AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

CASE STUDIES IN ENVIRONMENTAL MEDICINE (CSEM)

CARBON TETRACHLORIDE TOXICITY

Course: **WB2888**

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Key Concepts

- Chronic exposure to carbon tetrachloride (CCl_4) — and sometimes acute exposure to very high concentrations — produces liver and kidney damage.
- CCl_4 is highly toxic. It is reasonably anticipated to be a human carcinogen, based on sufficient evidence of carcinogenicity from studies in experimental animals.

About This and Other Case Studies in Environmental Medicine

This educational case study is one in a series of self-instructional modules designed to increase the primary care provider's knowledge of hazardous substances in the environment. The modules also promote medical practices that can aid in evaluating and caring for potentially exposed patients. The complete series of Case Studies in Environmental Medicine is available on the ATSDR website at: https://www.atsdr.cdc.gov/csem/csem.html. 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.

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Note: Each content expert for this case study has indicated that he or she has no conflict of interest that would bias the case study content.

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U.S. Department of Health and Human Services

Agency for Toxic Substances and Disease Registry

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Environmental Medicine Branch

Table of Contents

How to Use This Course

Introduction	The goal of *Case Studies in Environmental Med*icine (CSEM) is to increase the primary care provider's knowledge of hazardous substances in the environment and to help in the evaluation and treatment of potentially exposed patients. This CSEM focuses on carbon tetrachloride toxicity.
Availability	Two versions of the carbon tetrachloride toxicity CSEM are available. • The HTML version https://www.atsdr.cdc.gov/csem/csem.asp?csem=35&po=0 provides content through the Internet. • The downloadable PDF version http://www.atsdr.cdc.gov/csem/carbon_tetrachloride/docs/Carb_Tet-508.pdf provides content in an electronic, printable format, especially for those who might 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: • Take the Initial Check to assess your current knowledge about carbon tetrachloride 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 want free continuing education credit. You can print your continuing education certificate immediately after course 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 with which you are already familiar. The labels 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	Provides feedback to ensure you understand the content and can locate information in the text

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Learning Objectives

On completion of the Carbon Tetrachloride Toxicity CSEM you will be able to

Content Area	Learning Objectives

What Is Carbon Tetrachloride?	• Describe carbon tetrachloride (CCl_4).
Where Is Carbon Tetrachloride Found?	• Identify sources of carbon tetrachloride (CCl_4) exposure.
What Are Routes of Exposure to Carbon Tetrachloride?	• Identify the routes of exposure to carbon tetrachloride (CCl_4).
Who Is at Risk for Exposure to Carbon Tetrachloride?	• Identify who is at risk for exposure to carbon tetrachloride (CCl_4).
What Are Guidelines and Regulations for Carbon Tetrachloride Exposure?	• Describe current U.S. guidelines and regulations for carbon tetrachloride (CCl_4) exposure
What Is the Biologic Fate of Carbon Tetrachloride in the Body?	• Describe the characteristics of carbon tetrachloride (CCl_4) metabolism.
What Are the Toxicological Effects of Carbon Tetrachloride Exposure?	• Describe the toxicological effects associated with carbon tetrachloride (CCl_4) exposure.
Clinical Assessment – History and Physical Exam	• Describe what is included in the initial history and physical exam of patients potentially exposed to carbon tetrachloride (CCl_4).
Clinical Assessment - Laboratory Tests	• Describe tests that may assist with diagnosis of carbon tetrachloride (CCl_4) toxicity.

How Should Patients Exposed to Carbon Tetrachloride Be Treated and Managed?	• Describe treatment strategies for patients with carbon tetrachloride (CCl_4) poisoning.
What Instructions Should Be Given to Patients Exposed to Carbon Tetrachloride?	• Describe instructions that can be provided to patients exposed to carbon tetrachloride (CCl_4).

Initial Check

Instructions This initial check will help you assess your current knowledge about carbon tetrachloride toxicity. To take the initial check, read the case below and then answer the questions that follow.

Case

A hazardous waste worker has delayed-onset abdominal pain, nausea, vomiting, and diarrhea.

As the physician on duty at a hospital emergency department (ED) in an urban community, you are notified that an ambulance is bringing three hazardous waste workers—two males (ages 40 and 25 years) and a female (age 30 years)—directly from their worksite to your emergency room. All three workers are complaining of

- Headache,
- Dizziness, and
- Nausea.

You learn that the workers were handling several dozen barrels of a sweet-smelling hazardous waste liquid in a hot, unventilated room. Their work required taking samples from barrels obtained from a defunct chlorofluorocarbon manufacturing plant. All three workers were initially wearing full-face respirators and protective clothing. However, the younger of the two males removed his respirator early in the day. He said

he had a hangover with nausea and felt it was easier to work without being hampered by the respirator. The other two workers continued in full protective gear.

After 3–4 hours, all three workers began to experience headache, dizziness, and nausea and notified their supervisor.

On clinical evaluation at the ED, initial routine laboratory results were within normal limits for all three workers. Two of the workers (the older male and female) had resolution of their symptoms within 2 hours, had no abnormal physical findings, and were discharged. The third worker (younger male) did not show significant symptom improvement at 2 hours and developed mild ataxia and concentration deficits on mental status exam. He was kept in the ED under close observation. You learn from this patient that he has been in good health with no history of similar problems. The previous evening, in celebration of his birthday, he drank 9–12 beers, which accounts for his hangover this morning. He also mentions that this morning, while cleaning several wounds sustained in a fight the previous evening, he spilled isopropyl alcohol on his hands and clothing, but did not bother to change his clothing.

Six hours later, while still in the ED, the younger male becomes acutely ill. He has

- Abdominal pain,
- Nausea,
- Vomiting, and
- Diarrhea.

His rectal temperature is now 101°F, pulse 140/minute, and he has become disoriented and drowsy. Two days after hospital admission, he still has an elevated temperature and abnormal laboratory test results, as follows:

- Serum creatinine — 2.0 mg/dL (normal 0.7–1.5 mg/dL);
- AST (SGOT) — 80 U/L (normal 7–45 U/L);

- Total bilirubin — 2.4 mg/dL (normal 0.1–1.4 mg/dL);
- Prothrombin time (PT) — 15 seconds (normal 10–13 seconds).

Urinalysis reveals 2+ proteinuria, and urine output has decreased, despite intravenous hydration.

Initial Check Questions

1. How will you identify the material to which the workers have been exposed?

2. You discuss the acute exposures with the workers' company supervisor. He suspects that the waste barrels contain carbon tetrachloride (CCl_4) **—** a chemical with a sweet odor used as a starting material in the synthesis of chlorofluorocarbons. The 40-year-old (older) male worker in the case study has a full beard. He has a history of alcoholism, but he has been abstinent for several years. He also has a history of hepatitis B, the result of a blood transfusion more than 10 years ago. If the material in the barrels is CCl_4, is this worker at increased risk for CCl_4's adverse health effects?

3. The female co-worker later discovers she was almost 6 weeks pregnant at the time of this exposure episode. Her obstetrician calls you to discuss the implications of the exposure to the fetus. What is your recommendation? Explain.

4. Early that evening, the manager calls to inform you that the company has identified the hazardous waste as CCl_4. Now that you know the exposure is confirmed as CCl_4, do you consider the younger male worker to be at increased risk for acute health effects? Why?

5. What is the possible clinical course for the younger male?

6. What laboratory work-up is advised for patients exposed to CCl_4?

7. What initial action should be taken in the emergency department for patients exposed to CCl_4?

8. What treatment or antidote would you consider for the younger male worker?

9. What follow-up would you recommend for the younger male worker and his potentially exposed co-workers?

10. What specialized clinical resources are available for consultation or referral of patients exposed to hazardous substances, including CCl_4? What actions will the waste management company take to comply with the Occupational Safety and Health Administration (OSHA) Act and OSHA Hazard Communication Standard that protect workers from adverse health effects from exposure to hazardous substances in the workplace?

Initial Check Answers

1. History of the source plant as a chlorofluorocarbon manufacturer is suggestive of CCl_4. You can request a CCl_4 safety data sheet (SDS) from the company while awaiting their barrel sample test results. You can also consider clinical consultation with a medical specialist with expertise and experience evaluating and treating patients exposed to hazardous substances, including CCl_4. Publicly available information on these types of clinical consultation and referral resources are provided under “Clinical Resources” in the “Sources of Additional Information” section of this course.

More information for this answer can be found in the “What Is Carbon Tetrachloride?” and “Sources of Additional Information” sections.

2. The older male’s history of alcoholism and hepatitis B could put him at increased risk for CCl_4's adverse health effects. Underlying liver damage would

increase the risk for acute effects and subsequent hepatocellular carcinoma. Although he was working in an appropriate protective suit and full-face respirator, he still could have been exposed. For example, his beard might have prevented proper fit of the respirator face piece. His symptoms could also be the result of working in a hot, enclosed space, or they could be psychophysiological.

More information for this answer can be found in the "Who Is at Risk for Exposure to Carbon Tetrachloride?" section.

3. It is unclear if the female patient has been exposed to CCl_4. Her symptoms might be related to "morning sickness" associated with her pregnancy. Nevertheless, it is important that she discuss this possible exposure with her obstetrician.

CCl_4 is lipophilic and can readily pass through the placenta to the fetus after maternal exposure. However, studies have not found sufficient evidence to associate CCl_4 exposure and adverse birth outcomes in humans. In animal studies, CCl_4 can induce embryotoxic and embryo lethal effects, but only at doses that are toxic to the mother.

More information for this answer can be found in the "What Are the Toxicological Effects of Carbon Tetrachloride Exposure?" section.

