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

Course: **WB 1096**
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Table of Contents

Key Concepts	• Prevention is the key to managing cadmium exposure. No effective treatment for cadmium toxicity exists. • For the general public, the primary source of exposure to cadmium is dietary. • Smoking tobacco adds an additional burden of cadmium. • Nutritional deficiencies can increase the risk of cadmium toxicity. • Chronic cadmium exposure primarily affects the kidneys and secondarily the bones. • Acute inhalation of fumes containing cadmium affects the lungs.
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. Use of trade names and commercial sources is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry or the U.S. Department of Health and Human Services.
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How to Use This Course

Introduction	The goal of the 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 cadmium toxicity.
Available Versions	Two versions of the *Cadmium Toxicity* CSEM are available. • The HTML version http://www.atsdr.cdc.gov/csem/cadmium/ 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. • Take the Initial Check to assess your current knowledge about cadmium 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 exercises	Enables you to test yourself to determine whether you have mastered the learning objectives
Progress Check answers	Provide feedback to ensure you understand the content and can locate information in the text

Learning Objectives Upon completion of the Cadmium Toxicity CSEM, you should be able to:

Content Area	Objectives
What is cadmium	• Identify the chemical properties of cadmium.
Where found	• Identify sources of cadmium in the natural environment • Describe how manmade uses of cadmium disperse it through the environment.
Exposure pathways	• Describe the major ways the general population is exposed to cadmium. • Identify the major ways workers are exposed to cadmium.
Standards and regulations	• Identify U.S. guidelines and regulations for cadmium exposure.
Populations at risk	• Identify the groups in the United States most at risk from higher than average levels of cadmium.
Biologic fate	• Describe the biological fate of cadmium in the body.
Pathogenic effects	• Discuss how cadmium induces pathogenic changes in the body.
Health effects	• Describe the health effects of acute high-dose cadmium exposure.
Diseases from exposure	• Identify the health effects of chronic cadmium exposure. • Discuss the factors leading to the development of renal disease associated with chronic low-level cadmium exposure.
Risk factors	• Identify factors that increase the risk of developing disease following exposure to cadmium.
Clinical evaluation	• Describe the presentation of a patient with acute high-dose exposure to cadmium. • Describe the workup of a patient who presents with chronic low-level exposure to cadmium.
Diagnostic tests	• Describe the laboratory evaluation for the possible health effects of acute cadmium poisoning. • Describe the laboratory evaluation for the possible health effects of chronic exposure to cadmium.
Treatment and management	• Describe how patients with cadmium related diseases should be treated.
Patient instructions	• Describe preventive measures that patients affected by cadmium should follow.

Initial Check

Instructions	This Initial Check will help you assess your current knowledge about beryllium toxicity. To take the Initial Check, read the case below and then answer the questions that follow.
Case Study	***A 60-year-old woman with low back pain and waddling gait.***

A 60-year-old woman comes to your office with complaints of low back pain, which is causing progressive difficulty in walking. The pain has gradually increased since the onset of menopause five years ago. This discomfort is especially noticeable after prolonged sitting.

Social history reveals that the patient has been a housewife since her marriage 38 years ago. Her husband, who is in good health, owns and operates a small retail shop in their home. The patient has been making jewelry for sale in her husband's shop and as a hobby for about 35 years. They have two adult sons who are in good health.

The patient denies a personal or family history of kidney disease, hypertension, diabetes mellitus, or cardiovascular disease; she also denies history of back trauma or weight loss. She has smoked one to two packs of cigarettes a day for the past 40 years. She does not take estrogens, calcium supplements, vitamins, or other medications.

On examination you find a thin female with a slightly stooped posture and a waddling gait. Blood pressure is 120/70. Her teeth have a yellow discoloration above the crown, and her fingernails are stained with nicotine. She is anosmic on cranial nerve examination. Results of cardiovascular and abdominal examination are normal. The lower lumbar spine is tender to percussion, but the patient does not complain of pain on straight leg raising. Her deep tendon reflexes are intact, and the remainder of the physical examination, including neurological testing, is normal. Sensation and strength are normal in legs and feet. Range of motion is normal in hips and knees.

Initial laboratory data include a urinalysis showing 3+ proteinuria and glycosuria. Blood urea nitrogen (BUN), creatinine, and albumin levels are normal. Radiographs of the pelvis and lumbosacral spine reveal pseudofractures and other evidence of severe osteomalacia and mild osteoporosis. There are no osteolytic or osteoblastic lesions.

The patient maintains a jewelry fabricating and engraving area in the basement of her home where she uses abrasive grinders, engraving equipment, soldering tools, and various raw materials. She does not use a dust mask but does wear a face shield when

operating the grinder. The work area is dusty, with only two small windows near the top of one wall capable of providing ventilation. There is no local or general mechanical exhaust system. She admits to smoking and eating in the work area. The patient and her husband also tend a small garden in the backyard in which they grow vegetables for the table. A nearby wastewater treatment plant provides free fertilizer, which her husband applies to the garden every few weeks. The garden is irrigated with water from a municipal well.

Initial Check Questions

1. What should be included on the patient's problem list?
2. What are the potential sources of cadmium exposure for this patient?
3. Why is the patient described in the case study at increased risk of cadmium toxicity?
4. Is the patient's husband also at increased risk? Explain.
5. Could diet play a role in the condition of the patient described in the case study?
6. If you suspect cadmium poisoning, what other questions could help gauge the extent of exposure to the patient described in the case study?
7. What tests would be helpful in further evaluating the patient or in supporting a diagnosis of cadmium toxicity?
8. Assuming the patient described in the case study has cadmium toxicity, what would be a likely urinary cadmium level?
9. What treatment will you recommend for the patient described in the case study?
10. Should the patient's neighbors be evaluated for cadmium or other heavy-metal exposure? Explain.

Initial Check Answers

1. The patient's problem list includes

    - back pain,
    - glycosuria,
    - proteinuria,
    - severe osteomalacia and mild osteoporosis pseudofractures, and
    - yellow discoloration of the teeth.

    All of these problems are consistent with chronic cadmium toxicity. The patient is also a smoker. Chronic cadmium exposure primarily affects the bones and kidneys and possibly the lungs. Renal dysfunction in this patient is indicated by the laboratory findings. The stooped posture, waddling gait, lumbar pain, and pain induced by spinal percussion are the result of skeletal changes and deformities.

    The information for this answer comes from section: "What Health Effects Are Associated with Acute High-dose Cadmium

Exposure?"

2. Potential sources of cadmium are

   - cadmium fume (cadmium oxide) generated by use of gold and silver solders during jewelry fabrication,
   - cadmium dust produced in smoothing jewelry with abrasive grinding or in engraving cadmium-plated surfaces,
   - food and cigarettes in the workplace contaminated by cadmium-containing particulates and dust,
   - cigarette smoke, and
   - food grown in soil contaminated with cadmium-containing fertilizer obtained from the wastewater treatment plant

   The information for this answer comes from section: "Where is Cadmium Found?"

3. Risk factors are due to not only increased opportunity for cadmium exposure, but age and nutritional status as well. The patient's hobby, jewelry fabrication, may provide low to moderate chronic cadmium exposure. Lack of respiratory protection, poor ventilation, and poor hygiene in the work area increase the amount of her exposure. One of the major sources of cadmium exposure in smokers is inhaling cadmium from cigarette smoke. The amount of cadmium ingested from the vegetables grown in her garden is unknown, but sludge from wastewater treatment plants contains significant levels of cadmium. Factors that may enhance cadmium absorption from the gut are age and certain dietary deficiencies.

   The information for this answer comes from section: "What Are Routes of Exposure to Cadmium?"

4. Yes, the patient's husband also may be at increased risk of cadmium toxicity because of increased opportunity for exposure, although his risk is probably less than his wife's. The husband is exposed to cadmium by eating food from the contaminated garden and by inhaling environmental tobacco smoke from his wife's cigarettes (even more so if he smokes as well). In the basement work area, he may encounter cadmium fumes and dust as a result of his wife's hobby. He also may be exposed to the cadmium on his wife's clothing and skin if she does not shower and change clothes before leaving the work area.

   The information for this answer comes from section: "What Are the Routes of Exposure to Cadmium?"

5. Yes, diet could play an important role in the patient's condition, both for what it contributes and for what may be missing from it. For example, the homegrown vegetables from the garden, particularly leafy vegetables, and animal liver or kidney and shellfish could be contributing to her cadmium burden. If her diet is deficient in calcium, or if she is postmenopausal, she may be

absorbing cadmium more efficiently.

The information for this answer comes from section: "What Factors Increase the Risk of Developing Disease from Exposure to Cadmium?"

6. Most of your questions will probably center on the patient's hobby/home industry because it is the greatest potential source of cadmium exposure.

   Typical Environmental History questions.

   a. What types of materials and metals are used in making jewelry, and what are the ingredients of all composite products? When the patient then asks the doctor where this information can be obtained, the primary care physician must know where to refer the patient. The Material Safety Data Sheet (MSDS) and other chemical labeling of products used are ideal resources of chemical information. Employers are required to have a chemical safety plan and a hazard communication program in place to comply with mandated OSHA standards. However, the woman in question since she does not work outside the home would not be covered by such regulations. Other resources, such as those listed in the appendix, can provide additional guidance regarding other standards and regulations concerning cadmium.
   b. On a weekly basis, how many hours are spent fabricating jewelry in the basement?
   c. What type of face shield is used?
   d. Why is respiratory protection not used during grinding and soldering operations?
   e. Is the work area kept clean and free of dust? If so, how?
   f. Does the patient wash her hands before eating in the work area? Have procedures been developed to keep food and cigarettes from becoming contaminated by dust and particulates?
   g. Does she shower and change her clothes before leaving the work area?

