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

Course: **WB 1466**
Original Date: **December 18, 2008**
Expiration Date: **December 18, 2011**

Table of Contents

Key Concepts	• The toxicity of chromium compounds depends on the oxidation state of the metal. • Occupational exposure to chromium(VI) compounds has been associated with increased incidence of lung cancer. • Chromium(III) is an essential nutrient that can be toxic in large doses.
About This and Other Case Studies in Environmental Medicine	This educational case study document is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to promote the adoption of medical practices that aid in the evaluation *and care of* potentially exposed patients. The complete series of *Case Studies in Environmental Medicine* is located on the ATSDR Web site at www.atsdr.cdc.gov/csem/. In addition, the downloadable PDF version of this educational series and other environmental medicine materials provides content in an electronic, printable format, especially for those who may lack adequate Internet service.
How to Apply for and Receive Continuing Education Credit	See Internet address www2.cdc.gov/atsdrce/ for more information about continuing medical education credits, continuing nursing education credits, and other continuing education units.

Acknowledgments

We gratefully acknowledge the work that the medical writers, editors, and reviewers have provided to produce this educational resource. Listed below are those who have contributed to development of this version of the *Case Study in Environmental Medicine.*

Please Note: Each content expert for this case study has indicated that there is no conflict of interest to disclose that would bias the case study content.

CDC/ATSDR Author(s): Dianyi Yu, M.D.

CDC/ATSDR Planners: Charlton Coles, Ph.D.; John Doyle, MPA; Bruce Fowler, PhD.; Kimberly Gehle, MD; Sharon L. Hall, Ph.D.; Michael Hatcher, DrPH; Kimberly Jenkins, BA; Ronald T. Jolly; Barbara M. Riley, RN; Delene Roberts, MSA; Oscar Tarrago, MD, MPH, CHES; Brian Tencza, MS; Sharon Wilbur, MA; Dianyi Yu, MD.

Peer Reviewers: Jonathan Borak, MD, DABT; Dave Hewitt, MD.

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.

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

How to Use This Course

Introduction	The goal of *Case Studies in Environmental Med*icine (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 chromium toxicity.
Availability	Two versions of the Chromium Toxicity CSEM are available. • The HTML version www.atsdr.cdc.gov/csem/chromium/ 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 chromium toxicity. • Read the title, learning objectives, text, and key points in each section. • Complete the progress check exercises at the end of each section and check your answers. • Complete and submit your assessment and posttest response online if you wish to obtain continuing education credit. Continuing education certificates can be printed immediately upon completion.
Instructional Format	This course is designed to help you learn efficiently. Topics are clearly labeled so that you can skip sections or quickly scan sections you are already familiar with. This labeling will also allow you to use this training material as a handy reference. To help you identify and absorb important content quickly, each section is structured as follows:

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

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

Content Area	Objectives
Overview	• Explain what chromium is.
Exposure Pathways	• Identify sources of chromium exposure. • Identify the routes of exposure to chromium.
Who is at Risk	• Identify who is at risk of exposure to chromium.
Standards and Regulations	• Identify the OSHA permissible exposure limit (PEL) for chromium. • Identify EPA's maximum contaminant level (MCL) for chromium in drinking water.
Biological Fate	• Explain the metabolic difference between Cr(III) and Cr(VI).
Physiologic Effects	• List and describe the physiologic effects associated with chromium exposure.
Clinical Assessment	• Describe characteristic clinical presentations of patients with acute or chronic chromium exposure. • Identify important aspects of the exposure history. • Describe characteristic findings on patient examination. • Identify laboratory tests that can assist with diagnosis of chromium exposure.
Treatment and Management	• Describe the principal treatment strategies for managing chromium poisoning.
Patient Education and Counseling	• Identify instructions for patient self-care and for clinical follow-up.

Initial Check

Instructions	This Initial Check will help you to assess your current knowledge about chromium toxicity. To take the Initial Check, read the case below, and then answer the questions that follow.
Case	***A 35-year-old handyman has chronic skin ulcers and respiratory irritation.*** A 35-year-old man visits your family practice office near a large Midwestern city. He has complaints of "allergies" and sores on his hands and arms. Over the past 2 to 3 months, the patient has noticed the onset of runny nose, sinus drainage, dry cough, and occasional nosebleeds (both nares intermittently). No prior history of allergies exists. He has also had occasional nausea and is concerned because the sores and minor skin cuts on his hands do not seem to heal. The patient denies having fever, chills, dyspnea, or change in bowel or bladder habits, and he has not noticed excessive thirst or easy bruising. He recently began losing his appetite and losing weight without dieting. With the exception of the complaints mentioned, review of systems is otherwise unremarkable. The patient has used various over-the-counter remedies for his respiratory problems without relief. He did note however significant improvement in symptoms when he visited his sister in Chicago for 5 weeks at the end of the summer. Medical history reveals only usual childhood diseases. Other than over-the-counter (OTC) decongestants, he is taking no medications. He denies use of illicit drugs, but admits to occasional social use of alcohol. For the last 16 years, he has smoked 1 pack of low-tar cigarettes a day. The patient has been employed as a mathematics teacher for 13 years; he usually works summers as a self-employed handyman. His hobbies include reading and tennis. Two years ago he moved into a ranch-style house several hundred yards from a small manufacturing plant; a small pond sits between his house and the plant. The house has central air conditioning and gas heat; it is supplied with well water and uses a septic sewage system. Four months ago, the patient began digging up the sewage system to make repairs. Shortly after he began digging, he first noticed the sores on his hands and forearms. Physical examination reveals an alert white male with 10 erythematous papules of 5-10 millimeters in diameter located bilaterally on the dorsal forearm and hands; edema of the hands is present. The dermal lesions show small circular areas with shallow ulcerated centers. Ear, nose, and throat examination is unremarkable, and chest examination reveals a few scattered rhonchi that clear with coughing. His liver is slightly enlarged and tender to palpation. Cardiovascular, genitourinary, rectal, and neurologic examinations are unremarkable. Initial laboratory findings include evidence of 2+ proteinuria and hematuria, and slightly elevated bilirubin, aspartate aminotransferase [AST]; known as serum glutamic-oxaloacetic transaminase (SGOT), and alanine