4. Because the younger male removed his respirator and presumably breathed the solvent for a prolonged time, he is at higher risk for acute health effects from CCl_4 exposure. His previous ethanol intake and possibly his recent exposure to isopropyl alcohol increase his risk for CCl_4-induced adverse health effects. Alcohols can induce production of mixed function oxidase enzymes, thereby potentiating the formation of CCl_4 toxic intermediates and metabolites.

More information for this answer can be found in the "Who Is at Risk for Exposure to Carbon Tetrachloride?" section.

5. Acute hepatic necrosis and renal impairment can occur up to 2 weeks after a CCl_4 exposure. Other secondary health effects can include coagulation disorders, cardiac dysrhythmias, and pulmonary edema. Without improvement in the kidney and liver disorders, these effects are not likely to resolve. Because of the patient's multiple exposures to hepatotoxic agents (i.e., recent heavy consumption of ethanol and potential occupational exposure), acute care should begin as soon as possible as a preventive measure.

Note: Whether or not the isopropyl alcohol spilled on the patient's clothing will affect the patient's medical condition is unclear. Reports of isopropyl alcohol's ability to potentiate the harmful effects of CCl_4 are based on inhalation studies in experimental animals. Significant inhalation of isopropyl alcohol in this case is unlikely and intact skin does not readily absorb isopropyl alcohol.

Most cases of fatal, CCl_4-induced hepatotoxicity involve persons with a history of heavy ethanol abuse. Although the patient consumed ethanol the night before the incident, he denies frequent alcohol use, which might make it more likely that his liver is healthy. Nevertheless, exposure to ethanol within 12 hours before CCl_4 exposure will potentiate CCl_4's toxicity. If the patient survives the first 2 weeks, the prognosis is good for complete recovery or for only mildly compromised liver and kidney function.

More information for this answer can be found in the "What Are the Toxicological Effects of Carbon Tetrachloride Exposure?" section.

6. The following laboratory workup is recommended for patients exposed to any volatile solvent (including CCl_4): baseline hepatic and renal function tests (i.e., AST [SGOT], ALT [SGPT], bilirubin, alkaline

phosphatase, BUN, creatinine, electrolytes, urinalysis, PT, PTT, and CBC.

Some solvents might cause dysrhythmias and pulmonary edema (probably secondary to renal toxicity); therefore, you should obtain a baseline electrocardiogram and chest radiograph. To monitor the patient's condition, you should repeat these tests periodically. Acutely ill patients should have their blood oxygen levels and cardiac rhythm monitored.

You should also make sure appropriate public or occupational health reports are filed. Some states might require filing a doctor's first report of illness with the state health department. ED physicians might overlook filing these reports.

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

7. Initial actions include removing all contaminated clothing (dermal absorption of some solvents is high) and cleansing the skin with mild soap and water. Care should be taken to prevent exposure of ED personnel to fumes from and skin contact with contaminated clothing. If possible, decontaminate the patient before he or she enters the ED.

More information for this answer can be found in the "How Should Patients Exposed to Carbon Tetrachloride Be Treated and Managed?" section.

8. Treatment is generally supportive. Maintain an open airway and assist ventilation if necessary. Treat coma and arrhythmias. Avoid use of epinephrine and other sympathomimetic amines that might worsen any arrhythmias resulting from myocardial sympathomimetic sensitization caused by CCl_4. Treat tachyarrhythmias with propranolol or esmolol.

Case reports from Europe, where antioxidants such as N-acetylcysteine (NAC) (Mucomyst, Acetadote) are used, suggest that when these free-radical scavengers

are given intravenously within 12–16 hours after a high-level acute CCl_4 exposure, they might prevent or decrease hepatic and renal damage [De Ferreyra et al. 1974; De Ferreyra et al. 1977; Prescott et al. 1977; Kearney 2007]. No treatments (e.g., multi-dose activated charcoal, hemodialysis) are currently known to enhance CCl_4 elimination. Consider consulting with a medical toxicologist (poison center) or other medical specialist with expertise and experience treating and managing patients exposed to CCl_4, and also consulting with a gastroenterologist/hepatologist.

More information for this answer can be found in the "How Should Patients Exposed to Carbon Tetrachloride Be Treated and Managed?" section.

9. Immediate follow-up for the acutely ill patient includes monitoring liver and kidney function for up to 2 weeks. You should also periodically evaluate the patient's cardiac and pulmonary systems and clotting ability; abnormalities can occur secondary to hepatic and renal damage.

You should advise all three persons (the patient and his two coworkers) to avoid other hepatotoxic agents, such as ethanol, drugs, solvents, and chlorinated compounds. Both the 40-year-old male (with possible liver injury as a result of alcoholism and hepatitis B) who was discharged the morning after the incident and the acutely ill 25-year-old male patient might be at increased risk for hepatocellular carcinoma; they should be monitored periodically. If the 25-year-old patient's vaccinations are not up-to-date, advise him to get the hepatitis B vaccine. The 30-year-old female, who used full protective gear and whose symptoms disappeared quickly, is probably at minimal risk.

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

10. Typically, companies consult or hire health care providers with expertise in occupational health and safety to work with industrial hygienists and other

worksite health personnel to provide care and assist with development of worker health and medical surveillance programs required by the Occupational Safety and Health Administration (OSHA). This includes protocols for periodic health examinations of all employees and confidential maintenance and storage of employee medical records (which should contain a complete exposure history). Under the OSHA Hazard Communication regulation (right-to-know provisions), safety data sheets (SDSs) for hazardous chemicals in the workplace must be made available to the workers, to their physician, and to a designated worker representative. All employees using a respirator should be fit-tested and properly trained before entering a hazardous environment. Proper supervision is necessary at all times. Employees who are ill should not be allowed to remain at work, nor should employees be permitted to work without the requisite protective gear.

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

What Is Carbon Tetrachloride?

Learning Objective

After completing this section, you will be able to describe carbon tetrachloride (CCl_4).

Definition

Carbon tetrachloride (CCl_4) is a manufactured chemical that does not occur naturally in the environment. Its chemical structure is shown below:

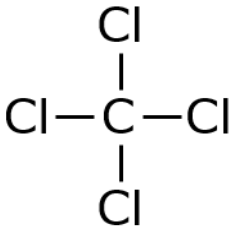

Figure 1. Carbon tetrachloride chemical structure

CCl_4 is a clear, nonflammable, heavy liquid that evaporates readily, producing a sweet characteristic odor similar to chloroform.

CCl_4 is classified as a volatile organic compound (VOC).

Properties

Although CCl_4 does not occur naturally, it is ubiquitous as a result of industrial uses. It is a stable compound, with a half-life of 6–12 months in water or soil and a half-life of 30–100 years in the atmosphere.

Synonyms

Common synonyms for carbon tetrachloride include

- Carbon tet,
- Freon 10,
- Perchloromethane,
- Tetrachloromethane.

A more detailed list of synonyms is available from: https://chem.nlm.nih.gov/chemidplus/name/carbon%20tetrachloride%20%5Bnf%5D.

Production and Usage

Historically, CCl_4 was mainly used to produce chlorofluorocarbons (CFCs), which are used as heat transfer agents in refrigerating equipment and as aerosol propellants [Holbrook 1991]. In the United States, CCl_4 was also an ingredient in many industrial fluids, and was an effective metal degreaser. It was found in household cleaning supplies and spot removers for carpets, clothing, and furniture [Doherty 2000; Odabasi 2008]. CCl_4 was also used as an antihelminthic, a grain fumigant, and a component in fire extinguishers.

Carbon tetrachloride's toxicity was recognized in the early 1900s [Abbott and Miller 1948; Hardin 1954], and most of the uses were discontinued by the mid-1960s. The U.S. Environmental Protection Agency cancelled CCl_4's use as a fumigant in 1986. In the United States, CCl_4 use is restricted to industrial and laboratory applications only [Seifert 1994; ATSDR 2005; NTP 2016]. It is not permitted in products intended for home use; however, chemicals containing CCl_4 can still be purchased online [EPA 2017].

Both the internationally ratified Montreal Protocol (which first went into effect in 1989) and the United States 1990 Clean Air Act Amendments were instrumental in reducing environmental concentrations of CCl_4 and other ozone-depleting chemicals [ATSDR 2005]. By 2009, the United States no longer regularly imported CCl_4; only 90 pounds (41 kilograms) were imported during 1996–2009. Likewise, U.S. production and export of CCl_4 dropped precipitously during this time [NTP 2016]. By 2009, only 26 manufacturers worldwide produced carbon tetrachloride, including three in the United States [NTP 2016].

Key Points

- Most industrial CCl_4 is used in the synthesis of CFCs and chlorinated solvents. Production of CCl_4 has been continuously declining in response to regulation.
- Because of CCl_4's toxicity, use in consumer products, and as a fumigant it is no longer permitted in the United States; only industrial uses and laboratory applications remain.

Progress Check

1. Which of the following statements regarding CCl_4 is correct?

   A. In the United States today, CCl_4 is used widely in the home to remove spots from clothing, furniture, and carpets.
   B. In the United States today, CCl_4 is used as a fumigant to kill insects in grain.
   C. The major use of CCl_4 has been to produce CFCs, which are used primarily as refrigerants.
   D. CCl_4 has a short half-life in the air.

   To review relevant content, see "Properties" and "Production and Usage" in this section.

Where Is Carbon Tetrachloride Found?

Learning Objective

After completing this section, you will be able to

- Identify sources of carbon tetrachloride (CCl_4) exposure.

Introduction

CCl_4 does not occur naturally, but has been released into the environment by human activities. Because of past and present releases, CCl_4 is still found in ambient air, water, and soil, but at very low background levels.

The U.S. public can be exposed to CCl_4 from ambient air. CCl_4 is one of the priority pollutants regulated by the U.S. Environmental Protection Agency (EPA) [EPA 2014].

