Agency for Toxic Substances and Disease Registry
Case Studies in Environmental Medicine
Tetrachloroethylene Toxicity

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Table of Contents

Key Concepts	• Tetrachloroethylene is used mainly as a solvent for dry cleaning and metal degreasing. • Like most chlorinated solvents, tetrachloroethylene can cause central nervous system depression. • Chronic exposure to tetrachloroethylene may adversely affect the neurological system, liver, and kidneys. • Tetrachloroethylene is reasonably anticipated to be a human carcinogen on the basis of limited evidence 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 URL: 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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Disclaimer

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

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U.S. Department of Health and Human Services
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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 help in evaluation and treating of potentially exposed patients. This CSEM focuses on tetrachloroethylene toxicity.
Available Versions	Two versions of the Tetrachloroethylene Toxicity CSEM are available: • the HTML version http://www.atsdr.cdc.gov/csem/pce/ 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 tetrachloroethylene 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 • complete and submit your assessment and posttest response 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	Enables you to test yourself to determine whether you have mastered the learning objectives.
Answers	Provide feedback to ensure you understand the content and can locate information in the text.

Learning Objectives Upon completion of the Tetrachloroethylene Toxicity CSEM, you will be able to:

Content Area	Objectives
Overview	• Describe the properties of tetrachloroethylene
Exposure Pathways	• Identify sources of tetrachloroethylene exposure • Identify the primary routes of exposure to tetrachloroethylene
Who is at Risk	• Identify the occupations most heavily exposed to tetrachloroethylene • Identify who is at risk of exposure to tetrachloroethylene
Standards and Regulations	• Identify the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for tetrachloroethylene • Identify the U.S. Environmental Protection Agency's (EPA) maximum contaminant level (MCL) for tetrachloroethylene in drinking water
Biological Fate	• Identify where tetrachloroethylene is most likely to be retained in the body • Explain the two major pathways of tetrachloroethylene metabolism in the body
Physiologic Effects	• Describe the physiologic effects associated with tetrachloroethylene exposure
Clinical Evaluation	• Identify the primary focuses of the exposure history • Describe characteristic clinical presentations of patients with acute tetrachloroethylene exposure • Describe characteristic clinical presentations of patients with chronic tetrachloroethylene exposure • Identify direct and measurements that can assist with diagnosis of tetrachloroethylene exposure. • Identify indirect measurements that can assist with diagnosis of tetrachloroethylene exposure.
Treatment and Management	• Describe the principal treatment strategy for managing tetrachloroethylene poisoning • Describe instructions for patient self care • Describe instructions for clinical follow-up

Initial Check

Instructions

This Initial Check will help you assess your current knowledge about tetrachloroethylene toxicity. To take the Initial Check, read the case below and then answer the questions that follow.

Case

A 37-year-old female clerical worker has headache, decreased concentration, and irritability

A 37-year-old woman who is four months postpartum is seen at your office with complaints of headache, increasing irritability, and difficulty concentrating. She says she has become impatient and short-tempered with her husband and new child; minor things make her angry. These feelings began about one month ago. She is most aware of them in the evenings, when they are sometimes accompanied by a throbbing frontal headache. She has no psychiatric history. She has been drinking three ounces of alcohol a day since her marriage four years ago. She did not drink during the pregnancy and does not use other drugs or medications. She has had no trouble sleeping.

Two weeks ago the patient and her family visited her parents for a week. During that time she felt well; the irritability and headaches subsided. Since she returned home last week, however, the symptoms have returned.

The patient is worried that something in the home is causing her symptoms. She reports that the house was sprayed for termites two years ago, but she does not remember the name of the pesticide used. Her husband feels fine and has not been ill. Her infant daughter's delivery was uneventful and the baby appears to be developing normally, but has been "very fussy" lately. The infant, whom you saw five weeks ago for otitis media, is still breast-feeding.

One month ago the patient returned to her job as a word processor. She works mornings and relaxes with her hobby, silk screening, in the afternoons. She gets along well with her employer and fellow employees, and the job is not generally stressful. However, she is concerned that a loss in typing accuracy and a decreased ability to concentrate may lead to conflict with her supervisor. The patient has no symptoms of postpartum depression and had no history of headaches before she resumed these activities.

Physical Examination

On physical examination, you find that the woman is slightly overweight. Her nail beds are pale. She has no skin rashes, lesions, or stigmata of liver disease. The conjunctiva are mildly injected, but the nares and oral mucosa are not swollen or injected. The thyroid is not enlarged, and no lymphadenopathy is present. She has no focal muscle tension or tenderness. Her liver is not enlarged and examination of the abdomen is unremarkable. Neurological examination results are within normal limits.

Recent and distant memory are intact. Proverb interpretation and Mini-Mental State Examination results are normal. Sensory and motor functions are normal, as are Romberg test results and gait. Deep tendon reflexes are normal and symmetrical.

- Blood pressure: 125/85 mmHg
- Pulse: 68 beats/minute and regular
- Temperature: normal

Initial Check Questions

1. What should be included in this patient's problem list?
2. What further information would assist in establishing a diagnosis?
3. What laboratory tests would you order for this patient?
4. On questioning, your patient explains that silk screening involves stretching a large piece of cloth across a form, like a picture frame, masking it to create a pattern, then dying the unmasked areas. Before masking the cloth, it must be cleaned. The patient mentions that she just started using a new fabric cleaner about five weeks ago. Her cousin, who also enjoys silk screening, assured her it was harmless and the best available. The product is called "Clean Cloth*," but the patient can remember little else about it.

   Assuming the label on the container does not list the contents, how will you determine the ingredients of this consumer product?

   ** It's fictional and not to be assumed to represent any actual product.*

5. The poison control center in your region informs you that Clean Cloth is 90% tetrachloroethylene and 10% Freon-12 (dichlorodifluoromethane). Might the infant described in the case study be at increased risk? Explain.
6. How could you determine if a patient has been exposed to tetrachloroethylene?
7. What will you tell your patient regarding the hazards of tetrachloroethylene?
8. What other history will help in determining if the neurological symptoms of the patient described in the case study are due to Clean Cloth?
9. The patient asks why her cousin, who uses Clean Cloth for the same purpose, has not been ill. What can you tell her?
10. The patient's laboratory tests show urinary trichloroacetic acid of 4.2 mg/L immediately after a 1-week exposure and a slightly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT). How do you interpret these results?
11. What recommendations can you make if the patient wishes to continue using Clean Cloth?
12. What authorities should be notified if you believe a product is being used improperly in an industrial setting? By a large number of hobbyists?

Initial Check Answers

1. Your patient is four months postpartum, has transient headaches, irritability, decreased ability to concentrate, slightly impaired coordination, and possible alcoholism.

2. More information about the history of her headaches and her silk-screening hobby would help in diagnosing her symptoms. An accurate history of her current drinking pattern using a specific questionnaire for alcohol or other drug-related problems would also be helpful (Ewing 1984).

   More information for this answer can be found in the section "What Are the Routes of Exposure for Tetrachloroethylene?

3. Because the patient is postpartum and possibly consumes alcohol in excess, you should rule out anemia and check renal and hepatic functions. A complete blood count, urinalysis, blood urea nitrogen (BUN), serum creatinine, and liver function tests would be appropriate.

   More information for this answer can be found in the section "Clinical Assessment - Laboratory Tests".