   It is also important to investigate smoking habits.

   The information for this answer comes from section: "Clinical Assessment – History and Physical Examination."

7. The most useful diagnostic test for cadmium exposure is a 24-hour urinary cadmium excretion standardized for creatinine. β_2-microglobulin levels, in the face of elevated cadmium excretion, will aid in evaluating subclinical renal dysfunction. Urinary protein and glucose tests may also be helpful in evaluating the patient. You could also measure blood cadmium levels.

   The information for this answer comes from section: "Clinical

Assessment – Laboratory Tests."

8. The patient is experiencing renal dysfunction, as evidenced by the 3+ level of proteinuria and glycosuria. When proximal tubular damage occurs, cadmium excretion can result from two sources: breakdown of the tubular epithelium and decreased reabsorption. Under these conditions, urinary cadmium levels are likely to be markedly increased and no longer reflect body burden. Exposed workers can excrete several hundred micrograms of cadmium per gram of creatinine, The geometric mean for urinary cadmium levels in the general population over age 21 is 0.210µg/gm creatinine (CDC, 2005). The patient therefore would be expected to have a urinary cadmium level of several hundred micrograms of cadmium per gram of creatinine, depending on her most recent exposure.

   The information for this answer comes from section: "Clinical Assessment – Laboratory Tests."

9. There is no effective treatment for cadmium toxicity. Chelation therapy has no role in cases of cadmium poisoning. Removal from the source of exposure and patient education to significantly reduce exposure are important, particularly before the condition has progressed to irreversible renal dysfunction. Supportive measures to alleviate symptoms should be provided such as supplementation with calcium and vitamin D if wasting or bone disease is present.

   The information for this answer comes from section "How Should Patients with Cadmium-related Diseases Be Treated and Managed?"

10. The neighbors should be evaluated and educated on the health dangers associated with exposure to high levels of cadmium. Even if they do not use the fertilizer from the wastewater treatment plant or water from the same irrigation source, runoff from the patient's land may contaminate their soil or well water. Consultation with the local or state health department is advisable if a potential public health hazard exists.

    The information for this answer comes from section: "What Factors Increase the Risk of Developing Disease from Exposure to Cadmium?"

What is Cadmium?

Learning Objectives

Upon completion of this section, you will be able to

- identify the chemical properties of cadmium.

Definition

Cadmium is an element. Its most abundant naturally-occurring isotope is non-radioactive. It is found in nature in mineral forms and is obtained for commercial uses principally from cadmium ore, called greenockite, which is commonly found in association with zinc ore. Commercial production of cadmium ore depends on the mining of zinc (ATSDR 1999).

Cadmium is commercially available as an oxide, chloride, or sulfide. Cadmium metal (Cd^{2+}) refined from the ore is a silver-white, blue-tinged lustrous heavy metal solid at room temperature (National Toxicology Program [NTP] 2004).

Chemical Properties

Cadmium is an element and is classified as a transition metal.

- Cadmium has a vapor pressure of 1 mmHg at 394ºC and is odorless.
- Cadmium is resistant to corrosion.
- Cadmium metal and its oxides are insoluble in water.
- Occurs in an oxidation state of +2.
- Solid cadmium is inflammable but powdered cadmium will burn and release corrosive and toxic fumes (Harbison 1998; NTP 2004; HSDB 2006; ATSDR 1999).
- Some cadmium salts are water soluble such as cadmium chloride, cadmium sulfate and cadmium nitrate; other insoluble salts can become more soluble by interaction with acids, light or oxygen.
- The melting point of cadmium is 321° C.

Key Points

- Cadmium, a heavy metal, is produced by refining zinc ores.
- Cadmium metal is practically insoluble in water but some cadmium salts are water soluble.
- Powdered cadmium will burn and can release corrosive fumes.

Progress Check

1. The physical and chemical properties of cadmium metal include

   A. Insolubility in water.
   B. No odor.
   C. Resistance to corrosion.
   D. All of the above.

   To review relevant content, see "Chemical Properties" in this section.

Where Is Cadmium Found?

Learning Objectives

Upon completion of this section, you will be able to

- identify sources of cadmium in the natural environment, and
- describe how manmade uses of cadmium disperse it through the environment.

Introduction

Cadmium, a rare but widely dispersed element, is found naturally in the environment. Most cadmium ore (greenockite):

- exists as cadmium sulfide,
- is refined during zinc production, and
- occurs in association with zinc.

It is released into the environment through mining and smelting, its use in various industrial processes, and enters the food chain from uptake by plants from contaminated soil or water.

Sources of Cadmium

Cadmium has been widely dispersed into the environment through the air by its mining and smelting as well as by other manmade routes:

- usage of phosphate fertilizers,
- presence in sewage sludge, and
- various industrial uses such as NiCd batteries, plating, pigments and plastics (ATSDR 1999).

Release by Industrial Processes

The most important sources of airborne cadmium are smelters. Other sources of airborne cadmium include burning fossil fuels such as coal or oil and incineration of municipal waste such as plastics and nickel-cadmium batteries (which can be deposited as solid waste) (Sahmoun *et al.* 2005). Cadmium may also escape into the air from iron and steel production facilities.

Cadmium is used mainly:

- in metal plating,
- in producing pigments,
- in NiCd batteries,
- as stabilizers in plastics, and
- as a neutron absorbent in nuclear reactors.

Contamination of the Natural Environment

When released into the atmosphere by smelting or mining or some other processes, cadmium compounds can be associated with respirable-sized airborne particles and can be carried long distances. It is deposited onto the earth below by rain or falling out of the air. Once on the ground, cadmium moves easily through soil layers and is taken up into the food chain by uptake by plants such as leafy vegetables, root crops, cereals and grains (ATSDR 1999).

	Cadmium concentrations in drinking water supplies are typically less than 1 microgram per liter (µg/L) or 1 part per billion (ppb) (ATSDR 1999). Groundwater seldom contains high levels of cadmium unless it is contaminated by mining or industrial wastewater, or seepage from hazardous waste sites. Soft or acidic water tends to dissolve cadmium and lead from water lines; cadmium levels are increased in water stagnating in household pipes. These sources have not been reported to cause clinical cadmium poisoning, but even low levels of contamination add to the body's accumulation of cadmium. Cadmium oxide also exists as small particles in air (fume) which are the result of smelting, soldering, or other high-temperature industrial processes. A certain percentage of these particles are respirable.
Cadmium in the Food Chain	From the soil, certain plants (tobacco, rice, other cereal grains, potatoes, and other vegetables) take up cadmium more avidly than they do other heavy metals such as lead and mercury (Satarag *et al.* 2003). Cadmium is also found in meat, especially sweetmeats such as liver and kidney. In certain areas, cadmium concentrations are elevated in shellfish and mushrooms (Jarup 2002). Cadmium can also enter the food chain from water. In Japan, zinc mining operations contaminated the local water supplies with cadmium. Local farmers used that water for irrigation of their fields. The soil became contaminated with cadmium which led to the uptake of cadmium into their rice (Jarup 2002).
Key Points	• Cadmium is mined and then released into the environment mainly through the air during smelting. • Once in the environment, cadmium moves easily through the soil and is taken up into the food chain. • Certain plants, such as tobacco, rice, other cereal grains, potatoes, and other vegetables, take up cadmium from the soil.
Progress Check	2. Cadmium, once mined and produced, enters the environment via A. The air by its mining and smelting. B. Into soil by its presence in phosphate fertilizers and sewage sludge. C. Various industrial uses such as in plating, NiCd batteries, pigments and plastics. D. All of the above. *To review relevant content, see "Sources of Cadmium" and "Release by Industrial Processes" in this section.*

3. Once in the environment, cadmium enters the food chain and

   A. Is commonly found in high levels in groundwater.
   B. From soil is taken up into cereal grains.
   C. Is never found in meats.
   D. None of the above.

   To review relevant content, see "Cadmium in the Food Chain" in this section.

What Are Routes of Exposure for Cadmium?

Learning Objective

Upon completion of this section, you will be able to

- describe the major ways the general population is exposed to cadmium, and
- identify the major ways workers are exposed to cadmium.

Introduction

The major ways cadmium exposure occurs in the general population are through:

- ingestion of cadmium found in certain foods, and
- cigarette smoking since the tobacco plant takes up cadmium avidly from the environment.

The non-smoking public receives the majority of their exposure through food. The main route of cadmium exposure for smokers is via tobacco smoke (National Toxicology Program 2004; Mannino *et al.* 2004).

Cadmium exposure in the workplace takes place during mining and work with cadmium containing ores. Additional occupational exposure may occur during manufacture of products containing cadmium such as paints and during work such as plating, soldering, and welding (National Institute of Occupational Safety and Health, 1990).

Inhalation

Inhalation is a major route of occupational exposure.

Cadmium air levels are usually thousands of times greater in the workplace than in the general environment. For example, the OSHA permissible exposure limit (PEL) of cadmium fume or cadmium oxide in the workplace is 0.1 mg/m^3, whereas concentrations of cadmium in ambient air are 1×10^{-6} mg/m^3 in non-industrialized areas and 4×10^{-5} mg/m^3 in urban areas (ATSDR 1999). Therefore, non-occupational exposures from air are not expected to pose hazards of adverse health effects.

Cigarette smokers in the general population are exposed to cadmium through inhalation.

There is about 2.0 µg of cadmium in a cigarette, of which nearly 2-10% is transferred to cigarette smoke (Mannino *et al.* 2004). Smokers typically have cadmium blood and body burdens more than double those of nonsmokers (Waalkes *et al.* 2003). Clinicians should be aware that, in general, smokers will have higher urinary cadmium than nonsmokers (Mannino *et al.* 2004).

