ATSDR

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Case Studies in Environmental Medicine

10

Cadmium Toxicity

Environmental ALERT . . .

- ☑ ***Prevention is the key to managing cadmium exposure; no effective treatment for cadmium toxicity exists.***
- ☑ ***Nutritional deficiencies can increase the risk of cadmium toxicity.***
- ☑ ***Cadmium affects primarily the renal and skeletal systems.***

This monograph is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to aid in the evaluation of potentially exposed patients. See page 21 for further information about continuing medical education credits and continuing education units.

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

ATSDR

How to use this issue...

This issue begins with a composite case study that describes a realistic encounter with a patient. This description is followed by a pretest. The case study is further developed through Challenge questions at the end of each section. To fully benefit from this monograph, readers are urged to answer each question when it is presented. (Answers to the Pretest and Challenge questions are found on pages 18-19.) The monograph ends with a posttest, which can be submitted to ATSDR for continuing medical education (CME) credit or continuing education units (CEU). See page 21 for further instructions on how to receive these credits.

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

- **Explain why cadmium is a chronic health hazard**
- **Describe the known factors contributing to cadmium poisoning**
- **Identify potential environmental or occupational sources of exposure to cadmium**
- **Identify evaluation and treatment protocols for persons exposed to cadmium**
- **List sources of information on cadmium**

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Case Study

Low back pain and waddling gait in a 60-year-old woman

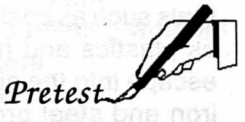
A 60-year-old woman comes to your office with complaints of low back pain, which is causing progressive difficulty in walking. The pain has gradually increased since the onset of menopause 5 years ago. This discomfort is especially noticeable after prolonged sitting.

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 neurologic 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. BUN, creatinine, and albumin levels are normal. Roentgenograms of the pelvis and lumbosacral spine reveal pseudofractures and other evidence of severe osteomalacia and mild osteoporosis. There are no osteolytic or osteoblastic lesions.



(a) What should be included on the patient's problem list?

(b) What additional information would be helpful in diagnosing this woman's condition?

(c) What further tests, if any, would you recommend?

(d) What treatment would be appropriate for this patient?

Answers to the Pretest are included in Challenge answers (6) through (9) on page 19.

Exposure Pathways

- **In the general population, exposure to cadmium occurs primarily by eating crops grown in contaminated soil and seafood.**
- **Airborne cadmium sources include combustion of fossil fuels, incineration of municipal waste, and smelter emissions.**

Pure cadmium is a silver-white, lustrous metal, but cadmium in this form is not common in the environment. It is most often encountered in the earth's crust combined with chlorine (cadmium chloride), oxygen (cadmium oxide), and sulfur (cadmium sulfide). Cadmium oxide also exists as small particles in air (fume), the result of smelting, soldering, or other high-temperature industrial processes. Most cadmium used in the United States is obtained as a byproduct of the smelting of zinc, lead, or copper ores. Cadmium is used mainly in metal plating; in producing pigments, batteries, and plastics; and as a neutron absorbant in nuclear reactors.

Foods are the most important source of cadmium exposure for the general population. Low levels of cadmium are found in basic foodstuffs, especially grains, cereals, and leafy vegetables, which readily absorb naturally occurring cadmium or cadmium in soil contaminated by sewage sludge, fertilizers, and polluted groundwater. In 1946, the inhabitants of the Jintzu River basin in Japan were afflicted with a disease characterized by pain and bone fractures (called itai-itai or ouch-ouch disease), which was caused by high levels of cadmium in water and rice, the result of using water contaminated by discharges from a local zinc-mining operation. Cadmium bioaccumulates in the food chain; consequently, ingestion of animal internal organs, such as liver and kidneys, and some types of fish and shellfish may result in increased exposure.

The greatest sources of airborne cadmium are burning fossil fuels such as coal or oil, and incineration of municipal waste such as plastics and nickel-cadmium batteries. Cadmium may also escape into the air from zinc, lead, or copper smelters, and from iron and steel production facilities. Like most plants, tobacco contains cadmium, which is inhaled in cigarette smoke.

Cadmium concentrations in drinking water supplies are typically less than 1 microgram per liter (µg/L) or 1 part per billion (ppb). 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 caused clinical cadmium poisoning, but even low levels of contamination presumably contribute to the body's accumulation of cadmium.

Cadmium is a component of *chuifong tokwan*, a pharmaceutical compound manufactured in Asia and sold illegally in the United States as a "miracle herb." Some artists' paints contain a yellow pigment made from cadmium sulfide. Cadmium at one time was a leachable component of the alloy used in ice cube trays.