	aminotransferase (ALT); known as serum glutamic-pyruvic transaminase (SGPT). Scrapings of the dermal lesions, done with potassium hydroxide preparation, show no fungal elements on microscopic examination. A nasal smear for eosinophils is within normal limits.
Initial Check Questions	1. Formulate an active problem list for this patient. 2. What clues indicate that this case might have an environmental etiology? 3. What further information will you seek before making a diagnosis? 4. In addition to the patient, who in the case study might be at risk of chromium exposure? 5. On further questioning, the patient described in the case study relates that when he had reached several feet in depth while digging to repair the sewage system, he noticed an oozing from the ground of sometimes yellowish sometimes greenish water; this persisted throughout the several weeks of digging. The nearby pond, which is murky, also has a generally yellow tint, at times with small areas of greenish color. Suspecting an environmental link, you contact the local health department. Levels of chromium are found in the pond water that exceed corresponding health screening values, and the investigators inform you that the nearby plant is electroplating auto parts with chromium. Discuss all sources and pathways by which this patient might be exposed to chromium. 6. Analysis of blood and urine specimens from the patient described in the case study reveals elevated Cr(III) serum and urine concentrations. Assuming that the patient was exposed only to Cr(VI), explain the presence of Cr(III) in each of these body fluids. 7. Could chromium toxicity account for the symptoms experienced by the patient described in the case study? Explain. 8. Is the patient at increased risk of chromium-induced lung cancer? 9. Analysis of the tap water in the patient's home reveals a greenish tinge and a chromium concentration of 746 micrograms per liter. Your diagnosis is chromium toxicity. Are there any other tests the patient should undergo? 10. The patient described in the case study insists on obtaining a hair analysis. The chromium content of the hair sample is 1,038 parts per million (ppm). How will you interpret this result? 11. What is the recommended treatment for the patient described in the case study?
Initial Check Answers	1. A problem list for this patient would include upper and lower respiratory irritation, multiple skin lesions and edema of the hands, loss of appetite and weight loss, liver and renal dysfunction, and cigarette smoking. *More information for this answer can be found in the "What are the physiologic effects of chromium?" section.* 2. Information suggesting an environmental etiology includes the following: onset of the patient's symptoms coincides with activity outside the usual routine; in addition, the patient mentions that he first noticed the sores on his hands and forearms while digging up the sewage system to make repairs. Another clue to a possible environmental cause is temporary relief of symptoms when the patient leaves his usual habitat, such as

when he visited Chicago. Proximity of the patient's home to an industrial facility (*i.e.*, the electroplating plant) is also an important clue.

More information for this answer can be found in the "Where is chromium found?" section.

3. You might identify possible causes for the dermal lesions by consulting with a dermatologist. The cause of the persistent respiratory symptoms (2 to 3 months) that do not respond to OTC decongestants in a person with no history of allergies should be pursued. The patient should be queried about whether the onset of symptoms coincided with the move to his home, whether odors have emanated from the plant, and so forth. More information regarding the patient's observations and activities while digging up the sewage system may also be helpful.

   More information for this answer can be found in the "Clinical assessment - history and signs and symptoms" section.

4. If effluent from the plant has reached the groundwater, community residents who drink well water might be at risk. Airborne plant emissions might have also reached nearby residents. Plant workers who are exposed to the plating baths and work near them might be receiving significant exposure.

   More information for this answer can be found in the "Who is at risk of exposure to chromium?" section.

5. The most important pathways for possible chromium exposure in this case are dermal contact during the unearthing of the sewage system; inhalation of emissions from the plant or soil particles if the pond dries up; and ingestion, if the drinking water has been contaminated by effluents from the plant. Minor inhalation sources of chromium might include road and cement dust, erosion products of brake linings and emissions from automotive catalytic converters, and tobacco smoke. Foodstuffs (ingestion) generally contain extremely low chromium levels.

   More information for this answer can be found in the "What are routes of exposure for chromium?" section.

6. Cr(VI) is a powerful oxidizing agent. In the plasma and cells, it is readily reduced to Cr(III), which is excreted in the urine.