Ingestion

Oral ingestion is the major route of exposure for the nonsmoking general population.

However, background levels of cadmium in food, water, and ambient air are not a health concern for the general North

	American population. Typical dietary intake is about 30-50 micrograms per day (µg/day), (Satarug 2003; NTP 2004) but normal individuals absorb only a small proportion of an orally ingested dose (1-10%) (Horiguchi *et al.* 2004). However, worldwide, there are areas with very high levels of cadmium in the soil. Crop uptake of cadmium in these areas can lead to significant dietary exposures to the people living nearby. For example, in the Jinzu and Kakehashi river basins in Japan, there are areas with soil contaminated with cadmium. Rice absorbs the cadmium and a lifetime of eating this cadmium-contaminated rice can lead to a serious kidney and bone disorder called "Itai-Itai" disease, especially in women (Kobayashi *et al.* 2006; Ezaki *et al.* 2003).
Skin	There are negligible amounts of cadmium exposure through the skin. It is not considered a major route of exposure to this chemical.
Key Points	• In the general population, exposure to cadmium occurs primarily by eating certain foods if grown ion contaminated soil. • In the general population, cigarette smoke is one of the highest sources of cadmium exposure for smokers. • People who work with cadmium can suffer from workplace exposures through inhalation if proper industrial hygiene does not occur.
Progress Check	4. In the general population, exposure to cadmium occurs through which of the following? A. Eating cadmium-contaminated foods such as rice and cereal grains. B. Inhaling cigarette smoke since tobacco plants take up cadmium from the soil avidly. C. Rarely by inhaling of fumes during hobbies such as jewelry making. D. All of the above. *For relevant information on this topic, see "Inhalation" and "Ingestion" in this section.* 5. Cadmium exposure in the workplace occurs during which of the following? A. Mining and work with ore containing cadmium. B. Manufacture of products such as paints. C. Industrial activities such as plating, soldering, and welding. D. All of the above. *For relevant information on this topic, see "Introduction" in this section.*

What Are the Standards and Regulations for Cadmium Exposure?

Learning Objectives

Upon completion of this section, you will be able to

- identify U.S. guidelines and regulations for cadmium.

Introduction

With increasing evidence of cadmium's toxicity, both national and international agencies have sought to regulate its exposure. Because much is known about the toxic and health effects of cadmium; there is a large database from which to set standards for occupational, health, and environmental levels (Satoh *et al.* 2002).

Workplace Standards

OSHA has established workplace levels to protect the health of people occupationally exposed to cadmium.

The OSHA limits are

- Permissible Exposure Limit- TWA (PEL): 5 $\mu g/m^3$ (fumes).

The National Institute of Occupational Safety and Health (NIOSH) has set an:

- Immediately Dangerous to Life and Health level (IDLH) which is 9 mg/m^3 (NIOSH 2006; NTP 2004).

Health Standards

Many health agencies have set exposure standards designed to protect the general public from excess cadmium exposure from various sources.

FDA

- Maximum limit of cadmium in bottled water: 0.005 mg/L.

ATSDR

- Chronic durational oral minimal risk level (MRL) of 0.0002 mg/kg/day of cadmium based on its renal effects.
- This MRL standard states how much cadmium can be taken in orally chronically without risk of adverse health effects (ATSDR 1999).

EPA

- Food – Reference dose is 1×10^{-3} mg/kg/day (ATSDR 1999).
- Water - Reference dose for human exposure is 5 x 10-4 mg/kg/day.
- Reference dose (Rfd) is an estimate of a daily exposure to the general population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effects during a lifetime (IRIS 2006).

	World Health Organization (WHO) • Tolerable weekly intake for cadmium at 7 µg/kg/body weight/week
Carcinogenicity	Positions on carcinogenicity of cadmium by U.S. and international health organizations. • EPA classifies cadmium as a probable human carcinogen (Group B1). • International Agency for Research on Cancer (IARC) classifies cadmium as a known human carcinogen. • American Conference of Industrial Hygienists (ACGIH) classifies cadmium as a suspected human carcinogen. • National Toxicology Program (NTP) classifies cadmium as known to be a human carcinogen (NTP 2004).
Environmental Standards	***EPA*** • Drinking water - maximum contaminant level for cadmium in drinking water is 0.005 mg/L. (ATSDR, 1999) • Air - Cadmium is on the EPA National Emission Standards for Hazardous Air Pollutants (NESHAP) list of 189 hazardous air pollutants. Cadmium is listed as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas (ATSDR 1999). • Soil – EPA biosolids rule states that the ceiling for the amount of cadmium that can be applied to land is 85 mg/kg fill material (NTP 2004).
Key Points	• Because much is known about the human health effects of cadmium, there is a large database from which to set standards. • With increasing evidence of its toxicity, both national and international agencies have sought to regulate cadmium exposure.
Progress Check	6. Guidelines issued by U.S. agencies are designed to protect human health and include which of the following? A. The ATSDR MRL, which states how much cadmium can be taken in orally chronically without risk of adverse health effects, is 0.0002 mg/kg/day of cadmium based on its renal effects. B. NIOSH has set an IDLH of 9 mg/m^3. C. The EPA reference dose for daily exposure to the general population that is likely to be without appreciable risk of deleterious effects during a lifetime is 5×10^{-4} mg/kg/day for water. D. The OSHA PEL for people occupationally exposed to cadmium is 5 $\mu g/m^3$ (fumes). E. All of the above. *To review relevant content, see all content in this section.*

Who Is at Risk of Cadmium Exposure?

Learning Objectives

Upon completion of this section, you will be able to

- identify the groups in the United States at risk from higher than average levels of cadmium exposure.

Introduction

For the average American, low levels of cadmium exposure occur through diet. Currently, these background exposures through diet are not believed to cause adverse health effects.

However, there are groups within the United States who suffer higher than average exposures to cadmium because of occupation, hobby, or personal habits such as smoking.

Additionally, there are certain regions of the globe, such as Japan, which are contaminated with high levels of cadmium in the environment. Because local food crops, such as rice, pick up high levels of cadmium, local people are exposed to cadmium through their diet.

Direct Occupational Exposure

In the United States in the 1990s, approximately 297,000 workers were estimated to be at greatest risk of cadmium exposure (NIOSH, 1990). There are no more recent estimates. The types of workers potentially exposed include

- alloy makers,
- aluminum solder makers,
- ammunition makers,
- auto mechanics,
- battery makers,
- bearing makers,
- braziers and solderers,
- cable and trolley wire makers,
- cadmium alloy and cadmium-plate welders,
- cadmium platers,
- cadmium vapor lamp makers,
- ceramic and pottery makers,
- copper-cadmium alloy makers,
- dental amalgam makers,
- electric instrument makers,
- electrical condenser makers,
- electroplaters,
- engravers,
- glass makers,
- incandescent lamp makers,
- jewelers,
- lithographers,
- lithopane makers,
- metal sculptors,
- mining and refinery workers,
- municipal solid waste recovery workers,

- paint makers,
- paint sprayers,
- pesticide makers,
- pharmaceutical workers,
- photoelectric cell makers,
- pigment makers,
- plastic products makers,
- smelterers,
- solder makers, and
- textile printers.

Smokers

Effects of cigarettes and smoking on cadmium exposure.

- A cigarette contains approximately 2.0 µg of cadmium, 2-10% of which is transferred to primary cigarette smoke (Mannino *et al.* 2004).
- Of the cadmium in the primary inhaled cigarette smoke, nearly 50% is absorbed from the lungs into the systemic circulation during active smoking (Satarug *et al.* 2003; Jarup 2002).
- Smokers typically have cadmium blood and body burdens more than double those of nonsmokers (Waalkes *et al.* 2003).
- Clinicians should be aware that smokers have a higher urinary cadmium levels than nonsmokers (Mannino *et al.* 2004).

Background Exposures

Background levels of cadmium in food, water, and ambient air are not a health concern for the general North American population. Typical dietary intake is about 30 micrograms per day (µg/day), (Satarug *et al.* 2003) but normal individuals absorb only a small proportion of an orally ingested dose (1-10%) (Horiguchi *et al.* 2004).

Key Points

- Workers in industries producing or using cadmium have the greatest potential for cadmium exposure.
- Hobbyists such as jewelry makers and artists may also be at increased risk.
- Cigarette smoke can add to the body's cadmium burden.

Progress Check

7. Hobbyists are at increased risk of cadmium exposure due to which of the following?

   A. Cadmium's presence in many gold and silver solders used in fabricating jewelry.
   B. The metal dust produced in grinding or engraving cadmium-plated surfaces.
   C. Poor ventilation in work areas.
   D. Eating and smoking in work areas.
   E. All of the above.

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

What Is the Biological Fate of Cadmium in the Body?

Learning Objective

Upon completion of this section, you will be able to

- describe the biologic fate of cadmium in the body.

Introduction

This section will discuss

- how cadmium is taken into the body,
- its absorption,
- how it distributes throughout the body, and
- why it accumulates in the human body due to its metabolism and excretion

How Cadmium Is Absorbed

The principal factor determining how much cadmium is absorbed is the route of exposure. Once exposed, how much cadmium is absorbed depends on many factors:

- age,
- gender,
- smoking, and
- nutritional status.

As a cumulative toxin, cadmium body burden increases with age. Women have been shown to have higher blood levels of cadmium than men. Typically women, with lower iron status, are believed to be at risk for greater absorption of cadmium after oral exposure (Olsson *et al.* 2002).