Workers involved in the manufacture or use of CCl_4 are more likely to have significant CCl_4 exposure than are members of the general public.

Environmental Sources

Air Contamination

People can be exposed to small amounts of CCl_4 through ambient air. The 2001–2002 National Health and Nutrition Examination Survey (NHANES) reported that for the U.S. population aged 20-59 years, the 95th percentile of blood CCl_4 concentrations was 0.02

nanograms per milliliter (ng/mL). In the 2003–2008 survey, the 95th percentile of blood CCl_4 concentration had fallen to less than 0.005 ng/mL [CDC 2017].

Using an analysis of 4,913 ambient air samples reported in the National Ambient Volatile Organic Compounds Database — including remote, rural, suburban, urban, and source dominated sites in the United States — the average carbon tetrachloride concentration was 0.168 parts per billion (ppb) (1.1 µg/m³) [Shah and Heyerdahl 1988]. More recent studies demonstrate a decrease in levels of CCl_4 (0.072-0.09 ppb) in the ambient air, which could be a reflection of the current drop in production. Nevertheless, the resistance to atmospheric degradation allows for levels to remain somewhat constant [Mohamed et al. 2002].

Concentrations in indoor air are usually higher than in outdoor air. A review of 2,120 indoor air samples in the late 1980s in the United States showed that the average CCl_4 concentration was 0.4 ppb (2.6 µg/m³) [Shah and Heyerdahl 1988]. Contemporary data suggest that this remains true today. A sampling of volatile organic compounds in day-care facilities in Washington, DC, found carbon tetrachloride air concentrations ranging from undetectable to 0.24 ppb (1.6 µg/m³) [Quirós-Alcalá 2016]. Household cleaning products containing bleach can produce volatile organic compounds, including chloroform and carbon tetrachloride [Odabasi 2008]. Use of these common agents might, in part, explain elevated indoor CCl_4 concentrations.

Although overall ambient air concentrations are slowly declining, some regions might still have above-average concentrations. These include some National Priorities List (also known as Superfund) sites [EPA 2017] and the few industrial locations where CCl_4 is still manufactured or used. A searchable database of current National Priorities List sites is available at: https://cumulis.epa.gov/supercpad/cursites/srchsites.cfm.

Water and Soil Contamination

CCl_4 can contaminate water, air, and soil if it is not properly discarded. According to the 2015 Toxic Release Inventory,

- More than 5.9 million pounds of CCl_4 were recycled,
- Approximately 12,600 pounds of CCl_4 were transferred to landfills or waste management sites, and
- Approximately 140,000 pounds of CCl_4 were discharged into air, water, and soil.

Persons living near hazardous waste sites where CCl_4 is actively being released into the surrounding environment could be at higher risk for exposure to CCl_4 in soil or water supplies.

Occupational Sources

Workers involved in the manufacture or use of carbon tetrachloride are more likely to have significantly higher exposure to CCl_4 than are other persons. CCl_4 is currently used to manufacture some of the following products:

- Brake cleaners,
- Electrical equipment and machinery cleaner,s
- Industrial-strength structural and plastic adhesives,
- Perchloroethylene (also known as PERC or tetrachloroethylene),
- Reference chemicals for laboratory applications, and
- Synthetic rubbers [EPA 2017].

Key Points

- Sources of environmental contamination include industrial facilities and hazardous waste sites.
- Household cleaning products containing bleach can produce volatile organic compounds, including chloroform and carbon tetrachloride. Use of these common agents might, in part, explain elevated indoor CCl_4 concentrations.
- Workers involved in the manufacture or use of CCl_4 are more likely to have significant CCl_4

exposure than are other persons.

Progress Check

2. Which of the following scenarios has/have the potential to increase the risk for overexposure to carbon tetrachloride?

   A. Living in areas near hazardous waste sites where discharges into air, water, or soil are not properly controlled.
   B. Exposure to CCl_4 contaminated indoor air.
   C. Working in manufacturing plants involved in the manufacture or use of CCl_4.
   D. All of the above.

   To review relevant content, see all content in this section.

What Are Routes of Exposure to Carbon Tetrachloride?

Learning Objective

After completing this section, you will be able to

- Identify the routes of exposure to carbon tetrachloride (CCl_4).

Introduction

Inhalation is the primary means of exposure to CCl_4. Rarely, people might ingest contaminated drinking water or absorb CCl_4 through skin contact.

Inhalation

Inhalation is the most common route of exposure to CCl_4.

Exposure can occur through breathing contaminated air

- During work with CCl_4 or
- While near others who are working with CCl_4.

CCl_4 might also be inhaled from

- Accidental spills or product use in small, enclosed spaces,
- Landfills in which it was disposed,
- Releases to air and water by evaporation or emissions from industrial plants, or
- Using contaminated tap water for bathing and other household purposes.

Adolescents and others might be exposed to carbon tetrachloride by intentionally inhaling hydrocarbons.

Ingestion

Exposure to carbon tetrachloride by ingestion can occur through consumption of contaminated drinking water or food.

Exposure from contaminated food is possible, but is not likely to be of much significance, because levels of carbon tetrachloride in most foods are below the limit of detection [NTP 2016]. Intentional ingestions of carbon tetrachloride in homicide or suicide attempts are beyond the scope of this case study.

Dermal

Although CCl_4 is absorbed through the skin [Stewart and Dodd 1964; Morgan et al. 1991], no studies to date suggest that dermal absorption from contaminated water, air, or soil is a significant route of human exposure. However, direct skin exposure to a high dose of CCl_4 can cause systemic effects (i.e., respiratory, cardiovascular, gastrointestinal, hepatic, renal, ocular, and dermal) in humans [ATSDR 2005; Gummin 2015].

Key Points

- Inhalation of contaminated air is the most common route of exposure to carbon tetrachloride in the United States.

Progress Check

3. Which of the followings is (are) the most common route(s) of exposure to carbon tetrachloride in the United States?

   A. Inhalation.
   B. Ingestion.
   C. Skin contact.
   D. Inhalation and ingestion.

   To review relevant content, see all content in this section.

Who Is at Risk for Exposure to Carbon Tetrachloride?

Learning Objective

After completing this section, you will be able to

- Identify who is at risk for exposure to carbon tetrachloride (CCl_4).

Introduction

Exposures that occur to workers involved in the manufacture or use of CCl_4 are potentially higher than exposures occurring in the general U.S. population.

People living near waste sites or areas of heavy carbon tetrachloride use might have an increased risk for exposure from contaminated media (air, water, or soil).

Workers

Workers employed in industries that manufacture or use CCl_4 are at greater risk for exposure to higher levels of CCl_4 than the general U.S. population.

Workers who might be exposed to CCl_4 include:

- Air transportation workers,
- Hazardous waste workers,
- Museum workers,
- Pharmaceutical manufacturers,
- Steel mill and blast furnace workers,
- Telephone and telegraph equipment manufacturers, and
- Workers in tin-waste recovery operations.

Other workers who no longer use CCl_4, such as the following, might have been exposed in the past:

- Automobile mechanics,
- Dry cleaners,
- Grain workers (inspection, storage, milling, processing), and
- Pesticide applicators.

Special Populations

Subsets of the U.S. population, such as people who live near hazardous waste sites or facilities that use or manufacture CCl_4, might be exposed to localized higher air concentrations of CCl_4.

General Populations

Because background levels of CCl_4 in ambient air are low and continue to decline, the U.S. general population is not likely to be exposed to large amounts of carbon tetrachloride. The 2015 annual report of the American Association of Poison Control Centers documented 52 CCl_4 exposures that had no major outcomes [AAPCC 2015].

Key Points

- Workers using CCl_4 or CCl_4-containing products are potentially at risk for exposure to higher levels of CCl_4 than the general U.S. population.
- People who live near hazardous waste sites or facilities that use or manufacture CCl_4, might be exposed to localized higher air concentrations of CCl_4.

Progress Check

4. Of the following, who is at risk for CCl_4 exposure? **Select the best answer.**

   A. Workers using CCl_4 or CCl_4-containing products.
   B. Residents near industrial locations where CCl_4 is used.
   C. People living near chemical waste sites where emissions to the environment might occur.
   D. All of the above.

   To review relevant content, see all content in this section.

What Are Guidelines and Regulations for Carbon Tetrachloride Exposure?

Learning Objectives

After completing this section, you will be able to

- Describe current U.S. guidelines and regulations for carbon tetrachloride (CCl_4) exposure.

Introduction

The U.S. government has developed regulations and guidelines for CCl_4. These are designed to protect workers and the U.S. public from potential adverse health effects from CCl_4 exposure. Table 1 summarizes the regulations and guidelines pertaining to CCl_4.

**Note: At the time of publication of this CSEM, the listed guidelines and regulations were up to date. Guidelines and regulations are subject to change. For the most up-to-date information, see the following websites:*

- *Occupational Safety and Health Administration (OSHA): https://www.osha.gov/dsg/annotated-pels/tablez-2.html*
- *National Institute of Occupational Safety and Health (NIOSH): https://www.cdc.gov/niosh/npg/npgd0107.html*
- *Environmental Protection Agency (EPA): https://nepis.epa.gov*
- *Food and Drug Administration (FDA): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=165.110*

Workplace Standards

Air

The Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) is an 8-hour time-weighted average (TWA) of 10 parts per million (ppm) in workplace air. This is the highest level of CCl_4 in air to which a worker may be exposed, averaged over an 8-hour workday for up to a 40-hour workweek.

The National Institute for Occupational Safety and Health (NIOSH) recommends a 60-minute time-weighted average (TWA) short-term exposure limit (STEL) of 2 ppm [NIOSH 2005]. The NIOSH immediately dangerous to life and health (IDLH) value for CCl_4 is 200 ppm.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends an 8-hour TWA of 5 ppm and a 15-minute STEL of 10 ppm [ACGIH 2017].