Who's at Risk

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 of cadmium per day (30 µg/day), a rate roughly 10 times lower than that required to cause critical renal effects. Acute cadmium toxicity is rare because very high levels are seldom encountered in the workplace today, and low doses are not acutely toxic. An acute oral dose of 50 µg/kilogram (kg) body weight (about 3500 µg in an adult) is considered the minimal amount capable of causing gastric irritation. Chronic exposures, however, can be a major concern because cadmium has a tendency to accumulate in the body.

- **Workers in industries producing or using cadmium have the greatest potential for cadmium exposure; hobbyists such as jewelry fabricators and artists may also be at increased risk.**
- **Cigarette smoke may add to the body's cadmium burden.**
- **Cadmium absorption may be increased in nutritionally deficient persons.**

Persons in the United States at greatest risk of cadmium exposure are 500,000 workers, including the following:

Alloy makers
Aluminum solder makers
Ammunition makers
Auto mechanics
Battery makers
Bearing makers
Braziers and solderers
Cable, trolley wire makers
Cadmium platers
Cadmium vapor lamp makers
Ceramics, pottery makers
Copper-cadmium alloy makers
Dental amalgam makers
Electric instrument makers
Electrical condenser makers
Electroplaters
Engravers
Glass makers
Incandescent lamp makers
Jewelers
Lithographers
Lithopone makers
Mining and refining workers
Paint makers
Paint sprayers
Pesticide makers
Pharmaceutical workers
Photoelectric cell makers
Pigment makers
Plastic products makers
Sculptors, metal
Smelterers
Solder makers
Textile printers
Welders, cadmium alloy and cadmium-plate

Hobbyists may also encounter cadmium in their pursuits. For example, cadmium is present in many gold and silver solders used in fabricating jewelry and in the metal dust produced in grinding or engraving cadmium-plated surfaces. The likelihood of cadmium inhalation is increased in poorly ventilated work areas, and cadmium ingestion is increased by eating and smoking in these areas.

Cadmium air levels are usually thousands of times greater in the workplace than in the general environment. For example, the permissible exposure limit (PEL) of cadmium fume or cadmium oxide in the workplace is 100 micrograms per cubic meter of air (100 $\mu g/m^3$), whereas concentrations of cadmium in ambient air rarely exceed 0.0025 $\mu g/m^3$ in nonindustrialized areas and 0.040 $\mu g/m^3$ in urban areas. The U.S. Environmental Protection Agency (EPA) has estimated that 24-hour, lifelong inhalation of air containing 1 $\mu g/m^3$ cadmium is associated with a lung cancer risk of, at most, 2 additional cases in 1000 persons exposed.

Each cigarette contains 2 µg of cadmium, with 50% absorbed from the lungs during active cigarette smoking. Persons who smoke one pack per day typically have cadmium blood and body burdens approximately twice as high as those of nonsmokers.

Nutritional factors affect the amount of cadmium absorbed. Persons with low calcium, protein, or iron reserves absorb cadmium more efficiently and may be at increased risk of developing toxicity. Age and gender may also play a role. Iron-deficient neonates absorb greater amounts of cadmium than iron-deficient adults; females absorb more than males. Iron deficiency, resulting in increased cadmium absorption, may have contributed to the high incidence of itai-itai disease in multiparous Japanese women.

(1) Additional information for the case study: The patient maintains a jewelry fabricating and engraving area in her home basement 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.

What are the potential sources of cadmium exposure for this patient?

_____

(2) Why is the patient described in the case study at increased risk of cadmium toxicity?

_____

(3) Is the patient's husband also at increased risk? Explain.

_____

_____

Biologic Fate

Respiratory absorption of cadmium in humans is estimated to be from 30% to 60% of an inhaled dose, depending on particle size. Only the smallest particles penetrate to the alveoli, the major site of absorption. As a result, cadmium particles in fumes and cigarette smoke, which are smaller, are more completely absorbed than most cadmium particles of industrial origin.

In humans, no more than 5% of ingested cadmium is absorbed from the gut into the blood or lymphatic fluid. Although some nutritional factors increase this absorption, zinc and chromium can decrease cadmium uptake. Absorption through the skin is not a significant route of cadmium entry.

- **Cadmium has no known beneficial function in the human body.**
- **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. Cadmium biologic half-life may be up to 30 years.**

Once absorbed, cadmium is distributed by the blood. Lymphocytes synthesize metallothionein, a metal-binding protein, which concentrates cadmium three-thousandfold. Cadmium does not undergo metabolic conversion in vivo.