Inhalation

Once in the lungs, from 10% to 50% of an inhaled dose is absorbed, depending on particle size, solubility of the specific cadmium compound inhaled, and duration of exposure (Jarup 2002). Absorption is least for large (greater than 10 micrometers [µm]) and water-insoluble particles, and greatest for particles that are small (less than 0.1 µm) and water soluble. A high proportion of cadmium in cigarette smoke is absorbed because the cadmium particles found in that type of smoke are very small (ATSDR 1999).

Ingestion

Most orally ingested cadmium passes through the gastrointestinal tract unchanged as normal individuals absorb only about 6% of ingested cadmium, but up to 9% may be absorbed in those with iron deficiency (ATSDR 1999). Also, cadmium in water is more easily absorbed than cadmium in food (5% in water versus 2.5% in food) (IRIS 2006). The presence of elevated zinc or chromium in the diet decreases cadmium uptake.

	Dermal Absorption through the skin is not a significant route of cadmium entry; only about 0.5% of cadmium is absorbed by the skin (ATSDR 1999).
Excretion of Cadmium	Absorbed cadmium is eliminated from the body primarily in urine. The rate of excretion is low, probably because cadmium remains tightly bound to metallothionein, MTN, which is almost completely reabsorbed in the renal tubules. Because excretion is slow, cadmium accumulation in the body can be significant. Cadmium concentration in blood reflects recent exposure; urinary cadmium concentration more closely reflects total body burden. However, when renal damage from cadmium exposure occurs, the excretion rate increases sharply, and urinary cadmium levels no longer reflect body burden.
Accumulation of Cadmium	The total cadmium body burden at birth is non-detectable (CDC 2005). It gradually increases with age to about 9.5 mg to 50 mg (ATSDR 1999). The kidneys and liver together contain about 50% of the body's accumulation of cadmium (HSDB 2006).
Cadmium Half-Life	The biologic half-life of cadmium in the kidney is estimated to be between 6 to 38 years; the half life of cadmium in the liver is between 4 and 19 years (ATSDR 1999). These long half-lives reflect the fact that humans do not have effective pathways for cadmium elimination. Cadmium has no known biologic function in humans. Bioaccumulation appears to be a by-product of increasing industrialization. Any excessive accumulation in the body should be regarded as potentially toxic.
Key Points	• Cadmium has no known beneficial function in the human body. • Cadmium is a cumulative toxin. • Cadmium is transported in the blood bound to metallothionein. • The greatest cadmium concentrations are found in the kidneys and the liver. • Urinary cadmium excretion is slow; however, it constitutes the major mechanism of elimination. • Due to slow excretion, cadmium accumulates in the body over a lifetime and its biologic half life may be up to 38 years.
Progress Check	8. Once an individual is exposed, which of the following factors influence the amount of cadmium absorbed by the body? A. Age. B. Gender of the exposed individual. C. Lower iron status. D. All of the above. *To review relevant content, see "How Cadmium is Absorbed" in this section.*

How Does Cadmium Induce Pathogenic Changes?

Learning Objective	Upon completion of this section, you will be able to • discuss how cadmium induces pathogenic changes in the body.
Introduction	Depending on the route of exposure, cadmium has differing rates of absorption and varying health effects. Cadmium is a cumulative toxin. Its levels in the body increase over time because of its slow elimination. It accumulates chiefly in the liver and kidneys. However, it also accumulates in muscle and bone. The principal organs affected by cadmium's toxicity, both acutely and chronically, are the: • kidneys, • bone, and • lungs. The lungs can be damaged by acute inhalation exposures as well as suffering effects from more chronic occupational exposures. The kidneys can be damaged with both acute high-dose but more commonly, long-term chronic exposures. The bone disease that occurs with above average chronic exposures is thought to be secondary to cadmium's effects on the kidney.
Target organs	The chief organs acted upon by cadmium with its chronic toxic effects are • kidneys, and • bone The lungs are a target organ in acute high-dose exposures to inhaled cadmium fumes.
Mechanisms of Toxicity	Cadmium is known to increase oxidative stress by being a catalyst in the formation of reactive oxygen species, increasing lipid peroxidation, and depleting glutathione and protein-bound sulfhydryl groups. Cadmium also can stimulate the production of inflammatory cytokines and downregulates the protective function of nitric oxide formation (Navas-Acien *et al.* 2004).
Genotoxicity	Cadmium expresses genotoxic activities in vitro in cells and in vivo in animals; and there is limited epidemiological evidence for in vivo human genotoxicity. • An occupational study showed increased numbers of chromosomal aberrations in the lymphocytes of cadmium-exposed workers (NTP 2004). • Cadmium has been found to cause chromosomal damage in animal experiments with subcutaneous administration (ATSDR 1999).

- Cadmium causes mutations, DNA strand breaks, chromosomal damage, cell transformation and impaired DNA repair in cultured mammalian cells (NTP 2004).
- Cadmium is known to modulate gene expression and signal transduction (Waisberg *et al.* 2003).

Carcinogenicity

There is sufficient evidence that cadmium metal and a number of cadmium compounds, such as cadmium chloride, oxide, sulfate, and sulfide, are carcinogenic in animals. Increased rates of testicular, prostate, and lung cancer in animals have been described (Sahmoun *et al.*, 2005; ATSDR,1999).

Current classification of cadmium's carcinogenicity by health agencies.

- EPA has classified cadmium as a Group B1 or "probable" human carcinogen.
- American Conference of Governmental Industrial Hygienists (ACGIH) considers cadmium a suspected human carcinogen.
- The World Health Organization's (WHO) International Agency for Research on Cancer (IRAC) classifies cadmium as a known human carcinogen.
- The National Toxicology Program (NTP) has characterized cadmium as known to be a human carcinogen (NTP 2004).

Occupational cohort studies have suggested possible associations between chronic exposure to cadmium, particularly cadmium oxide, and cancers of the lung, prostate, and genitourinary system such as renal carcinoma. The strongest evidence for a linkage between occupational exposure to cadmium and cancer is that of lung cancer. This linkage is the reason cited by the IARC in 1993 for designating cadmium as a known human carcinogen and by the NTP for its characterization of cadmium as a known human carcinogen in 2000.

The most positive evidence for the IARC's decision came from a series of studies of the "globe cohort" that showed a positive association between occupational cadmium exposure and lung cancer. However, there have been updated studies of that cohort and other evidence (Sorhan and Esmen 2004) since then as reviewed by Verougstraete *et al.* in 2003. These studies conclude that, to date the epidemiological evidence shows "a small increase in the relative risk of lung cancer in workers exposed to cadmium and cadmium compounds" (Verougstraete *et al.* 2003).

There is also a consensus that there is not enough evidence to definitely establish a link between cadmium exposure and renal and prostate cancer (Waalkes 2003; NTP 2004). There is no clinical or experimental evidence that background environmental exposures to cadmium causes cancer (Verougstraete *et al.* 2003).

Key Points	• Cadmium's toxicity primarily affects the lungs and kidneys, with secondary effects on the skeletal system. • Cadmium's carcinogenic effects have been demonstrated in experimental animals; evidence in humans is somewhat less conclusive.
Progress Check	9. Which of the following statements regarding cadmium as a carcinogen is true? A. Cadmium has evidence of carcinogenicity. B. Some agencies do not list cadmium as a known carcinogen. C. Cadmium probably causes lung cancer in humans. D. All of the above. *To review relevant content, see "Carcinogenicity" in this section.*

What Health Effects Are Associated With Acute High-Dose Cadmium Exposure?

Learning Objective

Upon completion of this section, you will be able to

- describe the health effects of acute high-dose cadmium exposure.

Introduction

Adverse effects of excessive acute cadmium exposure may include

- "food poisoning" (ingestion only),
- bronchitis (inhalation only),
- chemical pneumonitis (inhalation only), and
- pulmonary edema (inhalation only), a condition which can initially resemble metal fume fever.

Respiratory Effects

Severe, often fatal, pulmonary disease can result from brief inhalation exposure to high concentrations of cadmium compounds; however, such exposures are now very unusual.

These types of exposures can occur in occupational settings such as:

- cadmium alloy production,
- welding involving cadmium coated steel, and
- cadmium smelting and refining (Newman-Taylor 1998).

Onset of symptoms is usually delayed for 4 to 10 hours. Initial symptoms resemble the onset of a flu-like illness- chills, fever, and myalgias. Later symptoms include chest pain, cough, and dyspnea (Newman-Taylor 1998). Bronchospasm and hemoptysis may also occur. Histiologic findings in the lungs after such exposures include

- hyperemia of the trachea and bronchi,
- pulmonary edema,
- intra-alveolar hemorrhage,
- fibroblastic proliferation,
- hyperplasia of alveolar lining cells, and
- thrombosis of small blood vessels.

Differential Diagnosis

The symptoms of acute cadmium inhalation can initially resemble classic metal fume fever, a self-limited condition associated with fever, chills and possible decreases in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1). Although initially indistinguishable from cadmium poisoning, metal fume fever is a separate and relatively benign disorder that generally resolves within 48 hours. In contrast, patients who have more intense exposure to cadmium and do not improve after one to two days may progress in eight hours to seven days to acute chemical pneumonitis and pulmonary edema. This can result in prolonged recovery, permanent lung damage, or death (ATSDR 1999).

Gastrointestinal Effects

Cadmium ingested in high doses irritates the gastric epithelium. The most common way that acute poisoning via cadmium ingestion occurs is consumption of acidic food or beverages improperly stored in containers with a cadmium glaze (Lewis 1997). The symptoms of severe cadmium ingestion are

- nausea,
- vomiting,
- abdominal cramps and pain,
- diarrhea, and
- tenesmus (ATSDR 1999; Drebler *et al.* 2002).