Environmental Standards

Air

CCl_4 is on the list of 187 hazardous air pollutants listed in the Clean Air Act. The U.S. Environmental Protection Agency (EPA) classifies CCl_4 as a hazardous air pollutant [EPA 2014].

Water

The EPA maximum contaminant level (MCL) for CCl_4 in drinking water is 5 ppb [EPA 2008].

Federal regulations have banned the use of all pesticide products containing CCl_4. An exception is the use of CCl_4 on encased museum specimens.

Food

The U.S. Food and Drug Administration (FDA) classifies carbon tetrachloride as an indirect food additive for use only as a component of adhesives. FDA also monitors bottled water and uses a level of 5 µg/L as acceptable for bottled water [FDA, 2017].

Table 1. Regulations and Guidelines for Carbon Tetrachloride

Agency	Focus	Level	Comments
American Conference of Governmental Industrial Hygienists (ACGIH)	Workplace air	5 ppm (31 mg/m^3)	Advisory: 8-hour TLV-TWA* 10 ppm (63 mg/m3) = 15-minute TWA STEL†; skin absorption notation
National Institute for Occupational Safety and Health (NIOSH)	Workplace air	2 ppm (12.6 mg/m^3)	Advisory: REL‡ (60-minute STEL†)
Occupational Safety and Health Administration (OSHA)	Workplace air	10 ppm	Regulation: PEL§ as 8-hour TWA; 25 ppm = acceptable ceiling¶ concentration; 200 ppm = acceptable maximum peak above the acceptable ceiling concentration for an 8 hour shift (max duration = 5 minutes in any 4 hours).
U.S. Environmental Protection Agency (EPA)	Drinking water	5 ppb (0.005 mg/L)	Regulation: current MCL**

U.S. Food and Drug Administration (FDA)	Food: Bottled drinking water allowable Indirect food additive: adhesives	 5 µg/L Yes	Regulation

*TLV-TWA (threshold limit value–time-weighted average) — ACGIH TLVs are listed in the order of 8-hour time-weighted averages (TWAs during a 40-hour workweek, unless otherwise indicated), short-term exposure limits, and ceilings levels, if available. A TLV is a level to which it is believed a worker can be exposed day-after-day for a working lifetime without adverse health effects. These are not regulatory limits unless OSHA adopts them as a PEL.

†STEL (short-term exposure limit) — Unless noted otherwise, the STEL is a 15-minute TWA maximum exposure that should not be exceeded at any time during a workday (a single work shift) to prevent adverse health effects.

‡REL (recommended exposure limit) — NIOSH RELs are for up to 10-hour TWAs during up to a 40-hour work week, unless otherwise indicated (can also be a STEL or ceiling limit). These are not regulatory limits.

§PEL (permissible exposure limit) — OSHA PELs are 8-hour TWAs, unless otherwise indicated (can also be short-term exposure limits (STEL) or ceiling limits). The PEL represents an employee's average airborne exposure in any 8-hour work shift of a 40-hour work week, which shall not be exceeded. OSHA enforces these limits under section 5(a)(2) of the Occupational Safety and Health Act. The 8-hour TWA PEL is the level of exposure established as the highest level of exposure an employee may be exposed to without incurring the risk for adverse health effects.

¶Ceiling limit — A ceiling limit, unless otherwise noted, is a maximum concentration level of exposure that should not be exceeded at any time during a workday in an effort to prevent adverse health effects.

**MCL (maximum contaminant level) — The highest level of a contaminant that is allowed in drinking water.

Key Points

- The U.S. government has developed regulations and guidelines for CCl_4.

Progress Checks

5. Which of the following statements is **FALSE** regarding U.S. regulations and guidelines for CCl_4 levels?

   A. Federal regulations allow continued use of pesticide products containing CCl_4.
   B. EPA has set a maximum contaminant level for CCl_4 in drinking water.
   C. NIOSH has recommended a 60-minute exposure limit on CCl_4 exposure at the workplace.
   D. None of the above.

   To review relevant content, see all content in this section.

What Is the Biologic Fate of Carbon Tetrachloride in the Body?

Learning Objective

After completing this section, you will be able to

- Describe the characteristics of carbon tetrachloride (CCl_4) metabolism.

Introduction

CCl_4 is well absorbed from the respiratory and gastrointestinal tracts. Dermal absorption of liquid is possible, but dermal absorption of the vapor is limited. Absorbed CCl_4 is distributed throughout the whole body, with highest concentrations in liver, brain, kidney, muscle, fat, and blood.

CCl_4 is primarily metabolized in the liver, where it is transformed by cytochrome P450 enzymes to a toxic metabolite.

Any unchanged parent compound is eliminated primarily in exhaled air.

Absorption

Pulmonary: Absorption from the lung was estimated to be about 60% in humans [Lehmann and Schmidt-Kehl 1936; Astrand 1975].

Gastrointestinal: Results from several animal studies have shown that CCl_4 is rapidly and extensively absorbed from the gastrointestinal tract [Paul et al. 1963; Kim et al. 1990].

Dermal: Liquid CCl_4 is readily absorbed through the skin of humans. A study showed that immersion of both hands in liquid CCl_4 for 30 minutes would yield an exposure equivalent to breathing 100–500 ppm for 30 minutes [Stewart and Dodd 1964].

Distribution

CCl_4 is distributed to all organs [Bergman 1983; Paustenbach et al. 1986], and concentrates in the

- Fat,
- Liver,
- Bone marrow,
- Adrenals,

- Blood,
- Brain,
- Spinal cord, and
- Kidney.

Metabolism

Carbon tetrachloride is metabolized primarily in the liver.

The first step in metabolism is a phase I dehalogenation reaction, which converts CCl_4 to the trichloromethyl radical ($\bullet CCl_3$). This reaction is governed primarily by the cytochrome P450 isoform CYP2E1, though additional isoforms such as CYP3A4 can also metabolize CCl_4 when it is present in high concentrations [Slater 1984; Slater et al. 1985; Recknagel et al. 1989; Weber et al. 2003]. The centrilobular localization of CYP2E1 in the liver explains the histopathological findings of CCl_4-induced liver damage, which will be discussed in the following section ("What Are the Toxicological Effects of Carbon Tetrachloride?").

The $\bullet CCl_3$ radical can have several different fates (see Figure 2). It might

- React with intracellular molecules to cause lipid peroxidation and other forms of oxidative damage,
- Be converted to the trichloromethyl peroxy radical, $\bullet OOCCl_3$ [Weber et al. 2003],
- Acquire a hydrogen atom to form chloroform ($CHCl_3$),
- Combine with other $\bullet CCl_3$ radicals to form hexachloroethane (Cl_3CCCl_3), or
- Be further metabolized to carbon dioxide (CO_2) by successive oxidation reactions.

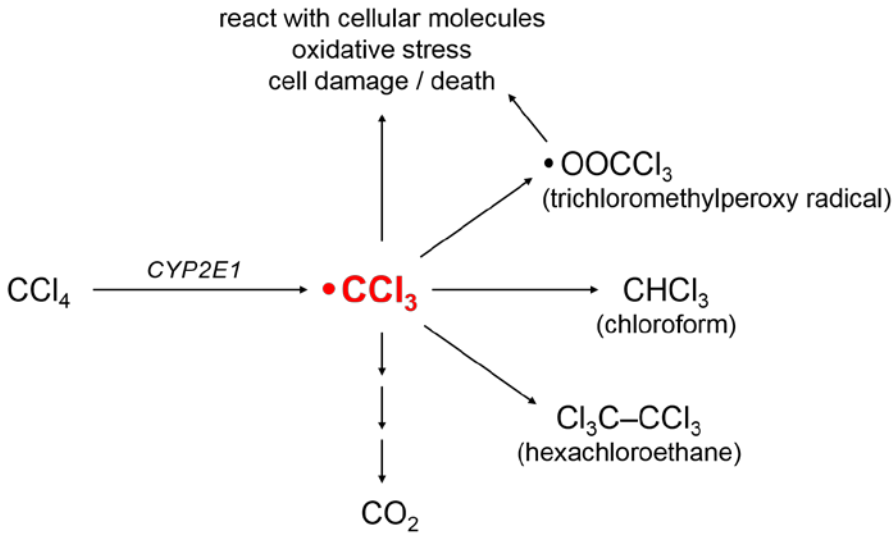

Figure 2. *Common metabolic fates of •CCl_3.*

One animal model estimates that 60% of an inhaled dose of CCl_4 is metabolized, and the remaining 40% is excreted unchanged. Approximately 96% of this metabolized CCl_4 generates free radicals, as described above; the remaining 4% is ultimately converted to CO_2 [Paustenbach et al. 1988].

Excretion

Animal studies evaluated elimination of carbon tetrachloride following oral or inhalation exposures. In rats receiving equivalent doses by inhalation or bolus gavage, terminal elimination half-lives (t1/2) were about 4 hours [EPA 2010].

In humans and animals exposed to carbon tetrachloride by any route, most of the unmetabolized parent compound is excreted in exhaled air. Animal studies show that volatile metabolites (such as chloroform [$CHCl_3$]) are released in exhaled air, whereas its nonvolatile metabolites are excreted in feces and, to a lesser degree, in urine [EPA 2010].

Key Points

- CCl_4 is well-absorbed by inhalation, ingestion, and dermal absorption.
- CCl_4 is metabolized primarily in the liver to the trichloromethyl free radical (•CCl_3).

- Approximately 40% of a CCl_4 dose is eliminated unchanged in exhaled air.