Cadmium is eliminated from the body primarily in urine. The rate of excretion is low, probably because cadmium remains tightly bound to metallothionein, which is almost completely reabsorbed from the glomerular filtrate. Because excretion is slow, cadmium accumulation can be significant. Whereas 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.

The total cadmium body burden at birth is less than 1 μg, which gradually increases with age to about 30 milligrams (mg). The highest cadmium concentration is found in the kidneys, especially the renal cortex, followed by the liver, pancreas, and adrenals. In the kidney, cadmium concentration steadily increases over time, then declines at 50 to 60 years of age. In the liver, however, cadmium concentration increases continuously with age. The kidneys and liver together total about 50% of the body accumulation in humans.

Both the liver and kidneys store cadmium as a metallothionein complex, which serves not only to transport cadmium but also acts as a defense mechanism against the toxicity of the unbound cadmium ion. Ironically, it is the cadmium-metallothionein complex that accumulates in the kidneys and is partially responsible for cadmium's toxic renal effects. Cadmium does not accumulate in bone, and the blood-brain barrier appears to limit its uptake into the central nervous system. The placenta acts only as a partial barrier to fetal exposure.

The biologic half-life of cadmium in the body is estimated to be 30 years. This long half-life is due to the body's inability to deal with increasing cadmium intake by homeostatic control mechanisms; humans do not have an effective cadmium elimination pathway. Cadmium has no known biologic function in humans, and bioaccumulation appears to be a byproduct of increasing industrialization. Any excessive accumulation in the body should be regarded as potentially toxic.

(4) Could diet play a role in the condition of the patient described in the case study?

_____

_____

Physiologic Effects

The mechanisms of cadmium toxicity are not fully understood but may involve binding of the metal to key cellular sulfhydryl groups, competition with other metals (zinc and selenium) for inclusion in metalloenzymes, and competition with calcium for binding sites on regulatory proteins such as calmodulin. The route and extent of cadmium exposure will influence the presentation of toxic effects.

- **Cadmium primarily affects the kidneys and skeletal system.**

Renal Effects

Nephrotoxicity may be caused by either chronic inhalation or chronic ingestion of the metal. Data from human studies suggest a latency period of approximately 10 years before clinical onset of renal damage, depending on intensity of exposure. Proteinuria appears to be irreversible, and continued exposure can lead to progressive renal dysfunction.

- **Cadmium toxicity may cause both tubular and glomerular damage with resultant proteinuria.**

Typically the proximal renal tubules are affected, resulting in a Fanconi-like syndrome with urinary excretion of low molecular weight proteins such as β_2-microglobulin, lysozyme, and retinol-binding protein. Glucosuria, aminoaciduria, increased excretion of calcium and phosphate, and decreased renal concentrating capacity also occur. Disturbances in calcium and phosphorus metabolism may subsequently lead to formation of kidney stones and demineralization of bones.

Tubular proteinuria may be accompanied by glomerular dysfunction with increased urinary excretion of high molecular weight proteins such as albumin, transferrin, and immunoglobulin G (IgG). An increased renal excretion of enzymes may also occur.

Skeletal Effects

- **Bone changes appear to be secondary to renal tubular dysfunction.**

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. Such fractures may have contributed to the waddling gait seen in Japanese patients with itai-itai disease.

Skeletal effects appear to be secondary to increased urinary calcium and phosphorus losses. These effects are compounded by inhibition of renal hydroxylation of vitamin D, which eventually leads to a deficiency of its active form. Some investigators believe cadmium also exerts an inhibitory effect on calcium absorption from the gastrointestinal tract.

Respiratory Effects

- **Acute cadmium inhalation may mimic metal fume fever.**
- **Chronic cadmium inhalation may result in impairment of pulmonary function with a reduction in ventilatory capacity.**

Acute cadmium oxide inhalation exposure occurs rarely, but has been reported to cause chemical pneumonitis and metal fume fever (a transient and generally benign syndrome of fever, malaise, and chest tightness). Studies have associated chronic cadmium inhalation with pulmonary function impairment, notably mild emphysema and pulmonary fibrosis with reduced ventilatory capacity. However, study limitations, such as small sample size, lack of a suitable cohort, and failure to control for the confounding effects of cigarette smoking, have raised questions about these findings. In one study of workers making copper-cadmium alloy, the largest reductions in forced expiratory volume in 1 second (FEV_1), its ratio to forced vital capacity (FEV_1/FVC%), and gas transfer were noted in those cadmium workers with the highest liver cadmium levels and the highest cumulative cadmium exposures. Pulmonary changes appear to occur after renal damage and are rarely seen today.