4. The quickest way to identify the ingredients in Clean Cloth may be to call your regional poison control center (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 on the internet at: http://www.who.int/ipcs/poisons/centre/directory/en/index.html). If this is unsuccessful, ask the patient to obtain a Material Data Safety Sheet (MSDS) for the product from the store that sells it or the manufacturer's sales representative or chemist. The MSDS (www.msds.com) will list ingredients in the product and describe their toxicity.

   More information for this answer can be found in the section "Sources of Additional Information".

5. Yes. Maternal exposure to tetrachloroethylene could result in the chemical being transmitted to the nursing infant, because the solvent selectively concentrates in breast milk. In addition, the infant may be exposed through inhalation if she is nearby when the fabric is being cleaned.

   More information for this answer can be found in section "What Are the Routes of Exposure for Tetrachloroethylene?"

6. Perhaps a first step would be to halt the exposure and determine if the symptoms resolve. Direct biologic indicators of tetrachloroethylene exposure may be obtained by measuring levels in breath or blood, or metabolites in urine. A laboratory that

performs these tests may be located by calling your local poison control center or by searching the internet. Consultation with a certified industrial hygienist may be helpful in locating a reputable laboratory and interpreting the results of biological indicators of exposure.

More information for this answer can be found in the section "Clinical Assessment – History, Signs and Symptoms".

7. You should inform your patient of the adverse effects of acute and chronic exposure to tetrachloroethylene. Advise her and her cousin to use a well-ventilated area when cleaning cloth during silk-screening. You should also review with her the potential long-term risks, particularly to nursing infants.

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

8. Questions about symptoms and temporal association of the use of Clean Cloth may reveal a direct connection. The type and amount of ventilation also may have an effect. (Your questioning reveals that the patient sprays the cloth in late afternoon in a small garage and keeps the door closed to prevent dust from entering. She recalls that one day last week, when it was hot, she felt particularly ill after spraying the cloth.)

   More information for this answer can be found in the section "What Are the Routes of Exposure for Tetrachloroethylene?"

9. You should review the factors that may reduce the cousin's actual exposure. For example, the cousin may work outdoors or in a better ventilated area, or she may not leave rags soaked with the compound lying around, follow directions on product, and so forth. You could also discuss individual variability (*e.g.*, breathing rate; effects of other exposures such as smoking, drugs, and alcohol on metabolic function; genetic differences in metabolic function) as a reason why some people become ill and others do not after similar exposures.

   More information for this answer can be found in the section "What Are the Routes of Exposure for Tetrachloroethylene?"

10. The urinary trichloroacetic acid level indicates an average ambient air exposure of about 30 ppm tetrachloroethylene (calculated using the occupationally based ratio in the "Direct Biologic Indicators" section within the laboratory evaluation discussion). Although this level indicates definite exposure, it may not be high enough to cause her symptoms. However, the patient could have been periodically exposed to short-term levels much higher than this average level, which could have caused her symptoms.

Although not relevant here, the linear correlation between urinary trichloroacetic acid and tetrachloroethylene exposure levels breaks down when the exposure is above 100 ppm tetrachloroethylene. The plateau effect resulting from saturation of the tetrachloroethylene metabolic pathway limits the effectiveness of the assay when the ambient level is above 100 ppm.

The slightly elevated levels of AST and ALT are inconclusive for tetrachloroethylene exposure because of the confounding factor of alcohol consumption. An AST:ALT ratio greater than 1 (i.e., AST greater than ALT) tends to support an alcoholic etiology; a ratio less than 1 (i.e., AST less than ALT) supports toxic, infectious, or other etiologies. The patient should be advised to reduce alcohol consumption and should possibly be counseled regarding alcoholism. Liver function tests should be repeated in several months.

More information for this answer can be found in the section "Clinical Assessment - Laboratory Tests".

11. It would be preferable for your patient to use a less toxic cleaner. However, if the patient insists on continuing to use Clean Cloth, you should advise her to get proper industrial hygiene consultation or other professional assistance. The local or state health department may be able to provide some information.

    Tetrachloroethylene crosses the placenta and can be found in breast milk; therefore, the fetus and nursing newborn may be at increased risk of adverse effects from maternal exposure. Women regularly exposed to tetrachloroethylene should carefully weigh the benefits of breast-feeding against possible risks, and reduce exposure to the extent feasible. If your patient starts using a Clean Cloth alternative that has no chlorinated solvents, the tetrachloroethylene presently in her milk can be eliminated in several days if she continues to pump her breasts.

    More information for this answer can be found in the section "What Instructions Should Be Given to Patients?"

12. OSHA has regulatory responsibility for the workplace and should be notified if employees may be dangerously exposed. You could also request that the National Institute for Occupational Safety and Health (NIOSH) initiate a health hazard evaluation of the workplace. A product with hazardous potential used by a number of hobbyists would be reported to the local or state health department.

    More information for this answer can be found in the section "What Are the Standards for Tetrachloroethylene Exposure?"

What Is Tetrachloroethylene?

Learning Objectives

Upon completion of this section, you will be able to

- describe the properties of tetrachloroethylene.

Definition

Tetrachloroethylene is a synthetic chemical. It is a clear, colorless, nonflammable liquid with a sweet, fruity odor like that of chloroform. It is volatile and readily evaporates at room temperature.

Uses

As of 1995 the estimated end-use pattern for tetrachloroethylene was (Agency for Toxic Substances and Disease Registry 1997.)

- chemical intermediates - 55%,
- metal cleaning and vapor degreasing - 25%,
- dry cleaning and textile processing - 15%, and
- other unspecified uses - 5%.

Tetrachloroethylene has also been used as (U.S. EPA 2005)

- an intermediate in the synthesis of fluorocarbons,
- an insulating/cooling fluid in electric transformers,
- a component in typewriter correction fluids,
- a veterinary medication against worms, and
- a grain protectant and fumigant.

Synonyms

Chemical synonyms for tetrachloroethylene include

- tetrachloroethene,
- perchloroethylene,
- 1,1,2,2-tetrachloroethylene, and
- ethylene tetrachloride.

Other commonly used names are

- PCE,
- Perc,
- perchlor, and
- Perclene.

Key Points

- Tetrachloroethylene is a synthetic chemical that is widely used for dry cleaning of fabrics and for metal-degreasing operations.
- Tetrachloroethylene is also used as a starting material for making other chemicals and is used in some consumer products.

Progress Check

1. Tetrachloroethylene is

   A. a clear liquid having low vapor pressures at room temperature
   B. volatile and readily evaporates at room temperature
   C. used mainly as a solvent and cleaner in consumer formulations
   D. all of the above.

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

Where Is Tetrachloroethylene Found?

Learning Objectives	Upon completion of this section, you will be able to • identify sources of tetrachloroethylene exposure.
Introduction	People can be exposed to tetrachloroethylene from environmental and occupational sources and from consumer products. It is released to air and water by evaporation or emissions from industrial and dry-cleaning plants, and from landfills, where it may be stored.
Environmental Exposures	***Air*** Approximately 85% of the tetrachloroethylene that is used annually is lost to the atmosphere. Concentrations in air have been reported to range from 30 part per trillion (ppt) in rural areas to as high as 4.5 part per billion (ppb) in urban or industrial areas (National Toxicology Program 2001). ***Water*** Tetrachloroethylene is frequently found in water. For example, it was found in 38% of 9,232 surface water sampling sites throughout the U.S. (Agency for Toxic Substances and Disease Registry 1997).
Occupational Exposures	People who work with tetrachloroethylene have the greatest chance of exposure to it. Common environmental levels (called background levels) of tetrachloroethylene are several thousand times lower than levels found in some workplaces (Agency for Toxic Substances and Disease Registry 1997).
Exposures from Consumer Products	Tetrachloroethylene is found as an ingredient in a number of consumer products such as fabric finishers and spot removers.
Key Points	• People can be exposed to tetrachloroethylene from environmental and occupational sources and from consumer products.
Progress Check	2. The most significant exposure pathway of tetrachloroethylene is A. environmental B. occupational C. hobbies related D. none of the above. *To review relevant content, see "Occupational Exposures" in this section.*

What Are the Routes of Exposure for Tetrachloroethylene?