   More information for this answer can be found in the "What is the biologic fate of chromium in the body?" section.

7. Yes. Persistent dermal ulcers, respiratory tract irritation, and pulmonary sensitization are all possible effects of chromium exposure.

   More information for this answer can be found in the "What are the physiologic effects of chromium exposure?" section.

8. The potential risk of chromium-induced respiratory system cancer from non-occupational exposure to Cr(VI) must be determined on a case-by-case basis. It is unlikely that the inhalation chromium exposure of this patient will cause lung cancer, although it cannot be ruled out. The patient should be advised to stop smoking cigarettes because smoking may act synergistically to increase risk and is itself a significant risk factor for lung cancer.

   More information for this answer can be found in the "What are the physiologic effects of chromium exposure?" section.

9. If exposure was recent, chromium levels in blood or urine may be used to confirm exposure. Renal function should be tested (urinalysis, blood urea nitrogen, creatinine, and ß2-microglobulin) to determine if renal tubular damage has occurred.

   More information for this answer can be found in the "Clinical assessment-laboratory tests" section.

10. A result of 1,038 ppm is beyond the range for unexposed persons (50 ppm to 1,000 ppm); however, the sample could have been environmentally contaminated with chromium from the water during bathing, or by chromium in ambient air polluted by the plant emissions. No standard methods exist for obtaining a hair sample or for washing and preparing the sample for analysis, and these techniques can greatly influence results. More importantly, no research exists to prove a correlation between chromium content of hair and exposure levels or physiologic effects; therefore, the result has no clinical significance.

    More information for this answer can be found in the "Clinical assessment-laboratory tests" section.

11. If the sources of chromium exposure can be eliminated for this patient, no further treatment would be required, except for the skin lesions. Topical ascorbic acid has been useful in the treatment of chrome ulcers, and 1% aluminum acetate wet dressings can be used to treat the dermatitis.

    This patient's case might be a sentinel for community exposure. You should contact the local health department, the Occupational Safety and Health Administration, and U.S. Environmental Protection Agency (EPA) to report your patient's adverse effects and discuss your suspicions of the chromium source. Chromium levels in and around the plant should be measured. It should be ensured that workers exposed to Cr(VI) are provided proper protective gear, trained, and medically monitored. Because EPA does not have an emission standard, it might be difficult to abate the atmospheric source of chromium. Decontamination of the pond might require regulatory action and litigation. Residents who use well water should be encouraged to use an alternative water source for drinking, cooking, and showering/bathing and any other use that results in dermal or oral exposure.

    More information for this answer can be found in the "How should patients exposed to chromium be treated and managed?" section.

What Is Chromium?

Learning Objectives

Upon completion of this section, you will be able to

- explain what chromium is.

Definition

Chromium is a hard steel-gray metal that is highly resistant to oxidation, even at high temperatures. It is the sixth most abundant element in the earth's crust, where it is combined with iron and oxygen in the form of chromite ore.

Uses

Chromium is used in three basic industries

- metallurgical,
- chemical, and
- refractory (heat-resistant applications).

These industries are the most important industrial sources of chromium in the atmosphere [EPA 1998; ATSDR 2000].

In the metallurgical industry, chromium is an important component of stainless steels and various metal alloys. Metal joint prostheses made of chromium alloys are widely used in clinical orthopedics.

In the chemical industry, chromium is used

- primarily in
    - chrome plating,
    - leather tanning,
    - paint pigments (chromium compounds can be red, yellow, orange, and green), and
    - wood treatment;
- smaller amounts in
    - catalysts,
    - copy machine toner,
    - corrosion inhibitors,
    - drilling muds,
    - magnetic tapes,
    - photographic chemicals,
    - safety matches, and
    - water treatment.

Refractory uses of chromium include magnesite-chrome firebrick for metallurgical furnace linings and granular chromite for various other heat-resistant applications.

Different Valence States

Chromium exists in a series of oxidation states from -2 to +6 valence. The most important stable states are 0 (elemental metal), +3 (trivalent), and +6 (hexavalent).

Chromium in chromite ore is in the trivalent state; industrial processes also produce the elemental metal and hexavalent chromium.

The health effects of chromium are primarily related to the valence state of the metal at the time of exposure. Trivalent (Cr[III]) and hexavalent (Cr[VI]) compounds are thought to be the most biologically significant. Cr(III) is an essential dietary mineral in low doses. Cr(VI) compounds are carcinogenic. Cr(VI) is generally considered 1,000 times more toxic than Cr(III) [EPA 1998; ATSDR 2000; Dayan and Paine 2001].

Essential Dietary Nutrient

Cr(III) is an essential dietary nutrient. It is required to potentiate insulin and for normal glucose metabolism. Cr(III) deficiency has been associated with

- cardiovascular disease,
- decreased lean body mass,
- decreased sperm count,
- elevated percent body fat,
- fasting hyperglycemia,
- glucosuria,
- impaired fertility,
- impaired glucose tolerance, and
- maturity-onset diabetes.

Cr(III) is found in most fresh foods and drinking water. Dietary sources rich in Cr(III) include

- breads,
- cereals,
- fish,
- fresh vegetables,
- meats, and
- spices.