Carcinogenic Effects

- **Cadmium's carcinogenic effects have been demonstrated in experimental animals; evidence in humans is less conclusive.**

Inhalation of cadmium chloride and intratracheal instillation of high doses of cadmium sulfide are associated with an increased frequency of lung tumors in rats. Inhalation of various cadmium compounds did not produce increased incidence of lung tumors in hamsters or mice, however.

Epidemiologic studies of workers suggest a possible association between cadmium inhalation and the development of lung, prostatic, and testicular cancer. Many of these studies failed to control for smoking or exposure to other chemicals, however, and only small numbers of persons were evaluated. No clinical or experimental evidence indicates that ingesting cadmium in food or drinking water causes cancer. This is also true in Japan, where oral intake of cadmium tends to be high. Despite the uncertainty regarding the carcinogenicity of cadmium in humans, EPA and the International Agency for Research on Cancer have classified cadmium as a probable human carcinogen when inhaled.

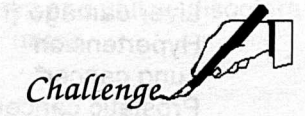
Developmental Effects

No conclusive evidence of cadmium-induced teratogenicity in either experimental animals or humans has been reported. In a Swedish epidemiologic study of pregnant women exposed to high cadmium concentrations in the workplace, an increased incidence of infants with low birth weight was reported.

❑ **No evidence of teratogenic effects in cadmium-exposed humans has been reported.**

Other Effects

Chronic cadmium exposure has been reported to cause mild anemia, anosmia, yellowing of teeth, and, occasionally, liver damage. There is no conclusive evidence that cadmium alone causes hypertension. However, cadmium-induced renal dysfunction can eventually manifest in hypertension.



(5) Could cadmium intoxication explain the problem list and initial laboratory findings for the patient described in the case study? Explain.

Clinical Evaluation

History and Physical Examination

- **Concomitant exposure to other heavy metals should be assessed.**

Detailed questioning about occupations and hobbies is the key to including chronic cadmium poisoning in the differential diagnosis. Inhalation exposure most often occurs among workers and hobbyists when cadmium fumes are produced by high-temperature processes such as welding, smelting, and soldering, and where cadmium dust results from grinding.

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, for example, children with pica who ingest contaminated soil.

Signs and Symptoms

Adverse effects of excessive cadmium exposure may include the following:

Acute Exposure
- Gastroenteritis (ingestion only)
- Bronchitis (inhalation only)*
- Interstitial pneumonitis (inhalation only)
- Pulmonary edema (inhalation only)

Chronic Exposure
- Proteinuria
- Osteomalacia (itai-itai disease)
- Pulmonary fibrosis (inhalation only)*
- Liver damage (rare)
- Hypertension
- Lung cancer*
- Prostatic cancer*
- Mild anemia
- Yellow discoloration of front teeth near gum line
- Anosmia

* Evidence of human health effects is inconclusive.

Acute Exposure

Most acute cadmium inhalation exposures involve initial symptoms and physical findings relating to the respiratory system. The first symptom, usually throat irritation, may not be severe enough to prompt the worker to leave the area. Symptoms, which may be delayed by hours or days, include pleuritic chest pain, dyspnea, cyanosis, fever, tachycardia, and nausea. Depending on the extent of exposure, noncardiogenic pulmonary edema may appear and progress to death.

- **Acute inhalation of cadmium may cause symptoms similar to those of metal fume fever.**

In the past, acute cadmium intoxication occurred after ingestion of acidic foods or beverages stored in cadmium-plated containers, with symptoms of severe nausea, vomiting, salivation, abdominal cramps, and diarrhea. Acute renal failure, cardiopulmonary depression, and shock due to fluid loss have also occurred. In humans, single lethal oral doses of cadmium have ranged from 350 to 8900 mg. An ingestion of 150 grams (g) of cadmium chloride was reported to produce facial edema, vomiting, hypotension, metabolic acidosis, pulmonary edema, oliguria, respiratory arrest, and, finally, death after 30 hours.

- **Acute oral ingestion results in severe gastroenteritis.**

Chronic Exposure

Effects of chronic cadmium exposure are dose-dependent. Low-level chronic exposure produces few early physical findings. Severe chronic exposure leads to manifestations of renal tubular dysfunction, especially in postmenopausal, multiparous females. This group typically has calcium and vitamin deficiencies that can increase the gastrointestinal absorption of cadmium. Other symptoms include low back pain and bone pain secondary to pseudo- and pathologic fractures. Chronic cadmium intoxication may also play a role in the development of hypertension, although the association is weak. Anosmia and yellow discoloration of teeth near the gum line may be noted.

