupational Medicine **27**(8): 577-9.

Smith, G. F. (1966). "Trichlorethylene: a review." British Journal of Industrial Medicine **23**(4): 249-62.

Spirtas, R., P. A. Stewart, *et al.* (1991). "Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results." British Journal of Industrial Medicine **48**(8): 515-30.

Stewart, R. D., C. L. Hake, *et al.* (1974). ""Degreaser's flush"." Arch Environ Health **29**(1): 1-5.

Stewart RD, H. C., Le Brun AI, et al, (1974a). "Effects of trichloroethylene on behavioral performance capabilities." In: Xintaras C, Johnson BL, Groot I, eds. HEW Publication no. (NIOSH)74-126. US Department of Health, Education and Welfare, Washington DC, 96-129.

Szlatenyi, C. S. and R. Y. Wang (1996). "Encephalopathy and cranial nerve palsies caused by intentional trichloroethylene inhalation." Am J Emerg Med **14**(5): 464-6.

Thiele, D. L., E. H. Eigenbrodt, *et al.* (1982). "Cirrhosis after repeated trichloroethylene and 1,1,1-trichloroethane exposure." Gastroenterology **83**(4): 926-9.

Tola, S., R. Vilhunen, *et al.* (1980). "A cohort study on workers exposed to trichloroethylene." Journal of Occupational Medicine **22**(11): 737-40.

U.S. EPA (2003). "Toxic Release Inventory." Washington, DC: U.S. Environmental Protection Agency.

US Environmental Protection Agency (1985). "Health assessment document for trichloroethylene. Final report." Washington: US Environmental Protection Agency. NTIS Report No. PB/85-249696.

Waksman, J. C. and S. D. Phillips (2004). "Biologic markers of exposure to chlorinated solvents." Clinics in Occupational & Environmental Medicine **4**(3): 413-21.

Waller, P. A., D. Clauw, *et al.* (1994). "Fasciitis (not scleroderma) following prolonged exposure to an organic solvent (trichloroethylene)." Journal of Rheumatology **21**(8): 1567-70.

Wartenberg, D., D. Reyner, *et al.* (2000). "Trichloroethylene and cancer: epidemiologic evidence.[see comment]." Environmental Health Perspectives **108 Suppl 2**: 161-76.

Waters, E. M., H. B. Gerstner, *et al.* (1977). "Trichloroethylene. I. An overview." Journal of Toxicology & Environmental Health **2**(3): 671-707.

WHO (1985). "Trichloroethylene." Environmental Health Criteria 50. World Health Organization, Geneva.

WHO (2005). "Trichloroethylene in Drinking Water: Background document for

development of WHO Guidelines for Drinking-water Quality." http://www.who.int/water_sanitation_health/dwq/chemicals/trichloroethenemay05.pdf.

Windham, G. C., D. Shusterman, *et al.* (1991). "Exposure to organic solvents and adverse pregnancy outcome." American Journal of Industrial Medicine **20**(2): 241-59.

Wu, C. and J. Schaum (2000). "Exposure assessment of trichloroethylene." Environmental Health Perspectives **108 Suppl 2**: 359-63.