Other significant sources of Cr(III) are mineral supplements, brewer's yeast, and beer.

The National Academy of Sciences has established a safe and adequate daily intake for Cr(III) in adults of 50 -200 micrograms per day. On the average, adults in the United States take in an estimated 60-80 micrograms of Cr(III) per day in food. Therefore, many people's diets may not provide enough Cr(III) [ATSDR 2000].

The biologically active form of an organic Cr(III) complex, often referred to as glucose tolerance factor (GTF), is believed to function by facilitating the interaction of insulin with its cellular receptor sites. Studies have shown that the Cr(III) supplementation in deficient and marginally deficient subjects can result in the rapid reversal of many of the symptoms of chromium-deficiency [Cohen, Kargacin *et al.* 1993; Mertz 1993].

Key Points	• Chromium exists in three common stable valence states: chromium (0), (III), and (VI). • Cr(III) is an essential dietary nutrient. Its deficiency in the body has been associated with diabetes, infertility, and cardiovascular disease. • Cr(VI) is carcinogenic. • The metallurgical, chemical, and refractory industries are the fundamental users of chromium.
Progress Check	1. Which of the following statements is correct? A. Chromium is highly resistant to reduction. B. Cr(III) is an essential dietary nutrient. C. The health effects of chromium are not related to the valence state of the metal. D. None of the above. *To review relevant content, see "Essential Dietary Nutrient" in this section.*

Answers	1.	The correct answer is B. Cr(III) is an essential dietary mineral in low doses. It is required to potentiate insulin and for normal glucose metabolism. Cr(III) deficiency has been associated with many chronic diseases such as diabetes, infertility, and cardiovascular disease.

Where Is Chromium Found?

Learning Objectives	Upon completion of this section, you will be able to • identify sources of chromium exposure.
Introduction	Naturally occurring chromium is usually present as trivalent Cr(III). Hexavalent Cr(VI) in the environment is almost totally derived from human activities [WHO 1990].
Air Contamination	According to the Toxics Release Inventory, in 1997, the estimated releases of chromium were 706,204 pounds to the air from 3,391 large processing facilities which accounted for about 2.2% of total environmental releases. Cr(III) and Cr(VI) are released to the environment primarily from stationary point sources (facilities that are identified individually by name and location) resulting from human activities. The estimates of atmospheric chromium emissions in 1976 and 1980 in the Los Angeles, CA and Houston, TX areas indicate that emissions from stationary fuel combustion are about 46-47% of the total, and emissions from the metal industry range from 26 to 45% of the total [ATSDR 2000]. Coal and oil combustion contribute an estimated 1,723 metric tons of chromium per year in atmospheric emissions; however, only 0.2% of this chromium is Cr(VI). In contrast, chrome-plating sources are estimated to contribute 700 metric tons of chromium per year to atmospheric pollution, 100% of which is believed to be Cr(VI) [ATSDR 2000]. Cr(III) in the air does not undergo any reaction. Cr(VI) in the air eventually reacts with dust particles or other pollutants to form Cr(III). However, the exact nature of such atmospheric reactions has not been studied extensively [EPA 1998].
Water Contamination	According to the Toxics Release Inventory, in 1997, the estimated releases of chromium was 111,384 pounds to water from 3,391 large processing facilities which accounted for about 0.3% of total environmental releases [ATSDR 2000]. Electroplating, leather tanning, and textile industries release relatively large amounts of chromium in surface waters. Leaching from topsoil and rocks is the most important natural source of chromium entry into bodies of water. Solid wastes from chromate-processing facilities, when disposed of improperly in landfills, can be sources of contamination for groundwater, where the chromium residence time might be several years. A survey conducted from 1974 to 1975 provides estimates of chromium concentrations in U.S. drinking water. The survey reported the concentration of chromium in tap water in U.S. households was from 0.4 to 8.0 micrograms per liter (µg/L). [ATSDR 2000] (EPA's maximum contaminant level for chromium in drinking water is 100 µg/L.)
Soil Contamination	According to the Toxics Release Inventory, in 1997 the estimated releases of chromium was 30,862,235 pounds to soil from 3,391 large processing facilities accounted for about 94.1% of total environmental releases [ATSDR

	2000]. Total chromium has been identified in 939 soil and 472 sediment samples collected from 1,036 National Priority Lists (NPL) hazardous waste sites [HazDat 2000]. Chromium waste slag containing potentially hazardous levels of Cr(VI) compounds was used as fill material at more than 160 residential, industrial, and recreational sites. Persons living or working in the vicinity of the sites may have been exposed through inhalation, ingestion, or skin contact with contaminated soils and dusts [Fagliano, Savrin *et al.* 1997]. Community exposure from this fill occurred in a variety of ways. Wind erosion of the soil could have made slag particles airborne, increasing the opportunity for inhalation of chromium. Chromium compounds leached by rainwater could have migrated through cracks in soil, asphalt roadways, and masonry walls, forming high-content chromium crystals on their surfaces. In soil and roadways, these particles might have been eroded by wind and foot traffic and carried as chromium-laden dust into homes and workplaces. Children playing in areas where the slag was used as fill might also have been exposed through skin contact with chromium-contaminated dust, dirt, and puddles and /or ingestion of contaminated soil.
Other Environmental Sources	Other environmental sources of chromium are cement-producing plants (cement contains chromium), the wearing down of asbestos linings that contain chromium, emissions of chromium-based automotive catalytic converters, and tobacco smoke. The general population is exposed to chromium by eating food or food supplements, drinking water, and inhaling air that contain chromium. The mean daily dietary intake of chromium from air, water, and food is estimated to be <0.2-0.4, 2.0, and 60 micrograms, respectively [ATSDR 2000]. One study found increased blood chromium level after total hip replacement using metal-metal pairings where metal ions of the alloys are released [Schaffer, Pilger *et al.* 1999].