- **Mild anemia and yellow discoloration of teeth may occur.**

- **Chronic exposure may result in back pain and renal dysfunction.**

Laboratory Evaluation

Initial laboratory evaluation should focus on the kidneys. Screening tests include measures of renal dysfunction such as BUN, serum and urinary creatinine, serum and urinary protein, and glucose. Complete blood count, liver function tests, and chest X ray (if

cadmium inhalation is suspected) should be performed. Specialized laboratory tests include direct measurement of cadmium levels and more sophisticated renal function tests.

Direct Biologic Indicators

- **The best screening and diagnostic test for chronic cadmium exposure is a 24-hour urinary cadmium level, normalized to creatinine excretion.**

Urine cadmium. With low to moderate chronic exposure, urinary cadmium reflects the total body burden. The average daily excretion of cadmium in persons with no known cadmium exposure is usually below 1 µg/L, or 1 µg/g creatinine, increasing with age and smoking. When all cadmium-binding sites in the kidney become saturated, however, renal dysfunction results and the direct relationship to body burden is lost. The amount of cadmium excreted then increases dramatically, reflecting recent exposure rather than total body burden. When urinary cadmium levels are less than 10 µg/g creatinine, renal dysfunction is considered unlikely.

Serum cadmium. Serum cadmium levels reflect recent exposure and generally are not useful for evaluating chronically exposed patients. Normal serum concentrations of cadmium in nonexposed persons range from 0.05 to 0.3 micrograms per deciliter (µg/dL). Occupationally exposed persons may have levels ranging from 1 to 10 µg/dL. A blood level of 5 µg/dL or higher is considered toxic.

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 a predictor of toxicity or as an indicator of occupational exposure.

Indirect Biologic Indicators

- **Urinary metallothionein and β_2-microglobulin excretion can be correlated with long-term cadmium exposure.**

The tests that follow have been used to determine renal damage in persons exposed to high cadmium levels. They may have little relevance in evaluating persons exposed to lower environmental levels, however.

Urinary β_2-microglobulin. This low molecular weight protein is found in increased amounts in the urine of patients with long-term cadmium exposure and is considered a more sensitive indicator of cadmium exposure than total proteinuria. However, other renal diseases, such as chronic pyelonephritis, also cause

increased β_2-microglobulin excretion. Excretion of β_2-microglobulin increases with age and cadmium exposure, but has been reported to average about 200 µg/g creatinine in unexposed persons.

Urinary metallothionein. Metallothionein is a low molecular weight protein synthesized in response to the presence of divalent metals such as cadmium, zinc, and copper. The protein is formed primarily in the lymphocytes, kidney, liver, and intestine. Its function appears to be the binding of metal ions, thus rendering them less toxic. Once metallothionein binds to cadmium, the complex preferentially accumulates in the kidney. Urinary levels of metallothionein correlate well with urinary cadmium levels and can reflect total cadmium body burden; however, urinary concentration of the cadmium-metallothionein complex increases significantly once renal dysfunction has developed.

Urinary retinol-binding protein. Retinol-binding protein is another low molecular weight protein appearing in the urine after chronic cadmium exposure. It is excreted when tubular reabsorption decreases due to any cause and, therefore, is nonspecific and can be used only as a supportive test in cases of suspected cadmium exposure.

(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?

_____

Treatment and Management

One exposed person often signals potential or actual exposure of others, with the possibility of a common exposure source. Such sources include the workplace, drinking water supply, community irrigation, proximity to a smelter, and so on. Public health authorities should be notified whenever cadmium toxicity is suspected in a patient so that case-finding may be initiated and preventive measures taken.

Acute Exposure

- **There is no specific antidote for cadmium poisoning.**

There is no effective treatment for cadmium poisoning. Standard chelation therapy using ethylenediaminetetraacetic acid (EDTA), British anti-Lewisite (BAL or dimercaprol), or dimercaptosuccinic acid (DMSA) has generally not proven effective. BAL is contraindicated because it may increase nephrotoxicity. Treatment remains supportive, including fluid replacement, supplemental oxygen, and mechanical ventilation, if necessary. 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.

Chronic Exposure

- **Prevention of further exposure is the most important step in management of patients with symptoms suggestive of cadmium intoxication.**

The mainstay of therapy in chronic poisoning involves removing the patient from further exposure. In the workplace, engineering controls, improved ventilation, and personal hygiene are the first line of defense. 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.

Challenge

(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.

_____

Standards and Regulations

With increasing evidence of its toxicity, both national and international agencies have sought to regulate cadmium exposure. These efforts encompass workplace and environmental guidelines or regulations for air emissions, drinking water, food, industrial discharges, and hazardous waste concentrations. Table 1 summarizes standards, regulations, and guidelines for cadmium.