Learning Objectives

Upon completion of this section, you will be able to

- identify the primary routes of exposure to tetrachloroethylene.

Introduction

Occupational exposure to tetrachloroethylene primarily occurs through inhalation and dermal contact with this compound at workplaces where tetrachloroethylene is produced or used.

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

Inhalation

The air pathway is a major route of exposure to tetrachloroethylene. Exposure scenarios include inhalation of contaminated air

- during work with tetrachloroethylene or
- while in the same space as others working with tetrachloroethylene.

Tetrachloroethylene may also be inhaled from

- accidental spills or product use in small, enclosed spaces,
- clothing or newly dry-cleaned fabrics in homes,
- landfills in which it may have been disposed,
- releases to air and water by evaporation or emissions from industrial and dry-cleaning plants,
- vapors formed from contaminated water used for bathing and laundering,
- vapors rising from contaminated groundwater seeping into a basement or crawl space, and
- worker's skin.

Ingestion

Ingestion—another major pathway of exposure—may be intentional or accidental. It occurs through swallowing

- food or drinking water contaminated with tetrachloroethylene or
- breast milk contaminated with tetrachloroethylene.

Skin

Dermal contact also may be a route of tetrachloroethylene exposure in the workplace and among the general public. However, the chemical is less easily absorbed through the skin than through inhalation and oral exposure routes.

Key Points

- The major routes of human exposure to tetrachloroethylene are by inhalation and ingestion.

Progress Check

3. Occupational exposure to tetrachloroethylene occurs generally by

   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 Exposure to Tetrachloroethylene?

Learning Objectives

Upon completion of this section, you will be able to

- identify the occupations most heavily exposed to tetrachloroethylene
- identify who is at risk of exposure to tetrachloroethylene.

Introduction

The National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1981 to 1983, estimated that 688,110 workers employed at 49,025 plant sites were potentially exposed to tetrachloroethylene in the U.S. during this period.

The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace (US Environmental Protection Agency 1985).

Worker Exposure

A NIOSH survey of 44 dry-cleaning facilities reported time-weighted average (TWA, see explanation in **Table 1**) exposures to machine operators ranging from four ppm to 149 ppm. Much higher tetrachloroethylene levels are associated with cleaning spills or replacing dry-cleaning filters (Centers for Disease Control 1983).

Increased potential for exposure may also be encountered by the following workers:

- those performing degreasing and metal cleaning,
- plastic extruders,
- electronic assemblers,
- workers manufacturing tetrachloroethylene-containing consumer, and products (Blair 1980; Materna 1985; Solet, Robins *et al.* 1990).

Commercial Uses

Exposures to consumer products containing tetrachloroethylene have led to acute toxicity.

Accidental ingestions or spills, and use of products in small, enclosed spaces, may place unsuspecting persons at risk. For example, a spot remover containing tetrachloroethylene, used to clean a carpet in a poorly ventilated area, can produce dangerously high levels of the chemical in the air.

Dry Cleaning Hazards

Clothes, drapes, and other dry-cleaned fabrics may serve as a source of tetrachloroethylene release. One study found that newly dry-cleaned garments stored in a residential closet resulted in tetrachloroethylene levels of 0.5 - 2.9 milligrams per cubic meter (mg/m^3) (74 - 428 ppb) in the closet after one day. Initial "airing out" of the clothes for four to eight hours had little effect on the resulting emissions (Tichenor, Sparks *et al.* 1990).

	In one report, a 53-year-old male dry cleaner died after being overcome by tetrachloroethylene fumes (Levine, Fierro *et al.* 1981) . A 2-year-old boy found dead 1.5 hours after he was placed in his room with curtains that had been incorrectly dry cleaned in a coin-operated dry cleaning machine (Garnier, Bedouin *et al.* 1996).
Indoor Air	Elevated indoor air levels may result from dry-cleaned fabrics. Other possible sources include "take home" contamination from exposed workers and contaminated water. Indoor air of exposed dry-cleaner workers' homes can contain levels of tetrachloroethylene nearly 10 times higher than the homes of non-exposed workers (Aggazzotti, Fantuzzi *et al.* 1994). Contaminated water used for bathing and laundering can emit vapors that increase indoor air levels of tetrachloroethylene.
Maternal Transmission	Data from animal and human studies indicate that tetrachloroethylene crosses the placenta. Although the effects are uncertain, this ease of distribution may place the fetus at increased risk (van der Gulden and Zielhuis 1989; Fredriksson, Danielsson *et al.* 1993). In addition, tetrachloroethylene, like most other chlorinated chemicals, can be transmitted in breast milk, thus subjecting the nursing newborn to prolonged exposure. In one case report, a nursing mother was repeatedly exposed to tetrachloroethylene fumes during lunch-hour visits with her husband at a dry-cleaning plant. She had tetrachloroethylene levels of 300 micrograms per deciliter (µg/dL) in blood and 1,000 µg/dL in breast milk. The nursing infant developed obstructive jaundice, possibly as a result of tetrachloroethylene exposure (Bagnell and Ellenberger 1977).
Key Points	• Workers in industries such as dry cleaning, machining, and electronics, as well as people, who use tetrachloroethylene-containing products, have an increased likelihood of exposure. • Persons using well water contaminated with tetrachloroethylene can be exposed through inhalation and ingestion. • Tetrachloroethylene crosses the placenta and can be found in breast milk; therefore, the fetus and nursing newborn may be at increased risk of adverse effects from maternal exposure.

Progress Check

4. Occupations that entail exposure to tetrachloroethylene include which of the following?

   A. workers performing degreasing and metal cleaning
   B. workers manufacturing tetrachloroethylene-containing consumer products
   C. machine operators in dry-cleaning plants
   D. all of the above.

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

5. Of the following, who is most likely to be at risk of tetrachloroethylene exposure?

   A. newborns of nursing mothers who are employed at a dry-cleaning plant
   B. residents who use well water for food preparation, bathing, and laundry
   C. consumers who use spot remover
   D. machine operators in a dry-cleaning plant

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

What Are the Standards for Tetrachloroethylene Exposure?

Learning Objectives

Upon completion of this section, you will be able to

- identify the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for tetrachloroethylene and
- identify the U.S. Environmental Protection Agency's (EPA) maximum contaminant level (MCL) for tetrachloroethylene in drinking water.

Introduction

Government regulations and standards have been developed for tetrachloroethylene. These are designed to protect the public and workers from potential adverse health effects.

Workplace Standards

OSHA has established a PEL in workplace air of 100 ppm measured as an 8-hour TWA (**Table 1**).

NIOSH recommends that tetrachloroethylene be treated in the workplace as a potential human carcinogen and that occupational exposure be reduced to the lowest feasible level (Agency for Toxic Substances and Disease Registry 1997).