Progress Check

6. Which of the following statements about the biologic fate of CCl_4 is **NOT** correct?

   A. Absorption across the lung was estimated to be about 60% in humans.
   B. Once absorbed, CCl_4 is evenly distributed to all organs in the body.
   C. Carbon tetrachloride is metabolized primarily in the liver.
   D. Most of the unmetabolized parent compound is excreted in exhaled air.

   To review relevant content, see all content in this section.

What Are the Toxicological Effects of Carbon Tetrachloride Exposure?

Learning Objective

After completing this section, you will be able to

- Describe the toxicological effects associated with carbon tetrachloride (CCl_4) exposure.

Introduction

The primary effects of CCl_4 in humans are on the central nervous system (CNS), liver, and kidneys. Symptoms of acute inhalation or ingestion of CCl_4 include

- Headache,
- Weakness,
- Nausea, and
- Vomiting.

Chronic exposure to carbon tetrachloride — and sometimes acute exposure to very high concentrations — produces liver and kidney damage [EPA 2000].

Neurologic Effects

Acute Effects

The immediate effect of acute CCl_4 exposure by all routes is CNS depression [Laine and Riihimaki 1986].

The intensity of the effects is proportional to exposure dose. Symptoms can include initial euphoria and disinhibition, followed by

- Dizziness,
- Nausea and vomiting,
- Incoordination,
- Paresthesia,
- Increased salivation, and
- Tachycardia.

The symptoms are generally transient, disappearing quickly after the exposure ends. Higher-dose exposures, however, can lead to

- Respiratory depression (as a result of CNS depression),
- Seizures,
- Coma, and
- Death [Rom and Markowitz 2007].

In fatal cases, autopsies reveal permanent damage to nerve cells, with focal areas of fatty degeneration and necrosis [Stevens et al. 1953; Cohen 1957].

Chronic Effects

The CNS effects of chronic exposure are open to question. Many of the impairments observed in workers chronically exposed to solvents could be attributable to other causes [Rom and Markowitz 2007], such as

- Chronic alcohol abuse,
- Other neurologic disorders, or
- Injuries.

Chronic neurologic effects can be classified as follows:

- Mild — consisting mainly of affective changes and loss of concentration,
- Moderate — with some impairment of concentration and memory, or
- Severe — with significant loss of intellectual functioning [WHO 1985].

Sensorimotor neuropathy and abnormalities of vision have been reported, but epidemiological data are insufficient to support an association between CCl_4 exposure and these effects [O'Donoghue 2000].

Hepatic Effects

Liver damage occurs more often from swallowing liquid CCl_4 than from inhaling CCl_4 vapor [Hathaway et al. 1991]. Direct skin exposure to high doses of CCl_4 can also cause hepatic effects in humans [ATSDR 2010; Gummin 2015].

Acute hepatic injury usually manifests after CNS effects have subsided, typically 1 to 4 days after acute exposure. Chronic hepatic injury (cirrhosis) takes longer to develop.

The typical signs of liver injury are nonspecific and include

- Swollen and tender liver (acute);
- Elevated levels of hepatic enzymes (e.g., AST and ALT);
- Elevated serum bilirubin levels, with or without jaundice;
- Decreased serum levels of proteins, such as albumin and fibrinogen; and
- Elevated prothrombin time (PT) or international normalized ratio (INR).

Acute exposure to CCl_4 causes a hepatocellular pattern of injury, with elevated AST and ALT and primarily centrilobular (zone 3) damage. This occurs because CYP2E1 enzymes are concentrated in the perivenous (zone 3) region of the hepatic acinus, and accordingly, the highest concentrations of $\bullet CCl_3$ are produced in this region first. In cases of lethal exposures, this histologic variation in injury is lost, and pronounced diffuse hepatic steatosis and frank liver necrosis can occur.

In the case of chronic exposure, ongoing subclinical cell death promotes activation of stellate cells and collagen deposition. Over time, this results in fibrosis and cirrhosis. As hepatic synthetic function fails, a decrease in clotting factors might predispose the patient to hemorrhage [Zimmerman and Ishak 2002; ATSDR 2005]. Additionally, continual oxidative stress from $\bullet CCl_3$ causes DNA damage, protein malfunction, and disrupted calcium homeostasis. These mechanisms, in addition to increased cell death and turnover, are thought to lead to steatosis and carcinogenesis [Palmer and Phillips 2007].

Persons at increased risk for CCl_4 induced hepatotoxicity

The toxic metabolites of CCl_4 are produced from reactions catalyzed by cytochrome P450 enzymes, particularly CYP2E1 and CPY3A4 [Zimmerman 1986; Recknagel et al. 1989; Weber et al. 2003; Manibusan et al. 2007]. Although no human data clearly define the relationship between CYP2E1 or CYP3A4 activity and CCl_4 toxicity, animal studies have shown that CYP2E1 activity is positively correlated with the degree of CCl_4-induced hepatotoxicity [Wong et al. 1998; Dai et al. 2014]. Thus, patients with a history of chronic, heavy alcohol intake (which induces CYP2E1) or patients who are on medications known to induce CYP3A4 (e.g., barbiturates, protease inhibitors) might be at increased risk for free radical damage resulting from increased bioactivation of CCl_4.

Renal Effects

Nephritis and nephrosis are common following CCl_4 exposure. A number of derangements might appear within hours to days after exposure:

- Proteinuria,
- Hemoglobinuria,
- Glucosuria,
- Oliguria, and/or
- Anuria.

The mechanism of nephrotoxicity is thought to be similar to the pathophysiology of liver toxicity: bioactivation by cytochrome P450 enzymes to the $\bullet CCl_3$ radical, with resulting oxidative injury [Abraham et al. 1999; Ozturk et al. 2003]. The intracellular and cell membrane damage is seen as proximal tubule cell edema and vacuolization, protein leakage into the tubule lumen, glomerular necrosis, and interstitial hemorrhage [Elmubarak 2015; Yoshioka et al. 2016; Yoshioka et al. 2016].

Respiratory Effects

Pulmonary effects can occur through various means of exposure:

- Inhalation [Kirkpatrick and Sutherland 1956; Love and Miller 1951],
- Oral [Ruprah 1985], and/or
- Parenteral [Das et al. 2014; Ferrari et al. 2012; Zhang et al. 2014].

Signs of respiratory damage appear to be exceedingly rare in human case reports. However, autopsies of humans and pathological evaluations in animal studies consistently show numerous gross and histological findings, including:

- Pulmonary edema,
- Interstitial and alveolar hemorrhage,
- Epithelial cell damage and death,
- Alveolar infiltrates,
- Damage to pulmonary vasculature,
- Alveolar wall thickening, and
- Fibrosis [Naz et al. 2014; Taslidere et al. 2014].

The mechanism of pulmonary toxicity is multifactorial and includes:

- Direct bioactivation of CCl_4 to $\bullet CCl_3$ and other free radicals by cytochrome P450 enzymes in the lung parenchyma [Boyd 1980], specifically by CYP2E1 [Gundert-Remy et al. 2014],
- Hepatopulmonary syndrome [Zhang et al. 2014], and
- Direct and indirect oxidative stress [Das et al. 2014; Ferrari et al. 2012].

Carcinogen -ic Effects

A number of epidemiological studies have evaluated the association between occupational exposure to CCl_4 and cancer risk. Evidence remains inadequate to make definitive conclusions about the carcinogenicity of carbon tetrachloride in humans [IARC 1999; ATSDR 2005; NTP 2016].

In animal studies [IARC 1999; Manibusan et al. 2007; Nagano et al. 2007], CCl_4 has induced hepatocellular carcinomas in rodents via all exposure routes. With sufficient evidence of carcinogenicity in experimental animals such as this, and limited evidence of carcinogenicity in humans, various agencies have concerns about the risks for cancer from CCl_4 exposure.

- The International Agency for Research on Cancer [IARC 1999] has determined that CCl_4 is *possibly* carcinogenic to humans (Group 2B).
- The National Institute for Occupational Safety and Health (NIOSH) has identified CCl_4 as a *potential* occupational human carcinogen [NIOSH 2005].
- The American Conference of Governmental Industrial Hygienists (ACGIH) considers CCl_4 to be a *suspected* human carcinogen [ACGIH 2016].
- The National Toxicology Program reports that CCl_4 is *reasonably anticipated* to be a human carcinogen [NTP 2016].

Genotoxic and Mutagenic Effects

CCl_4 has been extensively studied for its genotoxic and mutagenic effects, with largely negative results. When such changes have been seen, they have generally been related to hepatic cytotoxicity. Mutagenic effects, if they occur, would likely be generated through indirect mechanisms resulting from oxidative and lipid peroxidative damage [ATSDR 2005; Manibusan et al. 2007].

Developmental and Reproductive Effects

No information is available on the reproductive effects of CCl_4 in humans. Epidemiological studies have investigated possible associations between oral exposure to carbon tetrachloride and various adverse birth outcomes [Croen et al. 1997; Bove et al. 1995, 1992a, 1992b]. Because of multiple chemical exposures and insufficient power, these studies are considered limited and insufficient to determine whether carbon tetrachloride exposure and adverse birth outcomes are associated [EPA 2010]. CCl_4 can induce embryotoxic and embryo lethal effects, but only at doses that are toxic to the mother, as observed in the inhalation studies in rats and mice. No adequate reproductive toxicity studies have been conducted in animals exposed by the oral route. Teratogenicity has not been observed in the offspring of rats orally exposed to CCl_4 [ATSDR 2005; WHO 1999; EPA 2010].

Cardiac Effects

Most case reports of human CCl_4 toxicity do not have cardiovascular injury as a predominant feature. However, volatile hydrocarbons, particularly the *halogenated* hydrocarbons, are associated with cardiac dysrhythmias and sudden sniffing death [Adgey 1995; Williams and Cole 1998]. The mechanism is not fully known, but is thought to involve “sensitization” of the myocardium to the effects of catecholamines, increasing heart rate, QT dispersion, and the rate of after-depolarizations. A large acute exposure to CCl_4 could possibly produce similar clinical effects.