Summary of Environmental and Occupational Sources of Chromium Exposure

Environmental Sources	Environmental sources of chromium include • airborne emissions from chemical plants and incineration facilities, • cement dust, • contaminated landfill, • effluents from chemical plants, • asbestos lining erosion, • road dust from catalytic converter erosion and asbestos brakes, • tobacco smoke, and • topsoil and rocks.

Occupational Sources

Occupational sources of chromium include

- anti-algae agents,
- antifreeze,
- cement ,
- chrome alloy production,
- chrome electroplating (soluble Cr[VI]),
- copier servicing,
- glassmaking,
- leather tanning (soluble Cr[III]),
- paints/pigments (insoluble Cr[VI]),
- photoengraving,
- porcelain and ceramics manufacturing,
- production of high-fidelity magnetic audio tapes,
- tattooing,
- textile manufacturing,
- welding of alloys or steel, and
- wood preservatives, *i.e.* Acid Copper Chromate.

Key Points

- Chromium is released to air primarily by combustion processes and metal industries.
- Non-occupational sources of chromium include contaminated soil, air, water, smoking, and diet.

Progress Check

2. What sources does chromium contamination result from?

   A. Stationary fuel combustion (residential, commercial, and industrial).
   B. Leaching from topsoil and rocks is the most important natural source of chromium entry into bodies of water.
   C. Releases to soil from metal processing facilities.
   D. All of the above.

   To review relevant content, see "Air Contamination," "Water Contamination," and "Soil Contamination" in this section.

Answers

2. The correct answer is D. Cr(III) and Cr(VI) are released to the environment primarily from stationary point sources (facilities that are identified individually by name and location) resulting from human activities. The estimates of atmospheric chromium emission in 1976 and 1980 in the Los Angeles, CA and Houston, TX areas indicate that emissions from stationary fuel combustion are about 46-47% of the total environmental releases. According to the Toxics Release Inventory, in 1997, the estimated releases of chromium of 30,862,235 pounds to soil from 3,391 large processing facilities accounted for about 94.1% of total environmental releases. Leaching from topsoil and rocks is the most important natural source of chromium entry into bodies of water.

What Are the Routes of Exposure for Chromium?

Learning Objectives	Upon completion of this section, you will be able to • identify the routes of exposure to chromium.
Introduction	The entry routes of chromium into the human body are inhalation, ingestion, and dermal absorption. Occupational exposure generally occurs through inhalation and dermal contact, whereas the general population is exposed most often by ingestion through chromium content in soil, food, and water.
Inhalation	After human exposure to Cr(III) by inhalation, urinary concentrations of chromium were found to be increased indicating respiratory absorption [Aitio, Jarvisalo *et al.* 1984; Foa, Riboldi *et al.* 1988; Dayan and Paine 2001]. Data from a few animal experiments indicate that with equal solubility, Cr(VI) compounds are absorbed more readily than Cr(III) compounds, probably because Cr(VI) readily penetrates cell membranes [Mertz 1969; Wiegand, Ottenwalder *et al.* 1984]. Cr(VI) is reduced to Cr(III) in the lower respiratory tract by the epithelial lining fluid and by pulmonary alveolar macrophages [Dayan and Paine 2001]. One study showed that at equivalent numbers of cells, the reducing efficiency of alveolar macrophages by biochemical mechanisms was significantly greater in tobacco smokers than in nonsmokers [Petrilli, Rossi *et al.* 1986].
Ingestion	In general, Cr(VI) compounds are better absorbed through the intestinal mucosa than the Cr(III) compounds. However, due to the actions of stomach acid and other components within the gastrointestinal tract, most of an ingested Cr(VI) dosage is converted to Cr(III) [Cohen, Kargacin *et al.* 1993]. In humans and animals, less than 1% of inorganic Cr(III) and about 10% of inorganic Cr(VI) are absorbed from the gut; the latter amount is slightly higher in a fasting state [Donaldson and Barreras 1966; Dayan and Paine 2001].
Skin	Data from volunteers and indirect evidence from occupational studies indicate that absorption of Cr(VI) compounds can occur through intact skin [Baranowska-Dutkiewicz 1981]. Studies in experimental animals showed poor absorption of Cr(III) compounds following dermal route [Dayan and Paine 2001].
Key Points	• Occupational exposure generally occurs through inhalation and dermal contact, whereas the general population is exposed most often by ingestion through chromium content in soil, food, and water. • The majority of Cr(VI) that enters the body via inhalation or ingestion is quickly reduced to Cr(III).