The American Conference of Governmental Industrial Hygienists (ACGIH)(American Conference of Governmental Industrial Hygienists. 2001) recommends a threshold limit value (TLV) of 25 ppm and an 8-hour TLV/TWA of 100 ppm. ACGIH has also established the following biologic exposure indices (BEIs)

- 10 ppm tetrachloroethylene in end-exhaled air, sample collected before the last shift of the workweek,
- 1 mg/L tetrachloroethylene in blood, specimen collected before the last shift of the workweek, and
- 7 mg/L trichloroacetic acid in urine, specimen collected at end of the workweek

A BEI is a recommended "warning level," not an absolute threshold. It may be underprotective or overprotective, depending on individual susceptibility, body habits, level of activity, and concomitant exposures.

Environmental Standards

Air

EPA intends to propose air emission standards for tetrachloroethylene, but such standards have not yet been promulgated.

Water

The current EPA drinking water regulation for tetrachloroethylene is 5 ppb.

Table 1. Standards and Regulations for Tetrachloroethylene.

Agency	Focus	Level*	Comments
American Conference of Governmental Industrial Hygienists	Air: workplace	25 ppm	Advisory; TLV/TWA† STEL‡ of 100 ppm
National Institute for Occupational Safety and Health	Air: workplace	Not available	Advisory; lowest feasible level because of carcinogenicity
Occupational Safety and Health Administration	Air: workplace	100 ppm	Regulation; PEL§ over an 8-hour workday
U.S. Environmental Protection Agency	Air: environment	None	Listed as a hazardous air pollutant under Section 112 of the Clean Air Act
	Water: environment	5 ppb	Regulation; maximum level allowed in drinking water

*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 workweek to which nearly all workers may be exposed.

‡STEL (short-term exposure limit): usually a 15-minute sampling period.

§PEL (permissible exposure limit): highest level, averaged over a normal workday, to which a worker may be exposed.

Key Points

- EPA has established a drinking water maximum contaminant level (MCL) for tetrachloroethylene of 5 ppb (US Environmental Protection Agency 1986).
- The current OSHA's 8-hour TWA for tetrachloroethylene is 100 ppm.
- NIOSH considers tetrachloroethylene a potential carcinogen and recommends exposure in the workplace be reduced to the lowest possible level.

Progress Check

6. OSHA's PEL for tetrachloroethylene in the workplace is

   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 tetrachloroethylene in drinking water is

   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 Tetrachloroethylene in the Body?

Learning Objectives

Upon completion of this section, you will be able to

- explain the two major pathways of tetrachloroethylene metabolism in the body.

Introduction

In humans, about 75% of an inhaled tetrachloroethylene dose is absorbed by the lungs, and about 80% of an oral dose is absorbed by the gut. Tetrachloroethylene penetrates human skin slowly. Once tetrachloroethylene is absorbed, it is readily distributed to all body tissues. Because it is highly lipid soluble, it tends to concentrate primarily in adipose tissue.

Half-Life

More than 80% of inhaled tetrachloroethylene is eliminated unchanged by the lungs. The half-life of tetrachloroethylene in three major body compartments is calculated to be

- 12 - 16 hours for vessel-rich tissues,
- 30 - 40 hours for poorly perfused tissues such as muscle and
- 55 hours for adipose tissue

Metabolic Pathways

In humans, only 1% to 3% of the absorbed tetrachloroethylene is metabolized in the liver to trichloroacetic acid, which is then excreted in the urine. Small amounts of trichloroethanol have also been detected in the urine of workers exposed to tetrachloroethylene. The rate of urinary elimination is slower than the rate for exhalation.

Studies of dry-cleaning shop workers have shown that urinary metabolite levels increase linearly with air concentrations of up to 100 ppm tetrachloroethylene, then level off at higher concentrations. This indicates the saturability of the tetrachloroethylene metabolic pathways (Agency for Toxic Substances and Disease Registry 1997).

Metabolism of tetrachloroethylene occurs by cytochrome P450-dependent oxidation and glutathione conjugation. The cytochrome P450 pathway generates tri- and dichloroacetate as metabolites of tetrachloroethylene, and these are associated with hepatic toxicity and carcinogenicity. Glutathione conjugation pathway leads to selective formation of reactive metabolites in the kidneys. It is associated with tetrachloroethylene-induced renal toxicity and carcinogenicity (Lash and Parker 2001).

Key Points

- Once absorbed, tetrachloroethylene is eliminated unchanged in exhaled breath; a small amount is metabolized in the liver and excreted in urine as trichloroacetic acid and trichloroethanol.
- The elimination of tetrachloroethylene and its metabolites appears to be biphasic, with a rapid first phase (hours), and a slow second phase (days).

Progress Check

8. Once absorbed, most of the inhaled tetrachloroethylene is

   A. metabolized in the liver
   B. eliminated unchanged by the lungs
   C. metabolized in the kidney
   D. excreted in urine as trichloroacetic acid and trichloroethanol.

   To review relevant content, see "Half-Life" in this section.

9. Which of the metabolic pathway of tetrachloroethylene is associated with hepatic toxicity?

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

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

What Are the Physiologic Effects of Tetrachloroethylene Exposure?

Learning Objectives

Upon completion of this section, you will be able to

- describe the physiologic effects associated with tetrachloroethylene exposure.

Introduction

Exposure to tetrachloroethylene can affect the

- central nervous system (CNS),
- eyes,
- kidney,
- liver,
- lungs,
- mucous membranes, and
- skin

CNS effects have been noted most frequently.

Acute Exposure

Acute exposure to tetrachloroethylene at air levels of 100 - 200 ppm causes irritation of the skin, eyes and upper respiratory tract (Boulet 1988). Non-cardiogenic pulmonary edema, nausea, vomiting, and diarrhea can occur (HSDB 2005) .

CNS effects have also been observed with acute inhalation exposures of 50 - 300 ppm of tetrachloroethylene. At these levels, neuromotor effects may be seen (*e.g.*, the Romberg test may be positive), and results of certain coordination and behavioral tests may be abnormal. At higher concentrations in air, unconsciousness can occur.

Acute tetrachloroethylene ingestion has been reported. In one case, up to 16 g was ingested by a 6-year-old child, who recovered completely, without liver, renal, or CNS injury (Koppel, Arndt *et al.* 1985) .

In another report, a 32-year-old man became semicomatose and experienced oliguric acute renal failure after accidental ingestion of 75 g of tetrachloroethylene. He regained normal renal function after five hemodialyses and conservative treatment (Choi, Kim *et al.* 2003).

Chronic Exposure

Chronic exposure to tetrachloroethylene may have adverse effects on the hepatic, renal, and nervous systems, and on the skin. It may increase the risk of adverse effects in fetuses and newborns through maternal exposure.