Case reports have described cardiomegaly, congestive heart failure, and cardiac fibrosis after exposure to CCl_4. The cardiac effects are thought to occur largely secondary to the fluid overload caused by hepatic and renal damage.

More recently, multiple cytochrome P450 enzymes have been found in cardiac tissue, including the CYP 2E family of isoenzymes [Chaudhary et al. 2009]. Though the exact role of each CYP isoform in myocardial cells is not yet clear, many of these appear to be involved in lipid and drug metabolism. Rodents exposed to CCl_4 demonstrate increased markers of inflammation, myocyte injury (troponin, CK-MB) [Al-Rasheed et al. 2014], and oxidative stress in the heart [Manna et al. 2007; Jayakumar et al. 2008]. These biochemical changes might reflect a systemic increase in oxidative stress caused by CCl_4, local bioactivation of CCl_4 with resulting myocardial damage, or both.

Other Effects

Common gastrointestinal effects of exposure to CCl_4 include

- Nausea,
- Vomiting, and
- Abdominal pain.

Prolonged or repeated contact of skin with liquid CCl_4 can cause defatting of the skin and dermatitis, with redness and blister formation [NIOSH 1995].

Key Points

- The immediate effect of acute CCl_4 exposure by all routes is CNS depression.
- The NTP classified CCl_4 as “reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals” [NTP 2016].

Progress Checks

7. Which of the following is considered an immediate effect after acute exposure by all routes to CCl_4?

   A. Acute hepatitis.
   B. Acute renal failure.
   C. CNS depression.
   D. Pulmonary fibrosis.

   To review relevant content, see "Neurologic Effects," "Hepatic Effects," "Renal Effects," and "Respiratory Effects" in this section.

8. Which of following statements on carcinogenicity of CCl_4 is **NOT CORRECT**?

   A. CCl_4 is a possible human carcinogen.
   B. CCl_4 is a known animal carcinogen.
   C. Animal studies have shown that CCl_4 induces hepatocellular carcinomas in rodents by oral, inhalation, and skin exposure.
   D. Human studies have conclusive data on the carcinogenic effects of CCl_4.

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

Clinical Assessment – History and Physical Exam

Learning Objectives

After completing this section, you will be able to

- Describe what is included in the initial history and physical exam of patients potentially exposed to carbon tetrachloride (CCl_4).

Introduction

Symptoms and signs potentially associated with CCl_4 exposure are nonspecific making a careful medical and exposure history essential to diagnosis.

The initial history and physical exam of patients potentially exposed to CCl_4 can be used to

- Determine possible sources and pathways of exposure to CCl_4,
- Detect symptoms and signs that could be attributable to CCl_4 exposure, and
- Reveal history of any preexisting or underlying condition(s) that might complicate the diagnostic and clinical approach to the patient.

This information guides development of a differential diagnosis and selection of laboratory/imaging studies, which are discussed in the next section.

Patient History

An exposure history should be taken as part of the patient medical history. This should cover occupational and non-occupational CCl_4 exposure risks.

See the “Sources of Additional Information” section later in this CSEM for links to ATSDR’s Taking an Exposure History CSEM, Taking a Pediatric Exposure History CSEM, and Pediatric Principles CSEM.

Additionally, a link is provided to the Exposure History Form, which is available for download in a "fillable" PDF form that can be printed and saved:
Exposure History Form [PDF - 455 KB).

Environmental Exposure History

An environmental exposure history (non-occupational) for CCl_4 can be used to obtain the following information:

- Type of water supply,
- Location and duration of residence,
- Proximity to industry or National Priorities List (NPL) sites or both,
- The patient's hobbies, and
- History of exposure to other known hepatotoxic agents (e.g., medications and alcohol) .

Occupational Exposure History

The patient's occupational history is crucial. The information on the current occupation would be most valuable, especially in cases of acute toxicity. For each job held, the exposure history should include:

- Name and location of the company,
- Job title,
- Description of chemical processes used,
- Known toxic agents,
- History of worker illness,
- Enclosure of solvent-related processes,
- Use of hood or other ventilation, and
- Proper use of personal protective equipment (PPE).

Information on the specific constituents of the solvent-containing materials and other potentially hazardous substances used should be collected. This might necessitate requests for Safety Data Sheets (SDSs) from employers, suppliers, or manufacturers. Use and type of personal protective equipment should be determined. The occupational history should also include the patient's general assessment of the hygienic conditions of the work setting, including the availability of separate washing, changing, and eating facilities. Information about potential exposure(s) from the activities of coworkers should also be gathered from the patient.

Medical History

Medical history and a review of systems should include assessments of current and past diagnoses or symptoms of

- Neurologic,
- Hepatic,
- Renal, and
- Dermatologic disease.

It is important not to overlook the association between solvent exposure and conditions such as

- Glomerulonephritis,
- Contact dermatitis,
- Cognitive impairment, and
- Peripheral neuropathy [Rom and Markowitz 2007].

Patient's alcohol use should also be evaluated.

The patient's complaints should be identified in terms of

- Onset,
- Duration,
- Frequency and
- Intensity.

Symptoms that vary in time with exposure are a function of the anesthetic property of organic solvents. Specially, dizziness, light-headedness, impaired concentration, and headaches that have a temporal relationship to solvent exposure are likely the result of acute CNS effects [Meredith et al. 1989; Rom and Markowitz 2007]. These symptoms are likely to resolve quickly after removal from the contaminated environment into a fresh air environment and might significantly improve or resolve by the time the patient is evaluated at a health care facility.

Physical Examination

After an acute exposure, the initial physical examination should concentrate on the neurologic system. Within 1 to 6 days after an acute exposure, the patient might develop severe hepatic necrosis and renal failure, which

can affect the cardiovascular and pulmonary systems.

When performing the physical exam, emphasis should be placed on major organ systems likely affected by exposure to CCl_4 (e.g., CNS, gastrointestinal, dermal, and hepatic). Note that lack of clinical findings on initial exam does not exclude potential carbon tetrachloride toxicity. The patient might show subclinical, delayed, or individual variability in the initial presentation.

Vital signs should be recorded, especially noting any abnormalities of heart rate or rhythm. Head, eyes, ears, nose, and throat should be examined noting any inflammation or irritation. The skin should be inspected, especially the hands, for signs of

- Redness,
- Drying,
- Cracking, or
- Fissuring.

Also check for signs of jaundice.

Chest examination should include assessment of the heart and lungs.

Abdominal exam should include palpation for liver and spleen size (i.e., hepatomegaly, hepatosplenomegaly, etc.) and tenderness.

A mental status examination should be conducted to evaluate

- Alertness,
- Orientation,
- Cognition, and
- Short-term memory.

Peripheral nerve function should be evaluated by assessing

- Proprioception,
- Deep tendon reflexes,
- Motor strength,

- Postural stability (Romberg test), and
- Cutaneous sensibility to vibration, light touch, and pin prick (which should always be included in the evaluation).

Key Points

- The occupational and environmental exposure history is essential to diagnosing CCl_4 toxicity.
- The physical examination should focus on major organ systems likely affected by exposure to CCl_4 (e.g., CNS, gastrointestinal, dermal, and hepatic).

Progress Checks

9. Which of the following is true regarding goals of the initial history and physical exam of patients potentially exposed to CCl_4?

   A. To determine possible sources and pathways of exposure to CCl_4.
   B. To detect symptoms and signs that might be attributable to CCl_4 exposure.
   C. To obtain a history of any preexisting or underlying condition that might complicate the diagnostic and clinical approach to the patient.
   D. All of the above.

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

10. In general, patients over-exposed to CCl_4 by any route **PREDOMINANTLY** exhibit which of the following manifestations?

    A. CNS depression.
    B. Hepatomegaly.
    C. Pulmonary edema.
    D. Nephritis.

    To review relevant content, see "Possible Signs and Symptoms of CCl4 Toxicity" in this section.

Clinical Assessment — Laboratory Tests

Learning Objective

After completing this section, you will be able to

- Describe tests that may assist with diagnosis of carbon tetrachloride (CCl_4) toxicity.

Introduction

The laboratory evaluation for patients exposed to CCl_4 should be guided by a careful, thorough history and physical exam. Indiscriminate testing for all exposures is not warranted.

Direct Biologic Indicators

According to the results of the National Health and Nutrition Examination Survey (NHANES), the 95th percentile of blood CCl_4 concentrations was less than 0.005 ng/mL in the 2003–2008 survey years for the U.S. population aged 20–59 years [CDC 2017]. These concentrations reflect the known background exposure of the U.S. population.

While it is *technically* possible to measure CCl_4 in blood and exhaled air, these tests are not routinely recommended and are very rarely done due to practical and clinical limitations. Interpretation of CCl_4 concentrations is not straightforward. No human data explicitly associate specific organ damage with a given CCl_4 concentration in blood. The clinical response to a given exposure can also vary substantially from person-to-person. Thus, a patient's quantitative CCl_4 result cannot be correlated with clinical symptoms. Unless needed to confirm *recent, excessive* exposure, quantitative testing of CCl_4 in biological samples is not indicated because the results do not guide clinical management. If you are concerned that your patient needs such testing, referral to specialty providers in occupational medicine, medical toxicology, or environmental medicine is indicated.

Indirect Biologic Indicators

Testing for end-organ damage may be considered for patients who provide a history of potential above-background CCl_4 exposures.

Hepatic damage may be assessed with the following studies:

- Alanine aminotransferase (ALT [SGPT]),
- Aspartate aminotransferase (AST [SGOT]),
- Alkaline phosphatase,
- Serum albumin and total protein,
- Prothrombin time (PT) and/or international normalized ratio (INR), and
- Partial thromboplastin time (PTT).