Progress Check 3. Which of following statements regarding exposure pathway is correct?

A. Cr(VI) and Cr(III) have equal capacity to be absorbed through any routes into the human body.
B. Cigarette smoking has no impact on absorption of chromium.
C. The general population is exposed most often by ingestion through chromium content in soil, food, and water.
D. None of the above.

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

Answers

3. The correct answer is C. You can be exposed to chromium by breathing air, drinking water, or eating food containing chromium or through skin contact with chromium or chromium compounds. The level of chromium in air and water is generally low. People who work in industries that process or use chromium or chromium compounds can be exposed to higher-than-normal levels of chromium.

Who Is at Risk of Exposure to Chromium?

Learning Objectives	Upon completion of this section, you will be able to • identify who is at risk of exposure to chromium.
Introduction	Chromium is one of the most widely used industrial metals. Several million workers worldwide are estimated to be exposed to chromium compounds in an array of industries such as pigment production, chrome plating, stainless steel welding, and leather tanning. Additionally, it is one of the major contaminants in various hazardous waste sites worldwide, including the Superfund sites in the United States [EPA 2002; Medeiros, Rodrigues *et al.* 2003].
Worker Exposure	Workers in industries that use chromium are at increased risk of chromium's adverse health effects. Those workers at greatest risk are those involved in stainless steel welding, chromate production, chrome plating, and chrome pigment industries, where exposure is primarily to Cr(VI) via inhalation of aerosols. An estimated 558,000 workers in the United States are potentially exposed to chromium and chromium-containing compounds in the workplace. In many occupations, workers are exposed to both trivalent chromium (Cr[III]) and Cr(VI), as soluble and insoluble materials [ATSDR 2000; OSHA 2006].
General Public	The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium. The presence of chromium compounds at hazardous waste sites can contribute to the exposure of populations residing or working nearby such sites. These populations may be exposed through to air containing particulates or mists of Cr(VI) compounds, through drinking water if soluble forms of Cr(VI) leach into groundwater, or through skin contact with soil at hazardous waste sites. The potential for exposure to Cr(VI) at hazardous waste sites must be determined on a case-by-case basis.
Key Points	• Workers in industries producing and using chromium are at greatest risk of its adverse effects. • The general population is exposed to chromium by inhaling ambient air, ingesting food, and drinking water containing chromium.
Progress Check	4. Of the following, who is at risk of chromium exposure? A. Residents near chromate production facilities. B. Workers in industries that use chromium. C. Tobacco smokers. D. All of the above. *To review relevant content, see "Worker Exposure" and "General Public" in this section.*

Answers

4. The correct answer is D. Workers in industries producing and using chromium are at greatest risk of its adverse effects. Residents near chromate production facilities might be exposed to higher-than-background levels of Cr(VI). In addition, because tobacco contains chromium, tobacco smokers bear the risk of exposure to chromium as well.

What are the Standards and Regulations for Chromium Exposure?

Learning Objectives

Upon completion of this section, you will be able to

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

Introduction

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

Workplace Guidelines

OSHA

The Occupational Safety and Health Administration (OSHA) has established an 8-hour time-weighted average (TWA) exposure limit of 5 micrograms of Cr(VI) per cubic meter of air (5 µg/m³). This is a considerable reduction from the previous permissible exposure limit (PEL) of 52 µg/m³ [Federal Register 2006].

OSHA's standard is based upon the best evidence currently available that at the previous PEL for Cr(VI), workers face a significant risk to material impairment of their health. The evidence in the record for this rulemaking indicates that workers exposed to Cr(VI) are at an increased risk of developing lung cancer. The record also indicates that occupational exposure to Cr(VI) may result in asthma and damage to the nasal epithelia and skin. [Federal Register 2006].

The final rule also contains ancillary provisions for worker protection such as

- requirements for exposure determination,
- preferred exposure control methods, including a compliance alternative for a small sector for which the new PEL is infeasible,
- respiratory protection,
- protective clothing and equipment,
- hygiene areas and practices,
- medical surveillance,
- record keeping, and
- start-up dates that include four years for the implementation of engineering controls to meet the PEL [Federal Register 2006].

For Cr(II) and Cr(III) compounds, the PEL is an 8-hour TWA of 500 µg Cr/m³. For chromium metal and for insoluble compounds, the PEL is 1,000 µg Cr/m³[OSHA 2006].

NIOSH

The National Institute for Occupational Safety and Health (NIOSH) has recommended a 10-hour TWA exposure limit for all Cr(VI) compounds of 1 µg Cr(VI)/m³. For chromium metal and Cr (II) and Cr(III) compounds, the recommended exposure limit is 500 µg /m³ as an 10-hour TWA [NIOSH 2005].

On the basis of current evidence, NIOSH considers all Cr(VI) compounds potential occupational carcinogens.

Environmental Guidelines

Air

The U.S. Environmental Protection Agency (EPA) regulates chromium emissions under the Clean Air Act of 1990. EPA uses technology-based standards for categories of industries, rather than numerical emissions standards, to reduce chromium levels in ambient air. These maximum achievable control technology (MACT) standards are based on emissions levels already achieved by the best-performing similar facilities.