The U.S. Department of Health and Human Services (HHS) has determined that tetrachloroethylene is "reasonably anticipated to be a human carcinogen" (National Toxicology Program 2004). The International Agency for Research on Cancer (IARC) classified it as "probably carcinogenic to humans" [International Agency for Research on Cancer (IARC) 1979; International Agency for Research on Cancer (IARC) 1987; International Agency for Research on Cancer (IARC) 1995]. The classifications are based on sufficient evidence of tetrachloro-

	ethylene's carcinogenicity in animals, but inadequate evidence in humans.
Nervous System Effects	Acute exposures, depending on the concentration, can result in loss of coordination, reversible mood and behavioral changes, or potential anesthetic effects (Agency for Toxic Substances and Disease Registry 1997). Persons chronically exposed to tetrachloroethylene may experience • ataxia • disorientation • irritability • peripheral neuropathy • short-term memory deficits • sleep disturbances Studies of chronically exposed dry-cleaning workers have reported an increased prevalence of subjective neurological symptoms such as memory and concentration impairment, dizziness, and forgetfulness. Delayed reaction times also have been noted. In some patients, short-term memory impairments gradually cleared after exposure to tetrachloroethylene ceased. In such cases, patients may be mistakenly diagnosed with various forms of dementia, such as Alzheimer disease or other CNS disorders, when they in fact suffer from a preventable and possibly reversible toxic disorder (Seeber 1989). Reversibility depends on the degree of severity of the exposure and associated effects.
Hepatic and Renal Effects	Case reports of human exposure to tetrachloroethylene show that it causes hepatotoxic effects in humans, which include • abnormal liver function tests (Agency for Toxic Substances and Disease Registry 1997; Lash and Parker 2001) , • cirrhosis, • hepatitis, • hepatomegaly, and • liver cell necrosis. Most reported cases are due to accidental exposures or deliberate abuse of unknown dose and duration. Mild transient increases in serum transaminase values have occurred from brief but severe exposure in adults. Organ dysfunction has been noted only after months of exposure at tetrachloroethylene levels exceeding 100 ppm. There was one case report of diffuse fatty liver in a dry cleaner who died shortly after being exposed to tetrachloroethylene fumes (Levine, Fierro et al. 1981). In a mice study, hepatic lesions were observed at 37 ppm tetrachloroethylene and were noted to be most pronounced at exposures of 75 and 150 ppm (Kjellstrand, Holmquist et al. 1984). Nephrotoxic effects have also been described in humans(Mutti, Alinovi et al. 1992; Verplanke, Leummens et al. 1999; Lash and Parker 2001). Hematuria and proteinuria have been associated with anesthetic

	concentrations of tetrachloroethylene, and chronically exposed dry-cleaning workers have been reported to have increased urinary levels of lysozymes, β2-microglobulin, and other low-molecular-weight proteins, suggesting tubular damage. Tetrachloroethylene exposure causes a toxic nephrosis in male rats, with characteristic nonproliferative tubular lesions that have also been noted after exposure to other chlorinated hydrocarbon solvents. Such specific renal effects have not been described in humans(Solet and Robins 1991) and may be species specific.
Cardiac Effects	In humans, high-level acute exposure to tetrachloroethylene can produce arrhythmias and pulmonary edema. It may produce a decrease in the myocardial threshold to the arrhythmogenic effects of epinephrine, which has been confirmed in rabbits but not in dogs. Another source has stated it is unlikely to cause such cardiac effects (HAZARDTEXT 2005; HSDB 2005). Chronic exposure to tetrachloroethylene may cause ventricular arrhythmia or cardiomyopathy. An increased prevalence of heart disease was reported in one chronic exposure study, but cardiovascular problems were not more frequent in another (HAZARDTEXT 2005). A case report described a dry cleaner who had symptomatic ventricular ectopy that was temporally correlated with work-related elevations of plasma tetrachloroethylene (Abedin, Cook et al. 1980).
Reproductive and Developmental Effects	The Camp LeJeune study (1998) reported an association between the effects of tetrachloroethylene-contaminated drinking water and small for gestational age (SGA) and mean birth weight difference (Sonnenfeld, Hertz-Picciotto et al. 2001). The New Jersey study (Bove, Fulcomer et al. 1995) found oral cleft defects associated with tetrachloroethylene-contaminated drinking water. Tetrachloroethylene crosses the placenta and can be found in breast milk; therefore, the fetus and nursing newborn may be at increased risk of adverse effects from maternal exposure. The Nursing Mothers Study (Sheldon L 1985) identified PCE in blood, exhaled breath, personal air, and breast milk of 17 study participant. Bagnell and Ellenberger (Bagnell and Ellenberger 1977) reported a case of obstructive jaundice and hepatomegaly in a 6-week-old breastfed infant exposed to PCE, who improved clinically after breast-feeding was discontinued; liver function was normal during two years of follow-up. It is difficult to weigh the potential adverse effects of exposure to a contaminant via breast milk against the recognized benefits afforded by breast milk. Ideally, providing uncontaminated breast milk to an infant is the best choice. From a public health perspective, the avoidance of risk by minimizing exposure is sound public health policy. The risks associated with infant exposure to PCE are unnecessary risks since they can be reduced by avoiding exposure (Schreiber 1993). Several studies have suggested that occupationally exposed women might suffer higher rates of spontaneous abortion and menstrual

	irregularities (Ahlborg 1990; Olsen, Hemminki et al. 1990; Doyle, Roman et al. 1997). Results from inhalation studies in animals suggest that tetrachloroethylene is fetotoxic but not teratogenic at concentrations that are also maternally toxic (i.e., 300 ppm). Fetotoxicity is usually expressed by lower fetal weights and delayed skeletal ossification. In one animal study, (Fredriksson, Danielsson et al. 1993) gestational exposure resulted in behavioral and neurochemical alterations in some rats. Rats given oral doses of tetrachloroethylene for seven days became hyperactive, beginning at 10 days of age.
Carcinogenic Effects	The results of several studies suggest an association between tetra-chloroethylene exposure from drinking water and increased incidence of breast cancer, (Aschengrau, Paulu et al. 1998; Aschengrau, Rogers et al. 2003) lung cancer, (Paulu, Aschengrau et al. 1999) leukemia, (Cohn P 1994) non-Hodgkin's lymphoma, (Cohn P 1994) and other cancers, (Paulu, Aschengrau et al. 1999) although some uncertainties may exist in precision of the associations and exposure classification (Paulu, Aschengrau et al. 1999). Some epidemiologic studies of dry-cleaning workers have suggested a possible association between chronic tetrachloroethylene exposure and increased cancer risk, including lymphoma and various cancers of the lung, esophagus, skin, cervix, uterus, liver, kidney, and bladder (Blair, Stewart et al. 1990; Lynge and Thygesen 1990). However, subjects in many of those studies had been simultaneously exposed to other solvents;(Brown and Kaplan 1987) most studies lacked information of exposure dose; and many studies failed to control for smoking, socioeconomic status, and other relevant risk factors (Green, Odum et al. 1990; Volkel, Friedewald et al. 1998; Mundt, Birk et al. 2003). In studies using mice or rats, high-dose oral administration of tetrachloroethylene was associated with an increased incidence of hepatocellular carcinoma in mice of both sexes. Inhalation exposure was associated with leukemia in male and female rats, renal tubular cell adenomas and adenocarcinomas in male rats, and hepatocellular neoplasms in mice of both sexes (US Environmental Protection Agency. 1991). However, some studies indicated that tetrachloroethylene metabolism is significantly higher in rats than in humans, thus, using rat tumorigenicity data for human risk assessment of tetrachloroethylene exposure may overestimate human tumor risks (Green, Odum et al. 1990; Volkel, Friedewald et al. 1998). Opinions vary on the predictive validity of mouse liver and kidney tumors in assessing carcinogenic risk in humans. In general, one should be careful in extrapolating evidence of liver and kidney tumors in experi-mental animals to human risk assessment (US Environmental Protection Agency 1991; Lash and Parker 2001). Significant increases in the understanding of how tetrachloroethylene and its metabolites act in the liver and kidney should help improve the precision of risk assessment. Tetrachloroethylene has been clearly identified as a carcinogen in