Imaging studies, such as ultrasound or computed tomography (CT) scan, may also be considered.

Renal damage may be assessed with the following studies:

- Blood urea nitrogen (BUN) and serum creatinine (Cr),
- Chemistry panel to check electrolytes,
- Urinalysis (to assess for the presence of protein, blood, casts, or other findings suggestive of tubular or glomerular damage), and
- Complete blood count (CBC) to evaluate for anemia.

Imaging studies, such as renal ultrasound or CT scan, may also be considered.

Respiratory symptoms may be assessed as follows:

- Obtain a chest radiograph to evaluate for pulmonary edema,
- Institute continuous cardiac and respiratory monitoring with continuous pulse oximetry, and
- Consider arterial or venous blood gas analysis as warranted by patient's clinical condition.

An electrocardiogram (ECG) should be obtained for any patient with acute CCl_4 exposure.

It is critical to consider the role of confounding medical problems (e.g., diabetes mellitus, hypertension, structural or ischemic heart disease) and other exposures (e.g., alcohol, hepatotoxic medications) when interpreting these results.

Key Points

- Laboratory results need to be interpreted carefully within the context of other pertinent clinical information.

Progress Check

11. The following statements about laboratory tests are all correct **EXCEPT**:

    A. The laboratory evaluation for patients exposed to CCl_4 should be guided by a careful, thorough history and physical exam.
    B. A patient's quantitative CCl_4 result is correlated with clinical symptoms.
    C. Testing for end-organ damage may be considered for patients who provide a history of potential above-background CCl_4 exposures.
    D. It is critical to consider the role of confounding medical problems and other exposures when interpreting nonspecific laboratory results.

    To review relevant content, see all content in this section.

How Should Patients Exposed to Carbon Tetrachloride Be Treated and Managed?

Learning Objective

After completing this section, you will be able to

- Describe treatment strategies for patients with carbon tetrachloride (CCl_4) poisoning.

Introduction

Treatment for acute or chronic CCl_4 poisoning is primarily symptomatic and supportive.

Acute Exposure

Because liquid CCl_4 can be absorbed through the skin, remove clothing from persons exposed through this route and clean the skin with copious amounts of soap (or mild detergent) and water. If liquid CCl_4 is splashed in the eyes, irrigate the eyes for at least 15 minutes.

For patients who have ingested CCl_4, the practical value of gastric lavage and administration of activated charcoal is doubtful as absorption from a gastro-intestinal exposure is likely to be nearly complete by the time the patient reaches appropriate medical care. Patients with significant exposure might be clinically unstable and gastric lavage and/or activated charcoal might place the patient at increased risk for complications such as aspiration and chemical pneumonitis.

Induced emesis is contraindicated because of the risk for pulmonary aspiration.

Human case reports from Europe, where antioxidants such as

- Methionine,
- Cysteine, and
- N-acetylcysteine (NAC, Mucomyst, or Acetadote)

were used, suggest that when these free-radical scavengers are given intravenously within 12 to 16 hours after a high-dose acute CCl_4 exposure, they might prevent or decrease hepatic and renal damage [De

Ferreyra et al. 1974; De Ferreyra et al. 1977; Prescott et al. 1977; Kearney 2007].

Elevated oxygen concentrations in vitro and in vivo reduce lipid peroxidation and hepatotoxicity. Hyperbaric oxygen (HBO) has been found to play a therapeutic role in human and animal CCl_4 poisoning [Larcan et al. 1973; Truss et al. 1982; Burk et al. 1986; Burkhart et al. 1991]. HBO appears to inhibit the mixed function oxidase system responsible for conversion of CCl_4 to hepatotoxic free radicals. Because there are no proven antidotes for CCl_4 poisoning, HBO may be considered for potentially severe CCl_4 exposures. However, there might be a delicate balance between oxidative processes that are therapeutic and those that mediate hepatotoxicity. Therefore, when HBO is being considered, it should be instituted before the onset of liver function abnormalities [Thom 2006].

Hemodialysis has been used to treat renal failure, but it has not been proven successful in reversing CCl_4 pathology [Meredith 1989; Ruprah 1985].

Patients should be observed for onset of hepatic and renal effects for up to 2 weeks after exposure. To a large extent, survival depends on the patient's nutritional status and the underlying condition of the hepatorenal system.

Chronic Exposure

Other than removal from the source of exposure and avoidance of other hepatotoxins, there is no specific treatment for patients chronically exposed to CCl_4. The exposure dose along with individual risk factors will contribute to the likelihood of lasting adverse health effects from CCl_4 exposure.

Exposed patients should be instructed to avoid

- Stimulants,
- Ethanol,
- CCl_4 and
- Other hepatotoxicants.

Administration of the hepatitis B vaccine should be considered for unvaccinated persons.

Patients with complaints of persistent mood alteration or cognitive dysfunction, including memory loss, should be referred to a clinical neuropsychologist for evaluation. Those with persistent neurologic complaints, such as

- Numbness,
- Tingling,
- Weakness, or
- Pain,

should be referred for neurologic consultation or electrophysiologic evaluation of peripheral nerve function.

Exposure Intervention

Evaluation of an exposed worker provides an opportunity to reduce exposures and prevent additional health effects for the patient and his or her coworkers. When the results of a clinical evaluation suggest that significant exposure is occurring, the clinician should explore with the worker and the employer avenues of exposure reduction and prevention.

Clinical Consultation

Clinical consultation and referral information can be found in the "Sources of Additional Information" section. This publicly available information pertains to credentialed clinicians with expertise and experience treating patients exposed to hazardous substances including carbon tetrachloride.

Key Points

- N-acetylcysteine might reduce complications in patients with severe CCl_4 exposure.
- Hyperbaric oxygen treatment has been used as a therapeutic intervention for acute CCl_4 poisoning.
- Other than removal from the source of exposure and avoidance of other hepatotoxins, there is no specific treatment for patients chronically exposed to CCl_4.
- The exposure dose, along with individual risk factors, will contribute to the likelihood of lasting adverse health effects from CCl_4 exposure.

Progress Check

12. Strategies for managing patients with acute CCl_4 poisoning may include which of the following?

    A. Reduction or elimination of exposure.
    B. Supportive measures.
    C. Use of antioxidants (such as methionine, cysteine, and N-acetylcysteine) and hyperbaric oxygen intervention.
    D. All of the above.

    To review relevant content, see all content in this section.

What Instructions Should Be Given to Patients Exposed to Carbon Tetrachloride?

Learning Objective

After completing this section, you will be able to

- Describe instructions that can be provided to patients exposed to carbon tetrachloride (CCl_4).

Introduction

Patients over-exposed to CCl_4 need basic guidance on

- Self-care, so they can minimize further risks and avoid complications to the extent possible, and
- Potential health effects including symptoms and signs from exposure to carbon tetrachloride, so they understand when and why to return for further medical attention.

ATSDR has developed a patient education and care instruction sheet on CCl_4. It can be found at http://www.atsdr.cdc.gov/csem/carbon_tetrachloride/docs/Carbon_Tetra_Patient_Ed_Sheet-508

Self-care

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

At work

Employers are required to provide labeling, SDSs (formerly called material safety data sheets [MSDSs]), and training as part of the OSHA Hazard Communication Standard. Patients should be encouraged to protect themselves in the following ways.

- Use recommended personal protective equipment (PPE) such as gloves, goggles, masks, respirators, and other body protection specific to the type of work they do with CCl_4.
- Refer to employer provided SDSs (formerly called MSDS) on products used at work.
- Follow safe workplace practices, including labeling all containers for chemical(s) used at work.

- Be attentive during employer provided training on how to safely use chemicals at work.

At home

Patients should be encouraged to take steps such as the following to protect against the effects of CCl_4 exposure.

- Check labels of imported consumer products for CCl_4.
- Use safer alternatives to products with CCl_4.
- If they must handle CCl_4, check with the health department or poison control center for instructions and recommendations regarding respirators, gloves, and other necessary personal protective equipment.
- Avoid alcohol if exposure occurs.
- Discard any products that contain carbon tetrachloride at home, including products that may have been used in the past. Contact the local health department or poison center for instructions on disposal of these toxic substances.
- Store household chemicals out of the reach of children and in their original containers.
- Get well water tested if they live near an area contaminated with CCl_4.

Clinical Follow-up

Because CCl_4 is reasonably anticipated to be a human carcinogen, according to the National Toxicology Program of the U.S. Department of Health and Human Services [NTP 2016], periodic clinical assessments might be of value in detecting abnormalities at an early stage.

Advise patients to consult their physician if they develop any signs or symptoms of central nervous system (CNS) or other health changes, including those possibly related to the heart, liver, and kidney.

ATSDR's patient education and care instruction sheet on CCl_4 poisoning can be used as a job aid for patient education and follow-up care.