Recovery can occur from an acute episode of poisoning with no side effects. Given a sufficient dose however, hemorrhagic gastroenteritis, liver and kidney necrosis, cardiomyopathy, and metabolic acidosis can occur (Newman-Taylor 1998).

Key Points

- Acute inhalation of cadmium may cause symptoms similar to those of metal fume fever.
- Acute oral ingestion results in severe gastroenteritis.

Progress Check

10. The acute effects of high dose cadmium exposure by inhalation include which of the following?

    A. Bronchitis.
    B. Chemical pneumonitis.
    C. Pulmonary edema.
    D. All of the above.

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

What Diseases Are Associated with Chronic Exposure to Cadmium?

Learning Objective

Upon completion of this section, you will be able to

- identify the health effects of chronic cadmium exposure, and
- discuss the factors leading to the development of renal disease associated with chronic low-level cadmium exposure.

Introduction

This section describes the health effects that have been found in some individuals who have been exposed chronically to high levels of cadmium. As stated before, this can include

- groups of workers,
- heavy smokers,
- people living in areas with high levels of environmental cadmium, and
- special exposure scenarios such as hobbies.

Respiratory Effects

Most studies have associated chronic occupational exposure to cadmium fumes and dusts with increased risk of chronic obstructive lung disease and emphysema, but some studies reported no such association (Hendrick 1996 ; ATSDR 1999). Study limitations, such as small sample size, lack of suitable cohorts, and failure to control for smoking and other confounding effects, render the association uncertain.

There are also reports that respiratory effects caused by occupational exposure can reverse themselves if exposure stops (ATSDR 1999).

There have also been studies examining the role of cadmium in the development of chronic obstructive pulmonary disease (COPD) in smokers (ATSDR 1999). The most recent (Mannino *et al.* 2004) study showed that current and former smokers had higher body burdens of cadmium than non-smokers and that within smokers, the body burden of cadmium was related to lung injury related to smoking. The authors conclude that cadmium might be important in the development of tobacco related lung disease. Further work needs to be done on this topic.

Chronic cadmium inhalation is also suspected to be a possible cause of lung cancer (Sorhan and Esmen 2004; Verougstratete *et al.* 2003). Other respiratory effects of chronic occupational exposure to cadmium include chronic rhinitis, destruction of the olfactory epithelium with subsequent anosmia as well as the development of bronchitis (ATSDR 1999; Drebler 2002).

Cardiovascular Effects

In animals, chronic ingestion of cadmium causes increased systolic blood pressure in the absence of significant renal disease. Such pressor effects have been linked to depressed blood and tissue levels of atrial natriuretic peptide, increased blood levels of aldosterone, and retention of sodium and water (ATSDR 1999). This led to a hypothesis that cadmium exposure in humans might be related to hypertension.

Several studies have looked at this topic. The Cadmibel study, a prospective population study looking at the health effects of low-level environmental exposure to cadmium in the general population, found no effect of cadmium on the blood pressure of study subjects (Stassen J *et al.* 1991). A recent follow-up of the original Cadmibel cohort, the PheeCad study found the same result (Staessen J *et al.* 1999).

However, recent studies (Navas-Acien *et al.* 2004, 2005) have examined the contribution of cadmium and some other heavy metals to the development of peripheral artery disease. These studies found an association with cadmium exposure and the development of peripheral artery disease. In fact, the effect of smoking on peripheral artery disease decreased after adjustment for cadmium levels suggesting that the effect of smoking on the development of peripheral artery disease may be partially mediated by cadmium.

Renal Effects

The kidney is the principal organ targeted by chronic exposure to cadmium. Cadmium nephrotoxicity may follow chronic inhalation or ingestion. Data from human studies suggest a latency period of approximately 10 years before clinical onset of renal damage, depending on intensity of exposure. However, subtle alterations of renal function have been described after acute exposure in animals, and there are rare reports of renal cortical necrosis after acute high-dose exposure in humans.

Classically, chronic cadmium exposure is associated with progressive renal tubular dysfunction. The first sign of renal abnormalities occur at 2 µg/g creatinine and are microscopic tubular proteinuria – the biomarkers are β2-microglobulin, ά1-microglobulin. At urinary cadmium levels of 4 µg/gCr, enzymes such as N-acetyl-B-glucosaminidase (NAG) are elevated in urine and signs of glomerular damage including increased albumin in the urine and a decrease in glomerular filtration rate are seen. In the final stages of cadmium nephropathy, glycosuria, wasting of calcium and phosphate, and altered calcium metabolism with secondary effects on the skeleton of osteoporosis and osteomalacia are seen (Roels *et al.* 1999; Jarup *et al.* 2000).

Some experts believe the microproteinuria related to cadmium exposure is not invariably progressive and the level at which cadmium-induced nephropathy becomes progressive and irreversible, even after termination of exposure occurs at urinary

cadmium levels of >4 ug Cd/g c reatinine or at values of B2-microgloburia of > 1,000 ug/g creatinine (Ikeda *et al.* 2005; Kobayashi *et al.* 2006). Other experts believe that the renal tubular dysfunction associated with cadmium is irreversible (Iwata *et al.* 1993). Cadmium nephropathy is an important determinant of mortality in cadmium workers.

Toxic effects on the kidney are dose-related (Mueller *et al.* 1992). For workers, the risk of clinical nephropathy increases significantly with total airborne exposures greater than 300 mg/m^3, urine cadmium levels greater than 10 µg/g creatinine, and renal cortex levels greater than 200 ppm (Roels *et al.* 1999).

Early signs of renal damage have been reported in members of the general population at urine levels between 2-4 nmol/mmol creatinine. A number of studies over the years have looked at the effects of cadmium on the kidney in the environmentally exposed including

- Cadmibel (Buchet *et al.* 1990),
- Japan (Ikeda *et al.* 2003, 2005, 2006; Kobayashi *et al.* 2006),
- OSCAR (Jarup *et al.* 2000),
- Sweden, and
- United States, (Noonan *et al.* 2002).

These studies have found that even very low-levels of cadmium may have adverse effects on the kidney. WHO currently states that 200 µg/g levels wet weight in kidney causes adverse changes in 10% of the population (Satoh *et al.* 2002). In the past, several studies of occupationally and environmentally exposed populations have shown that the threshold for renal damage occurred at urinary cadmium levels of 2-4 nmol/mmol creatinine (Buchet *et al.* 1990); however, the OSCAR study found that those with a urine cadmium level of 1 nmol/mmol creatinine had a threefold risk of increased ȧ-1 microglobulin (Jarup *et al.* 2000). However, at this time, it is not known if these early subclinical changes in kidney biomarkers associated with low levels of environmental cadmium exposure have any correlation with continued decline in renal function to clinical levels of concern (Noonan *et al.* 2002).

Much work is underway to define the "critical renal concentration" at which cadmium-induced renal damage occurs. Recent studies in Japan estimate that the lifetime tolerable dose of cadmium is 2.0 grams for both men and women (Trzcinka-Ochocka *et al.* 2004; Watanabe *et al.* 2004). There is a very low margin of safety between reaching the critical renal concentration and body burdens found in smokers (Satarug and Moore 2004). Recent work also suggests that exposed children might be a susceptible population (Trzcinka-Ochocka *et al.* 2004).

At moderate, usual occupational levels of exposure, increased excretion of high-molecular-weight proteins, such as albumin and

transferrin, are early signs of glomerular damage from cadmium. Once begun, the glomerular damage is believed to be irreversible and the degree of damage is dose-dependent (Jarup 2002). The glomerular filtration rate (GFR) declines slowly but progressively, suggesting that cadmium accelerates the normal age-related decline in renal function. Clinical uremia is rare, but decreased filtration reserve capacity can be demonstrated in cadmium workers with normal baseline GFR and serum creatinine. Cadmium exposure may also potentiate the development of glomerulopathy in diabetic populations (Buchet *et al.* 1990).

Sufficient cadmium exposure can also lead to decreased GFR and chronic renal failure manifested by:

- aminoaciduria,
- glucosuria,
- hypercalcuria,
- hyperphosphaturia,
- polyuria, and
- reduced buffering capacity for acids (Jarup 2002).

Kidney stones are more common in cadmium-exposed populations, especially in exposed workers. Lifetime prevalence rates of 18%to 44% have been found, compared to rates less than 5% in control populations. Stone formation probably results from cadmium-induced renal damage leading to hypercalciuria and hyperphosphaturia, but other contributing factors may include uric aciduria, reduced urinary citrate, and renal tubular acidosis.

Skeletal Lesions

Although cadmium accumulates in bone, the bone disease that results from excessive cadmium exposure is believed to be secondary to changes in calcium metabolism due to cadmium-induced renal damage (ATSDR 1999). Clinically significant bone lesions usually occur late in severe chronic cadmium poisoning and include pseudofractures and other effects of osteomalacia and osteoporosis. Pseudofractures are spontaneous fractures that follow the distribution of stress in normal skeleton or occur at sites where major arteries cross the bone and cause mechanical stress through pulsation.

The OSCAR study in Sweden examined whether environmental cadmium exposure could be a risk factor for reduced mineral density in bone (Jarup *et al.* 2000; Alfven *et al.* 2002, 2004). The study authors found a negative correlation between urinary cadmium and bone density. Skeletal effects appear to be secondary to increased urinary calcium and phosphorus losses due to cadmium-induced renal effects (Jarup *et al.* 2000). These effects are compounded by inhibition of renal hydroxylation of vitamin D, which eventually leads to a deficiency of its active form (Nogawa *et al.* 2004). Some investigators believe cadmium also exerts an inhibitory effect on calcium absorption from the gastrointestinal tract. Enhanced secretion of prostaglandin E2 may also contribute to bone resorption.