	experimental animals (International Agency for Research on Cancer (IARC) 1979; US Environmental Protection Agency. 1985; National Toxicology Program (NTP) 1986; International Agency for Research on Cancer (IARC) 1987; US Environmental Protection Agency. 1991). The IARC (International Agency for Research on Cancer (IARC) 1979; International Agency for Research on Cancer (IARC) 1987; International Agency for Research on Cancer (IARC) 1995) considers it to be "probably carcinogenic to humans" and HHS believes it is "reasonably anticipated to be a human carcinogen" (National Toxicology Program 2004). These evaluations were based on the findings of limited evidence in humans and sufficient evidence in experimental animals of carcinogenicity.
Key Points	• As with most chlorinated solvents, acute exposure to tetrachloroethylene primarily affects the CNS and causes skin, throat, and eye irritation. • In addition to affecting the CNS and skin, tetrachloroethylene may also adversely affect the liver and kidneys. It may harm the fetus and newborns through maternal exposure. • IARC classified tetrachloroethylene as a probably human carcinogen. • CNS effects may be reversible once exposure ends. • Hepatic and renal toxicity may occur in humans exposed to tetrachloroethylene. • Tetrachloroethylene may affect the heart; however, no deaths due to cardiotoxicity have been reported in workers. • Several studies have reported reproductive or developmental abnormalities due to exposure to tetrachloroethylene in drinking water. • Tetrachloroethylene is reasonably anticipated to be a human carcinogen on the basis of limited evidence from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals.
Progress Check	10. Patients suffering from tetrachloroethylene exposure may be mistakenly diagnosed with various forms of dementia due to which of the following CNS symptoms? A. short-term memory deficits B. ataxia, irritability, and disorientation C. dizziness and sleep disturbances D. all of the above. *To review relevant content, see "Nervous System Effects" in this section.* 11. Which one of the following statements is not true? A. Hepatic and renal toxicity may occur in humans exposed to tetrachloroethylene. B. CNS effects may be reversible on cessation of exposure. C. Acute exposure to tetrachloroethylene primarily affects the CNS, and causes skin, throat, and eye irritation. D. Tetrachloroethylene is not considered to be carcinogenic to humans or animals. *To review relevant content, see "Carcinogenic Effects" in this section.*

Clinical Assessment – History, Signs and Symptoms

Learning Objectives	Upon completion of this section, you will be able to • identify the primary focuses of the exposure history, • describe characteristic clinical presentations of patients with acute tetrachloroethylene exposure, and • describe characteristic clinical presentations of patients with chronic tetrachloroethylene exposures.
Introduction	The physician should ask about previous occurrences of similar symptoms. If a temporal association between symptoms and exposure to certain products is suspected, the physician should try to identify the specific chemical ingredients involved. 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 occupational exposures, the employer or manufacturer is required by law to provide pertinent Material Safety Data Sheets (MSDS). The MSDS for a chemical product lists its ingredients, describes their potential toxicity, and suggests precautions for safe use.
Patient History	Determine whether other family members or co-workers may have similar symptoms. Note the time of the patient's last exposure to a suspected chemical, because a temporal relationship between onset of symptoms and work or other activity may provide important diagnostic clues. The physician should also evaluate the patient's general health and question the patient about alcohol and drug use.
Physical Examination	Record the patient's vital signs, especially abnormalities of heart rate or rhythm. Carefully examine eyes, nose, throat, and skin for inflammation or irritation. The conjunctiva may be injected. Nasal mucosa may be injected and swollen. Repeated inhalation exposures to tetrachloroethylene 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. Examine the patient for hepatomegaly and costovertebral angle tenderness. Also note any urinary abnormalities, such as hematuria (Ellenhorn MJ 1988). A complete neurological evaluation should be performed, with special attention to memory, gait, and balance. Short-term memory loss, if associated with tetrachloroethylene exposure, is generally transient. Patients with acute exposures have been tested positive on the Romberg balance test (Ellenhorn 1997).
Signs and Symptoms	***Acute exposure*** Background levels of tetrachloroethylene in air, water, and food have not been associated with symptoms. People can first smell tetrachloro-ethylene at about 1 ppm; but symptoms typically do not occur until concentrations reach approximately 50 ppm. Odor warning is not always reliable, however, because some people have a higher threshold of detection and may become acclimatize to the smell of

tetrachloroethylene.

The principal symptoms of acute inhalation exposure are eye and upper airway irritation (about 100 - 200 ppm) and CNS depression (at 50 - 300 ppm). Splash exposures of the eye can cause corneal burns and conjunctivitis. Skin contact may produce inflammation or chemical burns (Ellenhorn 1997).

The onset, intensity, and duration of symptoms can vary among identically exposed persons. The variability of toxicity is influenced by many factors, including respiratory rate, target organ sensitivity, body fat content, and general health. CNS symptoms can be similar to those of ethanol inebriation. Pulmonary edema due to accidental exposure was reported in a single worker, but this lesion may have been a secondary finding rather than a direct pulmonary effect of tetrachloroethylene itself.

Symptoms associated with acute high-level tetrachloroethylene exposure may include

- Nervous system
  - confusion,
  - dizziness,
  - euphoria,
  - forgetfulness,
  - headache,
  - irritability,
  - light-headedness,
  - loss of consciousness,
  - loss of coordination,
  - sleepiness, and
  - slurred speech.

- Gastrointestinal
  - Nausea

- Ear, nose, and throat
  - Cough,
  - eye and nose irritation, and
  - upper airway irritation.

- Cardiac

  - dysrhythmia (noted in one worker exposed occupationally to tetrachloroethylene, but no exposure-related cases of sudden cardiac deaths have been reported).

Chronic exposure

Mild CNS symptoms have been reported to result from exposure to tetrachloroethylene-containing household products in confined spaces, and after exposure in industrial settings. Reported symptoms have included

- ataxia
- disorientation
- irritability
- persistent headache
- short-term memory deficits
- sleep disturbances(Agency for Toxic Substances and Disease Registry 1997.)

Observation of experimental volunteers and exposed workers indicates that if the blood concentration of tetrachloroethylene does not exceed 1 mg/l, 16 h after the end of exposure, the time-weighted average exposure is likely to have been below 50 ppm. Exposure to such level for six years on the average does not seem to exert any adverse effect on the central nervous system, the liver and the kidney (Lauwerys, Herbrand *et al.* 1983).

The liver is the primary target organ in animals exposed chronically to tetrachloroethylene. In humans, chronic exposure has led to hepatitis and elevated transaminase levels (serum glutamic-oxaloacetic transaminase [SGOT] or aspartate aminotransferase [AST] and serum glutamic-pyruvic transaminase [SGPT] or alanine aminotransferase [ALT]).

Dysrhythmia was noted in one worker exposed occupationally to tetrachloroethylene, but no exposure-related cases of sudden cardiac deaths have been reported (Agency for Toxic Substances and Disease Registry 1997).

Tetrachloroethylene's defatting action on skin may cause dermatitis, thereby predisposing the skin to infection (HSDB 2005).

Key Points

- The physician should attempt to establish a temporal relationship between the patient's signs and symptoms and exposure to tetrachloroethylene.
- Effects of acute inhalation exposure include mucous membrane irritation and CNS depression.
- Chronic exposure may affect the neurological and hepatic systems and the skin.

Progress Check

12. A temporal association between signs and symptoms and exposure to tetrachloroethylene is one of the focuses of the patient exposure 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.

13. On patient examination, short-term memory loss, if associated with tetrachloroethylene exposure, is

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

    To review relevant content, see "Physical Examination" in this section.