Drinking Water

EPA has an enforceable maximum contaminant level of total chromium in drinking water of 100 µg/L (100 ppb) for public water systems [EPA 1999 h].

Table 1. Regulations and Guidelines for Chromium

Agency	Focus	Level	Comments
American Conference of Governmental Industrial Hygienists	Air: workplace	10 µg/m³ as Cr	Advisory; TWA* to avoid carcinogenic risk from insoluble Cr(VI) compounds
		50 µg/m³ as Cr	TWA for water-soluble Cr(VI) compounds
		500 µg/m³ as Cr	TWA for chromium metal and Cr(III) compounds
National Institute for Occupational Safety and Health	Air: workplace	1 µg/m³ as Cr	Advisory; TWA (10-hour) for chromic acid and all Cr(VI) compounds
		500 µg/m³ as Cr	Advisory; TWA (10-hour) for chromium metal and Cr(II) and Cr(III) compounds
Occupational Safety and Health Administration	Air: workplace	5 µg/m³ as Cr	Regulation; PEL† for chromic acid and chromates, (8-hour TWA)
		500 µg/m³ as Cr	PEL for Cr(II) and Cr(III) compounds (8-hour TWA)
		1,000 µg/m³ as Cr	PEL for chromium metal and insoluble compounds (8-hour TWA)

Environmental Protection Agency	Air: environment	Not available	Chromium is listed as a hazardous pollutant
	Drinking water	100 µg/L	Regulation; current MCL‡ for total chromium

*TWA (time-weighted average): TWA concentration for a normal workday and a 40-hour workweek to which nearly all workers may be repeatedly exposed.

†PEL (permissible exposure limit): highest level of chromium in air, to which a worker may be exposed, averaged over an 8-hour workday.

‡MCL (maximum contaminant level) enforceable level for drinking water.

Key Points

- OSHA has established an 8-hour time-weighted average (TWA) exposure limit of 5 micrograms of Cr(VI) per cubic meter of air (5 µg/m³). This is a considerable reduction from the previous PEL of 52 µg/m³.
- The current EPA maximum contaminant level for chromium in drinking water is 100 µg/L.

Progress Check

5. OSHA's PEL for Cr(VI) (chromic acid and chromates) in the workplace is which of the following?

   A. 5 µg CrO3/m³.
   B. 10 µg CrO3/m³.
   C. 52 µg CrO3/m³.
   D. 100 µg CrO3/m³.

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

Answers	5.	The correct answer is A. OSHA has mandated PEL ceiling of 5 µg /m^3 for chromic acid and chromates.

What Is the Biologic Fate of Chromium in the Body?

Learning Objectives

Upon completion of this section, you will be able to

- explain the metabolic difference between Cr(III) and Cr(VI).

Introduction

In vivo reduction of Cr(VI) to Cr(III) has been widely studied. Ingested Cr(VI) is efficiently reduced to the Cr(III) by the gastric juices [De Flora, Badolati *et al.* 1987]. Cr(VI) can also be reduced to the Cr(III) in the epithelial lining fluid of the lungs by ascorbate and glutathione (Petrilli, Rossi *et al.* 1986; Suzuki and Fukuda 1990).

Absorption

Rates of chromium uptake from the gastrointestinal tract are relatively low and depend on a number of factors, including

- valence state (with Cr[VI] more readily absorbed than Cr[III]),
- the chemical form (with organic chromium more readily absorbed than inorganic chromium),
- the water solubility of the compound, and
- gastrointestinal transit time.

Once absorbed into the bloodstream, Cr(VI) is rapidly taken up by erythrocytes after absorption and reduced to Cr(III) inside the red blood cells. In contrast, Cr(III) does not readily cross red blood cell membranes, but binds directly to transferrin, an iron-transporting protein in the plasma (EPA 1998; ATSDR 2000; Dayan and Paine 2001].

Reduction of Cr(VI) in the red blood cells occurs by the action of glutathione. Since the red blood cell membrane is permeable to Cr(VI) but not Cr(III), the Cr(III) formed by reduction of Cr(VI) is essentially trapped within the red blood cell. Eventually the diffusion of Cr(VI), the reduction to Cr(III), and complexing to nucleic acids and proteins within the cell will cause the concentration equilibrium to change [ATSDR 2000].

Regardless of the source, Cr(III) is widely distributed in the body and accounts for most of the chromium in plasma or tissues. The greatest uptake of Cr(III) as a protein complex is via bone marrow, lungs, lymph nodes, spleen, kidney, and liver. Autopsies reveal that chromium levels in the lungs are consistently higher than levels in other organs [ATSDR 2000].

Metabolic Pathways

The first defense against Cr(VI) after oral exposure is the reduction of Cr(VI) to Cr(III) in the gastric environment where gastric fluid [De Flora, Badolati *et al.* 1987] and ascorbate [Samitz 1970] play important roles [ATSDR 2000].

Excretion of absorbed chromium occurs primarily via urine. In humans, the kidney excretes about 60% of an absorbed Cr(VI) dose in the form of Cr(III) within 8 hours of ingestion. Approximately 10% of an absorbed dose is eliminated by biliary excretion, with smaller amounts excreted in hair, nails, milk, and sweat [Kiilunen, Kivisto *et al.* 1983; ATSDR 2000].