"Itai-Itai" Disease	"Itai-itai" or ouch-ouch disease was first described in post-menopausal Japanese women exposed to excessive levels of cadmium over their lifetimes. The women were exposed through their diet because the region of Japan in which they resided was contaminated with cadmium (Ikeda *et al.* 2000; Watanabe *et al.* 2000). Symptoms and signs of "itai-itai" disease include • severe osteoporosis and osteomalacia with simultaneous severe renal dysfunction, • normochromic anemia and low blood pressure sometimes also occur (Alfven *et al.* 2002; Nogawa *et al.* 2004), and • average urinary cadmium level in these patients is 20-30 µg/g-creatinine of cadmium in urine (Ezaki *et al.* 2003).
Other Effects	There is conflicting data that chronic cadmium exposure may cause mild anemia. Anosmia and yellowing of teeth have been reported.
Developmental Effects	In animals, cadmium crosses the placenta, and large parenteral doses during early gestation cause birth defects. During later pregnancy, doses greater than 2.5 mg/kg cause severe placental damage and fetal death. Cadmium has not been reported to induce birth defects in infants of women occupationally exposed to cadmium. However, there are reports that women in Japan with higher urinary cadmium levels have increased rates of preterm delivery than mothers with lower levels. These mothers also had infants with birth weights that were lower than those of newborns of unexposed women but this difference was felt to be due to the increased incidence of early deliveries (Nishijo *et al.* 2002). However, other studies have not shown cadmium to cause pre-term labor (Zhang *et al.* 2004). At this time, the evidence of cadmium's effects on pregnancy is inconsistent and requires further investigation.
Key Points	• Chronic cadmium inhalation may result in impairment of pulmonary function with obstructive changes. • Cadmium toxicity may cause renal dysfunction with both tubular and glomerular damage with resultant proteinuria. • Bone changes appear to be secondary to renal tubular dysfunction. • No evidence of teratogenic effects in cadmium-exposed humans has been reported.

Progress Check

11. Respiratory effects associated with chronic occupational exposure to cadmium include which of the following?

    A. Possible lung cancer.
    B. Chronic rhinitis.
    C. Destruction of the olfactory epithelium and subsequent anosmia.
    D. All of the above.

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

12. Toxic effects on the kidney from chronic cadmium exposure are dose related. For workers, the risk of clinical nephropathy increases significantly with total airborne exposures greater than

    A. 10 mg/m^3
    B. 50 mg/m^3
    C. 100 mg/m^3
    D. 300 mg/m^3.

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

What Factors Increase the Risk of Developing Disease from Exposure to Cadmium?

Learning Objectives	Upon completion of this section, you will be able to • identify factors that increase the risk of developing disease following exposure to cadmium.
Introduction	Cadmium is widespread throughout the environment due to its industrial uses. Whether or not an individual sustains an unusual exposure depends on many factors such as level in the diet, route of exposure, smoking, age, gender, and other physiological factors.
Level and Duration of Exposure	The body burden of cadmium increases with age due to its minimal elimination from the body (0.001% of cadmium is excreted per day) and its subsequent long half-life of 38years. Especially high exposures can occur through jobs that involve possible exposures to cadmium as well as in certain hobbies such as jewelry making which can increase exposures.
Unusual Dietary Exposure	In the Jinzu River basin in Japan, environmental contamination of cadmium from manmade activities resulted in the uptake of this metal into the local rice crop. This uptake resulted in unusual levels of exposure to cadmium and the development of a severe form of cadmium poisoning in elderly post-menopausal females in that area, called "itai-itai" disease. The intake of rice accounted for 40% of the exposure suffered by the affected people. Middle-aged women in Japan were ingesting 37.5 µg/day of cadmium which was two to three times higher than other populations in southeast Asia. For comparison's sake, the average daily intake of cadmium is 6.3-27 µg/day in Europe, and 5-15 µg/day elsewhere in Asia (Tsukahara *et al.* 2003).
Smoking	The tobacco plant preferentially concentrates cadmium regardless of the amount of cadmium in the soil. The average cigarette contains 2 µg cadmium; 2-10% of that dose is transferred by primary cigarette smoke (Mannino *et al.* 2004). Of that, 10% to 50% of cadmium in cigarette smoke is absorbed by the lungs. Therefore, the average smoker has two times the amount of long term cadmium in their bodies than non-smokers (Satarug and Moore 2004; Waalkes 2003).
Effects on Cadmium Absorption	Cadmium absorption from the intestine increases when the body's iron stores are depleted. Cadmium absorption is also increased during pregnancy (Satarug and Moore 2004; Akesson *et al.* 2002).
Key Points	• The body burden of cadmium increases with age due to its minimal excretion. • Smoking increases the body burden of cadmium due to the avidity of the tobacco plant for cadmium. • Cadmium absorption increases during certain physiological states such as iron deficiency and pregnancy.

Progress Check

13. Chronic cadmium poisoning has occurred with which of the following?

    A. In certain areas of the globe with cadmium contamination.
    B. With the practice of certain hobbies such as jewelry making.
    C. With skeletal lesions, as in "itai-itai" disease.
    D. All of the above.

    To review relevant content, see "Level and Duration of Exposure" and "Unusual Dietary Exposure" in this section.

Learning Objectives	Upon completion of this section, you will be able to • describe the presentation of a patient with acute high dose exposure to cadmium, and • describe the workup, including history and physical, of a patient who presents with chronic low-level exposure to cadmium.
Introduction	There are three clinical scenarios that can face the physician dealing with a patient with excessive cadmium exposures. • The complex picture of the respiratory injuries that inhalation of cadmium fumes can cause. • The insidious development of cadmium-related renal disease and the secondary effects on bone that can accompany excessive chronic cadmium exposure. • Increased risk of certain cancers due to chronically heavy cadmium exposures.
History and Presentation - Acute High-Dose Exposure	***Acute inhalation*** The history taken after acute cadmium inhalation usually involves signs and symptoms in the respiratory system. The first symptom, often throat irritation, may not be sufficient to cause exposed workers and others to leave the contaminated area. More striking signs and symptoms, which may be delayed by four to ten hours include • pleuritic chest pain, • dyspnea, • cyanosis, • fever, • tachycardia, and • nausea. Depending on the extent of exposure, sustained fever and noncardiac pulmonary edema may develop. Death has occurred in 20% of cases with pulmonary edema (Newman-Taylor 1998). Inhalation exposure can also result in acute hepatic and renal injury. ***Acute oral*** In the past, acute cadmium intoxication occurred after oral ingestion of acidic foods or beverages stored in cadmium-plated containers, with symptoms of: • abdominal cramps, • diarrhea, • salivation, • severe nausea, and • vomiting. In humans, single lethal oral doses of soluble cadmium salts have ranged from 30-40 mg. (ATSDR, 1999; Drebler, 2002)

Physical Examination of the Acutely Exposed Patient	The physical examination of the patient acutely exposed via inhalation to cadmium should emphasize respiratory signs of acute respiratory injury such as cough and the development of crackles indicating the serious complication of pulmonary edema. In cases of oral ingestion, the status of the gastrointestinal tract as well as the hepatic and renal systems should be monitored.
Approach to the Chronically Exposed Patient	Adverse effects of excessive chronic cadmium exposure may include • chronic obstructive pulmonary disease (inhalation only), • chronic renal failure, • kidney stones, • liver damage (rare), • lung cancer, • osteomalacia, • possibly hypertension, • prostatic cancer, and • proteinuria. Chronic cadmium exposure has been reported to cause mild anemia, anosmia, and yellowing of teeth.
Exposure History for the Chronically Exposed	Detailed questioning about occupations and hobbies is the key to including chronic cadmium poisoning in the differential diagnosis. Subjects for some of these questions include • industrial hygiene, • use of personal protective equipment including respirators or face shields, and • eating or drinking in the work place or in hobby areas where exposure to cadmium could occur. The history should also cover tobacco smoking as well as the use of nephrotoxic medications. The review of systems should pay special attention to the renal, cardiovascular, musculoskeletal and respiratory systems as well as eliciting any reproductive concerns (Lewis, 1997). For more information on taking a detailed environmental exposure history, please see ATSDR's Case Study on Environmental Medicine *Taking an Exposure History* (www.atsdr.cdc.gov/csem/exphistory/). In the general population, ingestion of cadmium-contaminated food is more likely to occur than inhalation of cadmium particles. Today, acute cadmium ingestion is unlikely to be a clinically significant source of exposure in North America. Chronic ingestion, however, is still possible in certain populations, such as children with pica who ingest contaminated soil.
Physical Examination for the Chronically Exposed	Low-level exposure among the general population produces few early physical findings on examination. Among those occupationally exposed or exposed to high levels in the environment, examination of the respiratory, musculoskeletal and genitourinary systems is indicated (Lewis 1997).