Table 1. Standards and regulations for cadmium

Agency *	Focus	Level	Comments
ACGIH	Air -Workplace		
	cadmium dust	0.05 mg/m^3	Advisory; TWA†
	cadmium fume	0.05 mg/m^3	15-minute ceiling limit
NIOSH	Air -Workplace	N/A	Advisory; lowest possible limit based on carcinogenic risk
OSHA	Air -Workplace		
	cadmium dust	0.2 mg/m^3	Regulation; PEL§
	cadmium fume	0.1 mg/m^3	
EPA	Air	N/A	Under review
	Water	0.01 ppm	Regulation; maximum contaminant level in drinking water; suggested revision to 0.005 ppm
WHO	Food	0.4-0.5 mg	Advisory; provisional tolerable weekly intake for adults

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

† TWA (Time-Weighted Average) = time-weighted average concentration for a normal 8-hour workday and 40-hour workweek to which nearly all workers may be repeatedly exposed.

§ PEL (Permissible Exposure Limit) = highest level averaged over a normal workday, to which a worker may be exposed.

Workplace

Air

The PEL for airborne cadmium in the workplace has been set by the Occupational Safety and Health Administration (OSHA) at 0.2 mg/m^3 as an 8-hour time-weighted average (TWA) for cadmium dust, and 0.1 mg/m^3 for cadmium fume (cadmium oxide). A 15-minute ceiling concentration of 0.6 mg/m^3 for cadmium dust

❑ OSHA has proposed lowering cadmium workplace exposures by 99%.

and 0.3 mg/m^3 for cadmium fume (cadmium oxide) has been mandated. OSHA's proposed 1990 ruling seeks to reduce permissible cadmium workplace exposures by 99%.

The National Institute for Occupational Safety and Health (NIOSH) recommends that cadmium be regarded as a potential carcinogen based on laboratory studies and epidemiologic studies of lung cancer among workers.

Environment

Air

No EPA air standard for cadmium currently exists.

Cadmium levels in the ambient atmosphere are generally low. Typically, cadmium concentrations range from 1 to 5 nanograms per cubic meter (ng/m^3) in sparsely populated rural areas and from 5 to 40 ng/m^3 in urban air. In the vicinity of active zinc or lead smelters, cadmium values of 300 to 700 ng/m^3 have been measured at distances of 0.5 to 1 kilometer from the smelter. Near incinerators, average cadmium air levels have been estimated to be 7 ng/m^3. EPA is seeking classification of cadmium as a hazardous air pollutant; however, no ambient air standard for cadmium currently exists.

Water

EPA has proposed lowering the regulated level of cadmium in drinking water.

EPA has established a maximum contaminant level (MCL) for cadmium in drinking water of 0.010 mg/L (0.01 ppm) and is currently seeking its revision to 0.005 mg/L (0.005 ppm). EPA and some states regulate the amount of cadmium discharged in industrial wastewaters.

Food

Dietary cadmium is not regulated.

Average daily dietary cadmium intake is 10 to 50 µg. The World Health Organization has recommended a provisional tolerable weekly intake of 400 to 500 µg cadmium for adults. Nevertheless, the exact amount of cadmium in the average American diet is difficult to control. For this reason, efforts have been directed toward reducing cadmium discharged into waterways and deposited on soil, which could eventually enter the food chain.

Soil

EPA regulates application of solid waste to topsoil.

A 1979 report noted that topsoils in the United States contain an average cadmium level of about 260 µg/kg. Levels in soil near sources of contamination may greatly exceed this value. Crops grown in contaminated soil are capable of translocating the metal and present a likelihood of exposure to consumers. Currently, there is no effective way to decontaminate soil. EPA regulation for application of solid waste to topsoil used in crop production for human consumption is 0.5 kg of solid waste per hectare annually.

Suggested Reading List

General

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Kazantzis G. The mutagenic and carcinogenic effects of cadmium: an update. Toxicological and Environmental Chemistry 1987;15:83-100.

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Renal Effects

Kido T, Honda R, Tsuritani I, et al. Progress of renal dysfunction in inhabitants environmentally exposed to cadmium. Arch Environ Health 1988;43:213-17.

Shaikh ZA, Tohyama C, Nolan CV. Occupational exposure to cadmium: effect on metallothionein and other biological indices of exposure and renal function. Arch Toxicol 1987;59:360-4.

Food and Diet

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Sherlock JC. Cadmium in foods and the diet. Experientia 1984;40:152-6.