14. Symptoms associated with acute high-level tetrachloroethylene exposure may include all of the following EXCEPT

    A. nausea
    B. cough
    C. confusion
    D. hepatomegaly.

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

Clinical Assessment - Laboratory Tests

Learning Objectives

Upon completion of this section, you will be able to

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

Introduction

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

Direct Biologic Indicators

In exposed persons, tetrachloroethylene may be measured in

- adipose tissue,
- blood,
- breast milk,
- expired air, and
- urine

Its metabolite, trichloroacetic acid (TCA), may be measured in

- blood or
- urine

However, exposure to other chemicals, such as 1,1,1-trichloroethane and trichloroethylene, also produce trichloroacetic acid in blood and urine, as does use of the prescription sedative chloral hydrate. Thus, the presence of this particular metabolite is not specific to tetrachloroethylene exposure.

If the cause of symptoms is questionable, direct biologic testing may be warranted to confirm tetrachloroethylene exposure.

Sample Collection

To measure tetrachloroethylene in blood or expired air, samples should be collected within 16 hours after exposure. Urine samples may remain positive up to five days after exposure, depending on the dose.

Few laboratories perform these specialized tests; regional poison control centers may be able to identify such facilities.

The method of sampling and sample storage must be coordinated with the laboratory to ensure proper specimen collection and processing.

The laboratory should provide reference values appropriate for the analytical method used, if they exist.

It is important to record the time of sample collection relative to the last exposure. Also note all possible sources of exposure, including the use of household products containing tetrachloroethylene and related chlorinated hydrocarbons.

Expired air and blood tetrachloroethylene levels and urine trichloroacetic acid levels have been linearly correlated with ambient air concentrations of up to 100 ppm (Agency for Toxic Substances and Disease Registry 1997).

In workers, a trichloroacetic acid level of 7 mg/L in urine, obtained at the end of the workweek, correlated with exposure to an average of 50 ppm tetrachloroethylene for 1 week. The same exposure level will result in approximately 100 µg/dL tetrachloroethylene in blood drawn 16 hours after the last work shift of the week (Agency for Toxic Substances and Disease Registry 1997).

Increased physical activity during exposure can result in higher levels (Agency for Toxic Substances and Disease Registry 1997).

It is important to note that the metabolism of tetrachloroethylene to trichloroacetic acid is inhibited by ethanol use; thus, a low trichloroacetic acid level cannot be used to assure safe exposure levels of tetrachloroethylene if the victim also uses alcohol (Reichert 1983).

Indirect Biologic Indicators

Although tetrachloroethylene may cause upper airway irritation and coughing, chest radiograph and function tests are usually normal.

In general, results of routine laboratory tests, including renal and liver function tests, will also be normal unless the patient has had an exposure significant enough to cause concurrent neurological symptoms.

One study sought to study subclinical hepatotoxicity in dry cleaners exposed to tetrachloroethylene. It compared the sensitivity of hepatic parenchymal ultrasonography with measurements of serum transaminases as biomarkers of liver function (Brodkin, Daniell *et al.* 1995; Lash and Parker 2001). The study found mild to moderate changes in hepatic parenchyma more frequently in workers exposed to tetrachloroethylene than in a control population that was not exposed to any chemicals. In contrast, the incidence of increased serum alanine aminotransferase activity in these same workers was much less than that of the changes in ultrasonography.

However, when assessing hepatic parenchymal changes determined by nonspecific ultrasonography, the clinician must take into account synergism with other hepatotoxic factors when making the final clinical assessment of hepatoxicity from tetrachloroethylene. Such factors can include prescription medications, alcoholism, nutritional and/or genetic factors, and preexisting disease of the liver (Brodkin, Daniell *et al.* 1995; Brautbar and Williams 2002).

Baseline

If acute exposure to tetrachloroethylene has resulted in marked CNS symptoms such as syncope, then the following should be obtained immediately to establish baseline

- liver function tests
- blood urea nitrogen (BUN)
- serum creatinine
- urinalysis

Testing should be repeated after several days to monitor for possible effects.

Liver function tests should include

- alkaline phosphatase
- ALT (SGPT
- AST (SGOT)
- bilirubin
- lactic dehydrogenase

Transient elevations of serum levels of liver enzymes have been reported in tetrachloroethylene exposure, but frank hepatic necrosis has only rarely been documented.

If enzyme levels are mildly elevated, tests should be repeated in several weeks to document return to baseline. If levels remain elevated, consider other causes of hepatic dysfunction and initiate appropriate clinical evaluation.

Deciding when to obtain a neuropsychological evaluation in an individual patient for differentiating between organic and functional impairment may be challenging, especially when no baseline evaluation is available. Such tests may be most useful for comparing exposed occupational populations to nonexposed control groups. Neuropsychological tests may provide data that may be used to raise suspicion of cognitive impairments that are not otherwise evident on mental status testing, and they serve to define a clinical baseline for follow-up. Referral to a neurologist or occupational medicine specialist may be useful to determine whether neuropsychological testing is indicated in individual patients.

Key Points

- Tetrachloroethylene itself may be measured in breath, blood, urine, breast milk, and adipose tissue; its metabolites can be measured in blood and urine.
- Significant exposure to tetrachloroethylene may result in elevated values from renal and liver function tests.

Progress Check

15. Which of the following indicator(s) confirm(s) tetrachloroethylene exposure?

    A. trichloroacetic acid in blood and urine
    B. tetrachloroethylene 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 Tetrachloroethylene Be Treated and Managed?

Learning Objectives

Upon completion of this section, you will be able to

- describe the principal treatment strategy for managing tetrachloroethylene poisoning.

Introduction

There is no antidote for tetrachloroethylene poisoning. Treatment consists of support of respiratory and cardiovascular functions.

Acute Exposure

No specific treatments are available for acute tetrachloroethylene exposures (Ellenhorn MJ 1988; Stutz DR 1992).

Data from humans are insufficient to determine an ingestion level at which emesis should be induced. If a gag reflex is not apparent, emetics should not be administered because the patient could breathe in the gastric contents. Gastric lavage may be useful if the person has recently ingested a large amount of tetrachloroethylene. The clinical value of charcoal and cathartics in this setting is not proven.

If a worker is exposed to a spill in which the clothing has become soaked with tetrachloroethylene, the contaminated clothing should be removed without endangering health care personnel. Supportive care directed to adequate ventilation and circulation should be provided. Moderately to severely exposed patients should have cardiac monitoring for possible dysrhythmias. Oxygen should be administered to those patients if respiratory depression has occurred.

CNS symptoms due to acute tetrachloroethylene inhalation exposure are transient but may linger for hours after exposure ceases. Patients usually recover rapidly without permanent neurological sequelae if hypoxia and shock have been prevented (Patel, Janakiraman *et al.* 1977) .

Because more than 80% of tetrachloroethylene is eliminated in exhaled air, controlled hyperventilation may enhance its elimination.

Hyperventilation therapy (volume, 10 liters/minute) was successfully used in a comatose 6-year-old who had ingested 8 -10 milliliters of pure tetrachloroethylene 2 hours before. The initial tetrachloroethylene blood level was 2,150 µg/dL. On the fifth day, when hyperventilation was terminated, the blood level had fallen to less than 100 µg/dL. However, the extent to which hyperventilation contributed to the child's recovery remains uncertain, and the effectiveness of hyperventilation in tetrachloroethylene overdose has not been adequately validated (Koppel, Arndt *et al.* 1985).

Chronic Exposure

Symptoms related to chronic exposure tend to worsen during exposure and improve when exposure ceases, such as over a weekend, during vacation, or after a job transfer. If there is no clear association between symptoms and exposure, other causes for symptoms should be considered.

For persons with tetrachloroethylene toxicity, the level of exposure either must be reduced or the source eliminated. In some occupational settings, it is possible to substitute an agent less hazardous than tetrachloroethylene. In other settings, it may be possible to eliminate hazards by increasing ventilation.