Key Points	• Acute high dose inhalation of cadmium fumes presents with respiratory symptoms. • Acute high dose ingestion of cadmium has a clinical presentation that resembles food poisoning. • Chronic cadmium intoxication can present with chronic renal failure, kidney stones, and in severe cases, secondary skeletal lesions.
Progress Check	14. The history taken after acute cadmium inhalation usually involves signs and symptoms in which of the following systems? A. Cardiovascular system. B. Renal system. C. Endocrine system. D. Respiratory system. E. Circulatory system. *To review relevant content, see "History and Presentation – Acute High-Dose Exposure" in this section.* 15. Adverse effects of chronic cadmium exposure may include which of the following? A. Proteinuria. B. Chronic renal failure. C. Kidney Stones. D. Osteomalacia. E. Pulmonary fibrosis. F. All of the above. *To review relevant content, see "Approach to the Chronically Exposed Patient" in this section.*

Clinical Assessment – Laboratory Tests

Learning Objectives	At the end of this section, you will be able to • describe the laboratory tests that can detect the effects of acute cadmium poisoning, and • describe the laboratory evaluation for the possible health effects of chronic exposure to cadmium.
Introduction	The health effects of both acute and chronic cadmium exposure are well known. Therefore, there are medical tests that can measure exposure and cadmium body burden as well as standard and specialized clinical tests to measure the health effects of cadmium exposure.
Laboratory Tests for Acute Exposure	Tests that should be performed if cadmium inhalation is suspected. • Chest X-ray – looking for chemical pneumonitis and pulmonary edema. • Measurement of oxygen saturation. • Renal and hepatic functions – to check for signs of liver or kidney damage. • Cadmium blood levels. Blood cadmium indicates recent exposure and urine cadmium indicates body burden (ATSDR 1999). Tests that should be performed in case of acute cadmium ingestion. • Hepatic and renal functions. • Electrolytes.
Approach to the Chronically Exposed Patient	Initial evaluation of patients with known or suspected chronic cadmium exposure should focus on the kidneys. Initial renal tests should include • BUN, • cadmium in blood and urine, • serum and urinary creatinine, • serum creatinine (and/or calculated creatinine clearance), • serum electrolytes, and • urinary protein (low-molecular-weight proteins such as β_2-microglobulin and RBP). Evaluation for chronic cadmium exposure may also include a complete blood count to check for anemia and liver function tests. In cases with renal complications, a set of skeletal X-rays should be ordered to check for bone-related complications of cadmium exposure such as osteomalacia, osteopenia, and skeletal fractures.

Direct Biological Measures

Urinary Cadmium

With low to moderate chronic exposure, urinary cadmium reflects integrated exposure over time and total body burden (Jarup 2002). Urinary cadmium levels do not rise significantly after acute exposure and are not useful for testing in the acute setting. In occupational settings, urine levels provide little or no useful information during the first year of exposure. According to the NHANES data, healthy young nonexposed nonsmokers in the United States have very low levels of urinary cadmium (average cadmium level of 0.08 µg/g creatinine; levels increase with age to .26 µg/gm of creatinine). "The Third National Report on Human Exposure to Environmental Chemicals" showed that during 2001-2002 the geometric means for adults age 20 and older was 0.210µg/gm creatinine, respectively (CDC 2005). The levels of cadmium increase with age. Clinicians should be aware that smokers in general will have higher urinary cadmium than non-smokers since tobacco smoke is a major source in non-occupationally exposed persons (Mannino *et al.* 2004).

If the kidney's cadmium binding sites all become saturated after chronic high-level exposure, renal dysfunction results and urine cadmium levels increase dramatically. In that setting, urine levels reflect recent exposure rather than total body burden. Renal dysfunction is considered unlikely when urinary cadmium levels are less than 10 µg/g creatinine (Roels *et al.* 1999).

Blood Cadmium

Elevated blood cadmium levels confirm recent acute exposure, (Jarup 2002; ATSDR 1999) but do not correlate with body burden or clinical outcome, and should not be used to determine the need for treatment. The 95% confidence limit for blood cadmium levels in the United States for healthy nonexposed, nonsmokers is 0.4 micrograms per liter (µg/L) (CDC 2005). Occupationally exposed persons may have higher blood levels than the general population. OSHA (www.osha.gov) considers a whole blood level of 5 µg/l or higher hazardous.

Cadmium in Hair

Studies of exposed workers have not found a quantitative relationship between hair cadmium levels and body burden. Because of the potential for sample contamination, hair levels are not reliable either as predictors of toxicity or as indicators of occupational exposure.

Indirect Measures of Exposure

The following tests have been used to screen for renal damage in workers occupationally exposed to high cadmium levels and, under some circumstances, are required by OSHA. Their relevance to the evaluation of persons exposed only to lower environmental levels is uncertain. These are biomarkers that may indicate early toxic effects on the kidney from cadmium exposure. There is occupational data on their significance in exposed workers. (Bernard, 1997)

Urinary β_2-microglobulin

This low-molecular-weight (LMW) protein had been found in increased amounts in the urine of patients with long-term cadmium exposure and is considered a sensitive indicator of cadmium-induced tubular injury. However, other renal diseases, such as chronic pyelonephritis, can also increase β_2-microglobulin excretion. In healthy, unexposed persons, β_2-microglobulin levels average about 200 µg/g creatinine. Excretion increases with age and cadmium exposure. In cadmium workers, urine levels greater than 300 µg/g creatinine indicate possible early kidney disease, and such workers should be further evaluated.

Urinary Retinol Binding Protein (RBP)

RBP is a low molecular weight (LMW) protein found in the urine after chronic cadmium exposure. However, it is a nonspecific finding whenever tubular reabsorption is decreased by any cause. Therefore, it should only be used as a confirmatory test in cases of suspected cadmium exposure.

Urinary metallothionein, MTN

Urinary metallothionein, MTN is another LMW protein synthesized in response to exposure to cadmium and other metals. Urinary levels of MTN correlate well with urinary cadmium levels and can reflect total cadmium body burden; however, urinary concentration of the cadmium-MTN complex increases significantly once renal dysfunction has developed.

Key Points

- The best screening and diagnostic test for chronic cadmium exposure is a 24-hour urinary cadmium level, normalized to creatinine excretion.
- Urinary metallothionein and β_2-microglobulin excretion can be correlated with long-term cadmium exposure.

Progress Check

16. The laboratory evaluation for **acute** cadmium inhalation includes which of the following?

    A. Chest X-ray.
    B. Pulse oximetry.
    C. Renal and hepatic functions.
    D. Cadmium blood levels.
    E. All of the above.

    To review relevant content, see "Laboratory Tests for Acute Exposure" in this section.

17. The laboratory evaluation for **chronic** cadmium exposure includes which of the following?

    A. Renal tests – serum electrolytes, BUN, serum and urinary creatinine, cadmium in urine and urinary proteins (such low-molecular weight proteins such as β_2-microglobulin and RBP).
    B. CBC and liver function tests.
    C. X-rays to check for skeletal lesions.
    D. All of the above.
    E. None of the above.

    To review relevant content, see "Approach to the Chronically Exposed Patient" in this section.

How Should Patients Exposed to Cadmium Be Treated and Managed?

Learning Objectives

Upon completion of this section, you will be able to

- describe how patients with cadmium related diseases should be treated and
- describe how patients with cadmium related diseases should be managed.

Introduction

One exposed person often signals potential or actual exposure of others with the possibility of a common exposure source. Such sources include

- the workplace,
- the drinking water supply,
- community irrigation, and
- proximity to a smelter.

Public health authorities should be notified whenever cadmium toxicity is suspected so that case-finding may be initiated and preventive measures taken.

Treatment of the Acute High-dose Exposure

The mainstay of management for most inhalation exposure victims is supportive treatment including

- fluid replacement,
- supplemental oxygen, and
- mechanical ventilation.

In cases of ingestion, gastric decontamination by emesis or gastric lavage may be beneficial soon after exposure. Administration of activated charcoal has not been proven effective.

Treatment and Management of the Chronically Exposed

For chronic poisoning victims, the most important intervention is prevention of further exposure.

Preventive measures in the workplace include

- improving ventilation by opening windows,
- installing or running an exhaust fan or a mechanical ventilation system, and
- wearing proper personal protective equipment such as respiratory protection, protective clothing, eye protection, and gloves.

Important hygiene preventive measures that are the first line of defense include

- maintaining a clean work area free of dust,
- showering and changing clothes immediately on completion of work in the jewelry area,
- disposing of the contaminated clothing at the work site,
- not tracking dust from the work area to the rest of the home,

	• not smoking in the work area, • no eating or drinking in the work area, and • washing hands well before smoking, eating, or drinking after work or during breaks. In addition, patient and worker education is vital in encouraging preventive behavior and in assisting early detection of cadmium toxicity. Respiratory protection should be worn in occupational or hobby settings where airborne concentrations may exceed allowable limits. Smoking, eating, and drinking in the work area should be discouraged.
Monitoring for Cadmium-Exposed Workers	OSHA requires a program of medical examination and biological monitoring for workers exposed to cadmium for 30 or more days a year at levels of 2.5 $\mu g/m^3$ in air or greater. The purpose of this program is to prevent cadmium induced disease. OSHA required medical monitoring includes • medical and work history, • examination of respiratory and urinary system, • blood pressure measurement, • chest X-ray, • spirometry, and • prostate exam if over 40 years of age. Increased medical monitoring and exposure review is required if urine cadmium is greater then 3µg/gm creatinine, or whole blood cadmium if greater than 5µg/l or urine β_2 microglobulin is greater than 300µg/gm creatinine. Removal from exposure is required if the urine cadmium is greater than 15 µg/gm creatinine or whole blood cadmium is greater than 15 µg/l or urine β_2 microglobulin than 1,500 ug/gm creatinine. A full description of required monitoring and actions required at different cadmium levels can be found at OSHA Standards - Cadmium (www.osha.gov/SLTC/cadmium/standards.html).
Key Points	• There is no specific antidote for acute cadmium poisoning. • Prevention of further exposure is the most important step in management of patients with symptoms suggestive of chronic cadmium intoxication.
Progress Check	18. What are the most effective treatments for acute cadmium poisoning by ingestion? A. Standard chelation therapy using calcium disodium ethylenediamine tetraacetic acid (EDTA). B. Standard chelation therapy using British anti-Lewisite (BAL or dimercaprol). C. Standard chelation therapy using dimercaptosuccine acid. D. None of the above. *To review relevant content, see "Treatment of the Acute High Dose Exposure" in this section.*

What Instructions Should Be Given to Patients Exposed to Cadmium?