Laboratory Evaluation

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Human Health Effects

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Hallenbeck WH. Human health effects of exposure to cadmium. Experientia 1984; 40:136-42.

Yost KJ. Cadmium, the environment and human health: an overview. Experientia 1984;40:157-64.

Related Government Documents

Agency for Toxic Substances and Disease Registry. Toxicological profile for cadmium. Atlanta: US Department of Health and Human Services, Public Health Service, 1989. NTIS report no. PB/89/194476/AS.

Environmental Protection Agency. Health effects assessment for cadmium. Washington, DC: Office of Health and Environmental Assessment. EPA report no. 540/1-86-038.

Environmental Protection Agency. Cadmium contamination of the environment: an assessment of nationwide risk. Washington, DC: Environmental Protection Agency. EPA report no. 440/4-85-023.

Answers to Pretest and Challenge Questions

Pretest is found on page 1. Challenge questions begin on page 5.

(1) Potential sources of cadmium are as follows:
   (a) cadmium fume (cadmium oxide) generated by use of gold and silver solders during jewelry fabrication
   (b) cadmium dust produced in smoothing jewelry with abrasive grinding or in engraving cadmium-plated surfaces
   (c) food and cigarettes in the workplace contaminated by cadmium-containing particulates and dust
   (d) cigarette smoke
   (e) food grown in soil contaminated with cadmium-containing fertilizer obtained from the wastewater treatment plant

(2) 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. The patient also inhales approximately 2 μg cadmium with each cigarette smoked. The amount of cadmium ingested from the vegetables grown in her garden is unknown, but sludges from wastewater treatment plants have been found to contain significant levels of cadmium. Factors that may enhance cadmium absorption from the gut are age and certain dietary deficiencies.

(3) 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 tobacco smoke from cigarettes, even more so if he smokes. 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.

(4) Yes, diet could play an important role in the patient's condition, both for what it contributes and for what it does not include. 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 iron, calcium, or protein she may be absorbing cadmium more efficiently.

(5) The patient's problem list includes the following:
   back pain
   severe osteomalacia and mild osteoporosis
   pseudofractures
   yellow discoloration of the teeth
   proteinuria and glycosuria

All of these are consistent with chronic cadmium toxicity. The patient is also a smoker. Chronic cadmium exposure primarily affects the kidneys and skeleton. 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.

(6) Most of your questions will probably center on the patient's hobby, as this is the greatest potential source of cadmium exposure. Typical questions would include the following:
   (a) What types of materials and metals are used in making jewelry? What are the ingredients of all composite products?
   (b) On a weekly basis, how many hours are spent fabricating jewelry in the basement?
   (c) What type of face shield is used? Why is respiratory protection not used during grinding and soldering operations?
   (d) Is the work area kept clean and free of dust? How?
   (e) Does she wash her hands before eating in the work area and are attempts made to keep food and cigarettes from becoming contaminated by dust and particulates?
   (f) Does she shower and change her clothes before leaving the work area?

   It is also important to investigate smoking habits.

(7) The most useful diagnostic test for cadmium exposure is a 24-hour urinary cadmium excretion standardized for creatinine. β_2-microglobulin levels, in conjunction with cadmium excretion, will aid in evaluating subclinical renal dysfunction. The following tests also may be helpful in evaluating the patient: urinary protein and glucose, LDH, SGPT or ALT, and SGOT or AST. A chest X ray and pulmonary function test should be obtained if cadmium inhalation is a factor.

(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; urinary cadmium levels in an unexposed population are typically between 1 and 10 µg cadmium/g creatinine. 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.

(9) There is no effective treatment for cadmium toxicity; chelation therapy has no role in 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.

10) The neighbors should be evaluated and educated. 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.

Sources of Information

More information on the adverse effects of cadmium and the treatment and management of cadmium-exposed persons can be obtained from ATSDR, your state and local health departments, and university medical centers. *Case Studies in Environmental Medicine: Cadmium Toxicity* is one of a series. For other publications in this series, please use the order form on the back cover. For clinical inquiries, contact ATSDR, Division of Health Education, Office of the Director, at (404) 639-6204.

Posttest and Credits

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

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

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

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

The **American Academy of Family Physicians (AAFP)**. This program has been reviewed and is acceptable for 1 prescribed hour by the American Academy of Family Physicians. (Term of Approval: beginning January 1992.) For specific information, please consult the AAFP Office of Continuing Medical Education.

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

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

The **American Association of Occupational Health Nurses (AAOHN)**. AAOHN has approved this program for 1.2 contact hours. Applicant will receive the assigned code number in the award letter.