Key Points	• Patients should be advised to avoid exposures and circumstances that might further increase their risk for adverse health effects from exposure to CCl_4 or worsen an existing health condition. • Advise patients to consult their physician if they develop any signs or symptoms of CNS or other health changes, including those possibly related to the heart, liver, and kidney.
Progress Check	13. Patients who have confirmed exposure to CCl_4 should A. Verify the source of exposure (if possible). 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.*

Sources of Additional Information

Introduction	Refer to the following resources for more information on the adverse effects of carbon tetrachloride, the treatment of carbon tetrachloride-associated diseases, and the management of persons exposed to carbon tetrachloride.
Carbon Tetrachloride Specific Information	• Agency for Toxic Substances and Disease Registry https://www.atsdr.cdc.gov o For chemical, emergency situations ▪ **CDC Emergency Response: 770-488-7100 and request the ATSDR Duty Officer** ▪ For chemical, nonemergency situations ❖ CDC-INFO https://www.cdc.gov/cdc-info/ (800-232-4636) TTY 888-232-6348 - 24 Hours/Day

	❖ Email: cdcinfo@cdc.gov NOTE: ATSDR cannot respond to questions about individual medical cases, provide second opinions, or make specific recommendations regarding therapy. Address those issues with your health care provider directly or with a medical consultant who has clinical experience treating patients with CCl_4 exposure and toxicity. o Toxicological Profile for Carbon Tetrachloride https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=196&tid=35 o TOXFAQs for Carbon Tetrachloride (English) https://www.atsdr.cdc.gov/toxfaqs/tf.asp?id=195&tid=35 • NIOSH Pocket Guide to Chemical Hazards — Carbon Tetrachloride https://www.cdc.gov/niosh/npg/npgd0107.html • EPA Technology Transfer Network Air Pollutants Website — Carbon Tetrachloride - https://www.epa.gov/technical-air-pollution-resources • Safety Data Sheet (SDS) online http://www.ilpi.com/msds/ • TOXNET https://toxnet.nlm.nih.gov/
Clinical Resources	• American College of Occupational and Environmental Medicine (ACOEM) http://www.acoem.org/ o ACOEM is the nation's largest medical society dedicated to promoting the health of workers through preventive medicine, clinical care, research, and education. o ACOEM members include physicians in a variety of medical practices who are united via the college to develop positions and policies on vital issues relevant to the practice of preventive medicine within and outside the workplace.

- American College of Medical Toxicologists (ACMT) http://www.acmt.net

  - ACMT is a professional, nonprofit association of physicians with recognized expertise in medical toxicology.
  - The college is dedicated to advancing the science and practice of medical toxicology through a variety of activities.

- Association of Occupational and Environmental Clinics http://www.aoec.org

  - The Association of Occupational and Environmental Clinics (AOEC) is a network of more than 60 clinics and more than 250 individuals committed to improving the practice of occupational and environmental medicine through information sharing and collaborative research.
  - Pediatric Environmental Health Specialty Units (PEHSUs) http:www.pehsu.net

    - PEHSUs form a respected network of experts in children's environmental health.
    - The PEHSUs were created to ensure that children and communities have access to, usually at no cost, special medical knowledge and resources for children faced with a health risk due to a natural or human-made environmental hazard.
    - Located throughout the United States, Canada, and Mexico, PEHSU professionals provide quality medical consultation for health professionals, parents, caregivers, and patients. The PEHSUs are also dedicated to increasing environmental medicine knowledge among health care professionals around children’s environmental health by providing consultation and training.

- Poison Control Center

	o Contact the American Association of Poison Control Centers for questions about poisons and poisonings. The website provides information about poison centers and poison prevention. AAPC does not provide information about treatment or diagnosis of poisoning or research information for student papers. o American Association of Poison Control Centers (1-800-222-1222 or http://www.aapcc.org
General Environmental Health Information	Please refer to the following Web resources for general information on environmental health. • Agency for Toxic Substances and Disease Registry https://www.atsdr.cdc.gov o To view the complete library of Case Studies in Environmental Medicine series (CSEMs) https://www.atsdr.cdc.gov/csem/ o Taking an Exposure History CSEM https://www.atsdr.cdc.gov/csem/csem.asp?csem=33&po=0 ▪ The Exposure History Form is available for download in a "fillable" PDF format form that can be printed and saved Exposure History Form [PDF - 455 KB • Centers for Disease Control and Prevention (CDC) https://www.cdc.gov o CDC works to protect public health and the safety of people, by providing information to enhance health decisions, and promotes health through partnerships with state health departments and other organizations. o The CDC focuses national attention on developing and applying disease prevention and control (especially infectious diseases), environmental health, occupational safety and health, health promotion, prevention, and education activities designed to improve the health of the people of the United States.

- National Center for Environmental Health (NCEH) https://www.cdc.gov/nceh/

  - NCEH works to prevent illness, disability, and death from interactions between people and the environment. NCEH is especially committed to safeguarding the health of populations particularly vulnerable to certain environmental hazards: children, the elderly, and people with disabilities.
  - NCEH works to achieve its mission through science, service, and leadership.

- National Institutes of Health (NIH) http://www.nih.gov

  - A part of the U.S. Department of Health and Human Services, NIH is the primary federal agency for conducting and supporting medical research.

- National Institute for Occupational Safety and Health (NIOSH) https://www.cdc.gov/niosh/

  - NIOSH is in the U.S. Department of Health and Human Services. NIOSH provides research, information, education, and training in the field of occupational safety and health to help assure safe and healthful working conditions for working men and women.

Posttest

Posttest

For each question, select the one best choice

1. Which of the following statements about carbon tetrachloride (CCl_4) is **INCORRECT**?

   A. CCl_4 is a manufactured chemical.
   B. Its chemical instability results in an atmospheric half-life of 24–48 hours.

C. CCl_4 is a clear, nonflammable, heavy liquid producing an odor similar to chloroform.
D. Because of CCl_4's toxicity, consumer uses of this chemical have been discontinued in the United States.

To review relevant content, please see "What is Carbon Tetrachloride?"

2. All of the following statements about exposure sources are correct **EXCEPT**:

A. U.S. public can be exposed to small amounts of CCl_4 through ambient air.
B. Across the U.S., overall ambient air concentrations are slowly declining.
C. Household cleaning products containing bleach can produce volatile organic compounds, including chloroform and carbon tetrachloride. Use of these common agents might, in part, explain elevated indoor CCl_4 concentrations.
D. It is not permitted in products intended for home use; however, chemicals containing CCl_4 can still be purchased online.

To review relevant content, please see "Where is Carbon Tetrachloride Found?"

3. Today, the U.S. general public is most commonly exposed to CCl_4 through

A. Use of consumer products that contain CCl_4.
B. Ingestion of contaminated food.
C. CCl_4-contaminated ambient air and drinking water.
D. All of the above.

To review relevant content, please see "What Are Routes of Exposure to Carbon Tetrachloride?"

4. Of the following occupations in the United States today, which is most likely to be at increased risk for exposure to CCl_4?

A. Pesticide applicators.
B. Dry cleaners.
C. Hazardous waste workers.
D. All of the above.

To review relevant content, please see "Who is at Risk for Exposure to Carbon Tetrachloride?"

5. Which of the following statements about CCl_4 is **NOT TRUE**?

A. Most inhaled CCl_4 is excreted unchanged in the urine.
B. Metabolism of CCl_4 is required for toxicity.
C. The $\bullet CCl_3$ radical is the key metabolite responsible for ultimate plasma membrane disruption and death of the cell.
D. Alcoholic patients are far more susceptible to hepatotoxic effects of CCl_4 than are others.

To review relevant content, please see "What is the Biologic Fate of Carbon Tetrachloride in the Body?"

6. All of the following statements are true **EXCEPT**

A. Liquid CCl_4 is not easily absorbed through the human skin.
B. Metabolism of CCl_4 is required for toxicity.
C. Mixed function oxidase inducers can increase the toxicity of CCl_4.
D. Unmetabolized CCl4 is eliminated primarily in exhaled air.

To review relevant content, please see "What is the Biologic Fate of Carbon Tetrachloride in the Body?"

7. Which of the following statements regarding U.S. guidelines and regulations for CCl_4 is **FALSE**?

A. EPA classifies CCl_4 as a hazardous air pollutant.
B. NIOSH has determined an air level of CCl_4 that might be immediately dangerous to life and health.

C. Use of pesticide products containing CCl_4 is a major source of exposure in the general public in the United States today.
D. EPA has set a maximum contaminant level for CCl_4 in drinking water.

To review relevant content, please see "What are Guidelines and Regulations for Carbon Tetrachloride Exposure?"

8. Which of the following statements regarding signs and symptoms in patients exposed to a high dose of CCl_4 is **INCORRECT?**

A. They will likely exhibit CNS and gastrointestinal effects.
B. Symptoms that persist beyond 24 hours are most likely psychophysiologic in nature.
C. Patients with acute and chronic exposures might exhibit some of the same symptoms.
D. Hepatic and renal injury might manifest in 48 hours.

To review relevant content, please see "What are the Toxicological Effects of Carbon Tetrachloride Exposure?"

9. In general, patients over-exposed to CCl_4 by any route **PREDOMINANTLY** exhibit which of the following symptoms?

A. Hepatomegaly.
B. CNS depression.
C. Nephritis.
D. Pulmonary edema.

To review relevant content, please see "Clinical Assessment – History and Physical Exam."

10. Which of the following is a direct biomarker of exposure to carbon tetrachloride?

A. Kidney function tests.
B. Blood CCl_4

C. Liver function tests.
D. None of the above.

To review relevant content, please see "Clinical Assessment — Laboratory Tests."

11. Treatment for a patient with acute exposure to CCl_4 might include all of the following **EXCEPT**

A. Administration of a free-radical scavenger such as N-acetylcysteine.
B. Hyperbaric oxygen therapy.
C. Irrigation of eyes and skin.
D. Induced emesis for patients who have ingested CCl_4.

To review relevant content, please see "How Should Patients Exposed to Carbon Tetrachloride be Treated and Managed?"

12. Patients should be advised on ways to avoid CCl_4 exposure and educated about possible health effects from exposure to CCl_4. Which of the following should be discussed with a patient exposed to CCl_4?

A. The use of safer alternatives to products with CCl_4.
B. The use of CCl_4-appropriate personal protective equipment (PPE), such as gloves, goggles, and respiratory protection.
C. Increased area air ventilation when using products containing CCl_4.
D. All of the above.

To review relevant content, please see "What Instructions Should be Given to Patients Exposed to Carbon Tetrachloride?"

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