Learning Objective	Upon completion of this section, you will be able to • describe preventive measures that patients affected by cadmium should follow.
Introduction	Since cadmium is a cumulative toxin, the most important recommendation that a physician can make to a patient is to avoid or minimize known sources of exposure to cadmium.
Preventive Measures	Instructions for patients in order to prevent or minimize further exposures to cadmium. • Stop smoking. Tobacco smoke contains cadmium and cadmium is absorbed into the system through the lungs. • Be sure of adequate iron in the diet. People who are iron deficient will absorb more oral cadmium into their system. • Practice good occupational hygiene if involved in work with cadmium or in hobbies involving cadmium exposure such as jewelry making or paints using cadmium. If the patient believes that the excessive exposure to cadmium is due to on the job exposures, a good source of information for the occupationally exposed patient is the NIOSH *Pocket Guide to Chemical Hazards* (www.cdc.gov/niosh/npg/).
Clinical Follow-up	If a patient believes that they have been excessively exposed to cadmium, they should come to their family physician for a thorough exposure history, a complete physical, and for appropriate testing. Depending on the findings of the exam, referral to a specialist in pulmonary, renal, and/or skeletal disease may be required.
Key Points	• Patients exposed to cadmium should be instructed how to prevent or minimize further exposures as well as advised of the health risks associated with cadmium exposure.
Progress Check	19. Ways to minimize exposure to cadmium include which of the following? A. Stop smoking. B. Ensure good nutrition and adequate iron intake. C. Maintain good industrial hygiene. D. All of the above. *To review relevant content, see "Preventive Measures" in this section.*

Sources of Additional Information

ATSDR Sources of Information

Sources of information about the adverse effects of cadmium and the management of people exposed to cadmium.

- For emergency situations involving chemical exposures and possible human health effects call

  CDC Emergency Response: 770-488-7100 and request the ATSDR Duty Officer

- For non-emergency situations regarding need for information on health effects of chemicals, contact

  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. We can provide toxicological information on chemicals as well as referral sources to specialists in occupational and environmental medicine.
  - ATSDR Toxicological Profile for Cadmium (www.atsdr.cdc.gov/toxprofiles/tp5.html)
  - ATSDR Toxic Substances and Health - Cadmium (www.atsdr.cdc.gov/substances/cadmium)
  - ATSDR Minimal Risk Level – Cadmium (www.atsdr.cdc.gov/mrls/index.html)
  - ATSDR Division of Toxicology and Environmental Medicine (www.atsdr.cdc.gov/dt/)

Additional Sources of Information

Additional sources of information on cadmium.

- American Association of Poison Control Centers (1-800-222-1222 or www.aapcc.org). The Poison Control Center may be contacted for questions about poisons and poisonings. The web site 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.
- EPA Search Results - Cadmium (nlquery.epa.gov/epasearch/epasearch?querytext=cadmium).
- FDA Website Search Results - Cadmium (google2.fda.gov/search?q=cadmium).
- International Agency for Research on Cancer – Search Results - Cadmium (www.google.com/search?q=site:www.iarc.fr+cadmium).
- NIOSH Safety and Health Topic - Cadmium

(http://www.cdc.gov/niosh/topics/Cadmium/)
- NIOSH Pocket Guide to Chemical Hazards (www.cdc.gov/niosh/npg/).
- National Toxicology Program – Search Results - Cadmium (ntp.niehs.nih.gov:8080/query.html?qt=cadmium).
- OSHA – Safety and Health Topics - Cadmium (http://www.osha.gov/SLTC/cadmium/index.html)
- OSHA Standards - Cadmium (www.osha.gov/SLTC/cadmium/standards.html) includes a full description of required monitoring and actions required at different cadmium levels.
- World Health Organization – Search Results - Cadmium (search.who.int/search?&q=cadmium).
- National Library of Medicine Environmental Health and Toxicology (http://sis.nlm.nih.gov/enviro.html).
- State and local health departments.
- University medical centers affiliated with the American Association of Occupational and Environmental clinics (AOEC).

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Other CSEMs	*Case Studies in Environmental Medicine*: *Cadmium Toxicity* is one monograph in a series. For other publications in this series, please go to: http://www.atsdr.cdc.gov/csem/

Posttest

Introduction

ATSDR seeks feedback on this course so we can asses its usefulness and effectiveness. We ask you to complete the assessment questionnaire online for this purpose.

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

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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 Click on the correct answers. There may be more than one correct answer for each question.

1. The following clinical sequelae may result from chronic exposures to cadmium

   A. Sensory neuropathy in hands and feet.
   B. Renal damage.
   C. Impaired lung function.
   D. Loss of hearing at high frequencies.
   E. Bone fractures.

2. Which of the following statements are true?

   A. Municipal waste incinerators can be a source of airborne cadmium.
   B. Cadmium accumulates in the food chain.
   C. Cigarette smoke is a source of cadmium.
   D. Iron deficiency may decrease a person's risk of cadmium toxicity.
   E. Like lead, cadmium accumulates mostly in bones and teeth.

3. Clues to the diagnosis of chronic cadmium poisoning may include

   A. Hepatomegaly.
   B. Frank wrist drop.
   C. Hyperthyroidism.
   D. Yellow tooth discoloration.
   E. Increased excretion of β_2-microglobulin.

4. The effect of cadmium on the kidney

   A. Can lead to increased urinary excretion of β_2-microglobulin.
   B. Is associated with both renal tubular damage and decreased GFR.
   C. May be worse in cigarette smokers.
   D. Is treatable by chelation.
   E. Leads to increased density of the renal shadow on flat plate of the abdomen.

5. Treatment for acute cadmium poisoning by inhalation may include

   A. Oxygen.
   B. Fluid replacement.
   C. Hemodialysis.
   D. Peritoneal dialysis.
   E. Urinary acidification.

6. The body systems or organs affected by chronic cadmium exposure may include

   A. Olfactory epithelium.
   B. Kidneys.
   C. Adrenals.
   D. Reproductive.
   E. Skeletal.

7. Cadmium toxicity might be suspected in

   A. Rubber workers.
   B. Solderers.
   C. Battery makers.
   D. Jewelry fabricators.
   E. Tree sprayers.

8. Cadmium is a natural element that is classified as a transition metal. Its chemical properties include which of the following?

   A. Is a lustrous blue-tinted solid.
   B. Produced in association with zinc production.
   C. Commonly occurs in a +2 oxidation state.
   D. All of the above.

9. Which of the following statements regarding the biologic fate of cadmium in the body are true

   A. Cadmium is transported in the blood bound to metallothionein.
   B. The greatest cadmium concentrations are found in the kidneys and the liver.
   C. Urinary cadmium excretion is slow; however, it constitutes the major mechanism of elimination.
   D. Due to slow excretion, cadmium accumulates in the body over a lifetime and its biologic half-life may be up to 38 years.
   E. All of the above.

10. Certain factors can increase the body burden of cadmium

    A. Younger age.
    B. Non-smoking.
    C. Pregnancy.
    D. All of the above.
    E. None of the above.

11. During the exposure history, the key to including chronic cadmium intoxication in the differential diagnosis is

    A. A history or smoking tobacco.
    B. A history of febrile illnesses.
    C. Recent physical exercise.
    D. The use of nephrotoxic medications.
    E. Detailed questioning regarding occupations and hobbies.

12. Workers in certain industries are generally exposed to higher levels of cadmium than the general populations since

    A. Cadmium air levels are thousands of times higher in the workplace than in the community.
    B. Workers have lower levels of smoking than the general population.
    C. Ingestion is the main route of exposure in the workplace.
    D. None of the above.

13. The workup for a patient with an acute inhalation exposure to cadmium includes

    A. A exposure history.
    B. Physical with emphasis on the respiratory system.
    C. Chest X-ray.
    D. Pulse oximetry.

14. In order to detect **renal** disease from higher than average chronic exposures to cadmium, one should:

    A. Look for yellow discoloration of teeth.
    B. Order a thorough panel of renal tests including electrolytes, BUN, serum and urinary creatinine, and urinary proteins such as β2-microglobulin and RBP.
    C. Order a set of skeletal X-rays.
    D. Order chest X-ray.

15. Advice the physician can give the patient in order to prevent further exposures to cadmium include

    A. Avoid eating, drinking, and smoking in the workplace.
    B. Eat large amounts of cereal grains and sweetmeats.
    C. Exercise.
    D. None of the above.

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

Question	Location of Relevant Content
1	What diseases are associated with chronic exposure to cadmium?
2	Where is cadmium found? What are routes of exposure for cadmium?
3	What diseases are associated with chronic exposure to cadmium?
4	What diseases are associated with chronic exposure to cadmium?
5	How should patients exposed to cadmium be treated and managed?
6	What diseases are associated with chronic exposure to cadmium?
7	Who is at risk of cadmium exposure?
8	What is cadmium?
9	What is the biologic fate of cadmium in the body?
10	What factors increase the risk of developing disease from exposure to cadmium?
11	Clinical assessment – History and physical examination
12	What are the routes of exposure for cadmium?
13	Clinical assessment – History and physical examination Clinical assessment – Laboratory tests
14	Clinical assessment – Laboratory tests
15	What instructions should be given to patients exposed to cadmium?

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