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

To receive continuing education credit (CME or CEUs), complete the Posttest on page 22 in the manner shown in the sample question below. **Circle all correct answers.**

Which of the following is known to precipitate migraine headaches?

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

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

POSTTEST: CADMIUM TOXICITY

Circle **all** correct answers and transfer your answers to page 23.

1. The following clinical sequelae may result from cadmium intoxication:
   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. An effect associated with exposure to cadmium is
   a. lung toxicity, particularly after inhalation of metal fumes
   b. acute hepatic necrosis
   c. chronic renal disease
   d. cancer of the pancreas
   e. atopic dermatitis
5. The effect of cadmium on the kidney
   a. can lead to increased urinary excretion of β_2-microglobulin
   b. in occupational settings can lead to acute renal failure
   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
6. Treatment for acute cadmium poisoning may include
   a. oxygen
   b. fluid replacement
   c. dialysis
   d. chelation
   e. urinary acidification
7. The body systems or organs affected by chronic cadmium exposure include
   a. central nervous system
   b. kidneys
   c. adrenals
   d. reproductive
   e. skeletal
8. Cadmium toxicity might be suspected in
   a. rubber workers
   b. solderers
   c. battery makers
   d. jewelry fabricators
   e. tree sprayers

CASE STUDIES IN ENVIRONMENTAL MEDICINE: CADMIUM TOXICITY

If you wish CME credits or CEUs, please indicate your answers to the Posttest questions on page 22 by circling the letters below for the correct answers. Complete the evaluation questionnaire and fill in the information requested on the reverse side. Tear off this last page, fold, staple, and mail to Continuing Education Coordinator, Agency for Toxic Substances and Disease Registry, Division of Health Education, E33, 1600 Clifton Road, Atlanta, GA 30333.

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

Evaluation Questionnaire

Please complete the following evaluation by circling the appropriate number.

	STRONGLY DISAGREE	DISAGREE	NEITHER AGREE NOR DISAGREE	AGREE	STRONGLY AGREE
1. As a result of completing this monograph, I will be able to:					
Explain why cadmium is a chronic health hazard.	1	2	3	4	5
Describe the known factors contributing to cadmium poisoning.	1	2	3	4	5
Identify potential environmental or occupational sources of exposure to cadmium.	1	2	3	4	5
Identify evaluation and treatment protocols for persons exposed to cadmium.	1	2	3	4	5
List sources of information on cadmium.	1	2	3	4	5
2. The monograph addressed the objectives printed on the inside front cover.	1	2	3	4	5
3. I am more likely to ask patients questions regarding possible environmental exposures as a result of reading this issue.	1	2	3	4	5
4. Independent study was an effective teaching method for the content.	1	2	3	4	5
5. How much time (in minutes) was required to read this monograph and complete the posttest?	40	60	80	100	120

Comments:_____

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

- ☐ Arsenic
- ☐ Asbestos
- ☐ Benzene
- ☐ Beryllium
- ☐ Cadmium
- ☐ Carbon Tetrachloride
- ☐ Chlordane
- ☐ Cholinesterase Inhibitors
- ☐ Chromium
- ☐ Cyanide
- ☐ Dioxins
- ☐ Ethylene/Propylene Glycols
- ☐ Exposure History
- ☐ Gasoline
- ☐ Jet Fuel
- ☐ Lead
- ☐ Mercury
- ☐ Methanol
- ☐ Methylene Chloride
- ☐ Nitrates/Nitrites
- ☐ Pentachlorophenol
- ☐ Polyaromatic Hydrocarbons (PAHs)
- ☐ Polychlorinated Biphenyls (PCBs)
- ☐ Radiation
- ☐ Radon
- ☐ Reproductive and Developmental Hazards
- ☐ Skin Lesions
- ☐ Stoddard Solvent
- ☐ Tetrachloroethylene
- ☐ 1,1,1-Trichloroethane
- ☐ Trichloroethylene
- ☐ Toluene
- ☐ Vinyl Chloride

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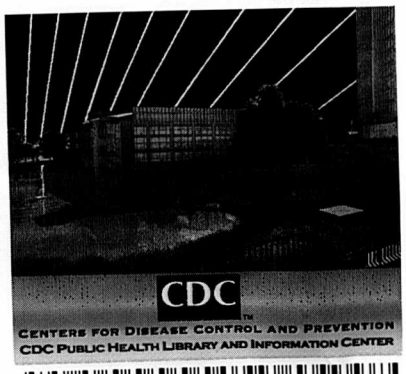

The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and is often uncertain. In this monograph, the Agency for Toxic Substances and Disease Registry (ATSDR) has made diligent effort to ensure the accuracy and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

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