High levels of exposure can occur during cleanup of contaminated equipment and spills, and may require use of an approved full facepiece self-contained breathing apparatus or similar device. Procedures for spill cleanup should be established in advance. All containers of liquid tetrachloroethylene should be capped; rags soaked with tetrachloroethylene should be stored in sealed containers.

Key Points

- There is no antidote for tetrachloroethylene toxicity; supportive measures should be administered.
- In a patient who ingested tetrachloroethylene, controlled hyperventilation therapy was apparently successful.
- Long-term management requires reduction or elimination of exposure.

Progress Check

16. The primary strategy for managing a tetrachloroethylene-poisoned patient may include

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

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

17. Which one of the following statements **IS NOT** correct?

    A. Symptoms related to chronic exposure tend to worsen during exposure and improve when exposure ceases.
    B. CNS symptoms due to acute tetrachloroethylene 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 tetrachloroethylene poisoning.

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

What Instructions Should Be Given to Patients?

Learning Objectives

Upon completion of this section, you will be able to

- describe instructions for patient self care and
- describe instructions for patient clinical follow-up.

Introduction

All patients exposed to tetrachloroethylene 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 tetrachloroethylene that you might find useful. It can be found at www.atsdr.cdc.gov/csem/pce/pated_sheet.html

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 your employer for 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's Hazard Communication Standard. It's the law!

At Home

- Search for safer alternatives to products with tetrachloroethylene.
- When using products containing tetrachloroethylene, open all windows and use fans in your workspace.
- Wear a respirator or protective gloves, or both, when using products that contain tetrachloroethylene.

Clinical Follow-Up

Tetrachloroethylene has been implicated as a probable cause of cancer. Periodic physical exams may help detect abnormalities at an early stage, if they occur.

Patients should be advised to consult their physician if they develop signs or symptoms of

- central nervous system disorders or
- other health changes (especially those possibly related to heart, liver, and kidney problems).

ATSDR's patient education sheet on tetrachloroethylene 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 tetrachloroethylene 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	18. Patients who have been exposed to tetrachloroethylene 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 "Self Care and Clinical Follow-up" in this section.*

Sources of Additional Information

For More Information	Please refer to the following Web resources for more information on the adverse effects of tetrachloroethylene, the treatment of tetrachloroethylene poisoning, and management of persons exposed to tetrachloroethylene. You may also contact ATSDR (see URLs provided below), your state and local health departments, and university medical centers.
ATSDR Sources of Additional Information	**For emergency situations** **CDC Emergency Response: 770-488-7100 and request the ATSDR Duty Officer** For non-emergency situations CDC-INFO 800-CDC-INFO (800-232-4636) TTY 888-232-6348 24 Hours/Day E-mail: cdcinfo@cdc.gov **PLEASE NOTE** ATSDR cannot respond to questions about **individual medical cases**, provide second opinions or make specific recommendations regarding therapy. Those issues should be addressed directly with your health care provider. ATSDR Toxicological Profile for Tetrachloroethylene http://www.atsdr.cdc.gov/toxprofiles/tp18.html ToxFAQs™ for Tetrachloroethylene http://www.atsdr.cdc.gov/tfacts18.html
ATSDR Division of Regional Operations	The Division of Regional Operations fulfills the Agency's directives at the regional level by staffing an ATSDR Regional Office within each of the 10 EPA Regional Offices. The regional representatives are essential liaisons with all NCEH/ATSDR divisions and offices and facilitate the implementation of their specific programs in the regions. Through the working relationships they have established with EPA, other federal and state agencies, individual citizens, and community groups, regional representatives are able to maintain current and historic knowledge of the sites and issues in their regions. This information enables ATSDR to address regional issues with appropriate sensitivity and make informed decisions. ATSDR's Regional Offices, along with the states and territories that they cover as well as contact information, can be found at www.atsdr.cdc.gov/DRO/dro_contact.html

Other Sources of Information

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

Other CSEMs

Case Studies in Environmental Medicine: Tetrachloroethylene 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/csem.html

Posttest Instructions

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.

In addition, if you complete the assessment and posttest online, you can receive continuing education credits as follows.

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 **1.25** *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 **1.25** 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 **1.5** 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 **0.1** of CEU's to participants who successfully complete this program.

Disclaimer

In compliance with continuing education requirements, all presenters must disclose any financial or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters as well as any use of unlabeled product(s) or product(s) under investigational use.

CDC/ATSDR, our planners, and the presenters for this seminar do not have financial or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. This presentation does not involve the unlabeled use of a product or product under investigational use.

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 tetrachloroethylene?

   A. shoe polish
   B. laundry soaps
   C. spot removers
   D. insect repellents.

2. People can be exposed to tetrachloroethylene from

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

3. The exposure pathway to tetrachloroethylene that most commonly leads to illness is through

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

4. All of the following persons have an increased likelihood of tetrachloroethylene exposure except?

   A. machinists and metal degreasers
   B. dry-cleaning workers
   C. breast-fed infants of exposed mothers
   D. tree sprayers.

5. NIOSH considers tetrachloroethylene a potential carcinogen and recommends exposure in the workplace be reduced to

   A. 25 ppm
   B. 100 ppm
   C. 50 ppm
   D. the lowest possible level.

6. Which of the following statement(s) about tetrachloroethylene is (are) true?

   A. it is well absorbed from the lungs
   B. an ingested dose can result in gangrene
   C. most of an absorbed dose is metabolized in the liver
   D. most of an inhaled dose is eliminated in urine.

7. Renal failure after acute tetrachloroethylene exposure is probably

   A. caused by an excess of hydrogen chloride resulting from the solvent's metabolism
   B. caused by a rise in urobilinogen
   C. a result of vascular collapse after CNS depression
   D. associated with generation of reactive metabolites selectively in the kidney.

8. CNS effects due to tetrachloroethylene include all of the following except

   A. can occur in the absence of liver toxicity
   B. are enhanced in a person exposed to tetrachloroethylene while exercising
   C. are due to trichloroacetic acid, a major metabolite of tetrachloroethylene
   D. can result in a positive Romberg test at high exposure levels.

9. Which one of the following is CNS effect of chronic inhalation exposure to tetrachloroethylene?

   A. paranoid psychosis
   B. dysesthesia
   C. disorientation
   D. tactile hallucinations.

10. Patients with acute tetrachloroethylene poisoning can have all of the following except

    A. slurred speech
    B. jaundice
    C. memory deficit
    D. upper respiratory irritation.

11. To measure tetrachloroethylene in blood or expired air after exposure, samples should be collected within

    A. 1 hour
    B. 6 hours
    C. 16 hours
    D. 24 hours.

12. Treatment(s) for acute inhalation of tetrachloroethylene include(s)

    A. oxygen
    B. activated charcoal
    C. emesis
    D. ethanol administered intravenously

Relevant Content	To review content relevant to the posttest questions, see:

Question	Location of Relevant Content
1	What is tetrachloroethylene?
2	Where is tetrachloroethylene found?
3	What are routes of exposure for tetrachloroethylene?
4	Who is at risk of tetrachloroethylene exposure?
5	What are standards for tetrachloroethylene exposure?
6	What is the biological fate of tetrachloroethylene in the body?
7	What is the biological fate of tetrachloroethylene in the body?
8	What are the physiologic effects of tetrachloroethylene exposure?
9	What are the physiologic effects of tetrachloroethylene exposure?
10	Clinical assessment – history and signs and symptoms
11	Clinical assessment – laboratory tests
12	How should patients exposed to tetrachloroethylene be treated and managed?

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