Clearance from plasma is generally rapid (within hours), whereas elimination from tissues is slower (with a half-life of several days). Doses of Cr(VI) administered to volunteers were more rapidly eliminated than doses of Cr(III) [ATSDR 2000].

Key Points	• Cr(VI) is better absorbed from the lungs, gut, and skin than is Cr(III). • After absorption, Cr(VI) is reduced to Cr(III). • The difference in bioavailability and bioactivity between Cr(III) and Cr(VI) might account for the differences in toxicity. Cr(III) is an essential dietary nutrient whereas Cr(VI) poses a significant risk of lung cancer. • Cr(III) is excreted, primarily in the urine.
Progress Check	6. Which of the following statements about metabolism of an absorbed dose of chromium is correct? A. Cr(VI) is rapidly taken up by erythrocytes after absorption and reduced to Cr(III) inside the red blood cells. B. Cr(III) is widely distributed in the body and accounts for most of the chromium in plasma or tissues. C. Excretion of absorbed chromium occurs primarily via urine. D. All of the above. *To review relevant content, see "Absorption" and "Metabolic Pathways" in this section.*

Answers

6. The correct answer is D. Once absorbed into the bloodstream, Cr(VI) is rapidly taken up by erythrocytes after absorption and reduced to Cr(III) inside the red blood cells. Regardless of the source, Cr(III) is widely distributed in the body and accounts for most of the chromium in plasma or tissues. The greatest uptake of Cr(III) as a protein complex is via bone marrow, lungs, lymph nodes, spleen, kidney, and liver. Excretion of absorbed chromium occurs primarily via urine, with no major retention in organs.

What Are the Physiologic Effects of Chromium Exposure?

Learning Objectives	Upon completion of this section, you will be able to • describe physiologic effects, other than cancer, associated with chromium exposure and • describe the carcinogenic effects associated with Cr(VI) exposure.
Introduction	Major factors governing the toxicity of chromium compounds are oxidation state and solubility. Cr(VI) compounds, which are powerful oxidizing agents and thus tend to be irritating and corrosive, appear to be much more toxic systemically than Cr(III) compounds, given similar amounts and solubilities. Although mechanisms of biological interaction are uncertain, this variation in toxicity may be related to the ease with which Cr(VI) can pass through cell membranes and its subsequent intracellular reduction to reactive intermediates.
Mechanism of Chromium Toxicity	Since Cr(III) is poorly absorbed by any route, the toxicity of chromium is mainly attributable to the Cr(VI) form. It can be absorbed by the lung and gastrointestinal tract, and even to a certain extent by intact skin. The reduction of Cr(VI) is considered to serve as a detoxification process when it occurs at a distance from the target site for toxic or genotoxic effect while reduction of Cr(VI) may serve to activate chromium toxicity if it takes place in or near the cell nucleus of target organs [Dayan and Paine 2001]. If Cr(VI) is reduced to Cr(III) extracellularly, this form of the metal is not readily transported into cells and so toxicity is not observed. The balance that exists between extracellular Cr(VI) and intracellular Cr(III) is what ultimately dictates the amounts and rates at which Cr(VI) can enter cells and impart its toxic effects [Cohen, Kargacin *et al.* 1993]. Cr(VI) enters many types of cells and under physiological conditions can be reduced by hydrogen peroxide (H_2O_2), glutathione (GSH) reductase, ascorbic acid, and GSH to produce reactive intermediates, including Cr(V), Cr(IV), thiylradicals, hydroxyl radicals, and ultimately, Cr(III). Any of these species could attack DNA, proteins, and membrane lipids, thereby disrupting cellular integrity and functions [De Mattia, Bravi *et al.* 2004].
Respiratory Effects	Occupational exposures often include mixed exposure to both Cr(III) and Cr(VI) [EPA 1998]. Human occupational experience clearly indicates that, when inhaled, chromium compounds are respiratory tract irritants, resulting in airway irritation, airway obstruction, and lung, nasal, or sinus cancer. Dose, exposure duration, and the specific compound involved can determine chromium's adverse health effects. Pulmonary irritant effects following inhalation of chromium dust can include • asthma, • chronic bronchitis, • chronic irritation, • chronic pharyngitis, • chronic rhinitis,

- congestion and hyperemia,
- polyps of the upper respiratory tract,
- tracheobronchitis, and
- ulceration of the nasal mucosa with possible septal perforation [Lindberg and Hedenstierna 1983; Dayan and Paine 2001].

Radiographic analysis from several reports revealed enlargement of the hilar region and lymph nodes [PHS 1953; Sluis-Cremer and du Toit 1968]. Consistent associations have been found between employment in the chromium industries and significant risk for respiratory cancer (see Carcinogenic Effects).

A delayed anaphylactoid reaction was reported in a male worker occupationally exposed to chromium vapors from Cr(VI) trioxide baths and chromium fumes from stainless steel welding. A subsequent inhalation challenge with sodium chromate resulted in a reaction including late-onset urticaria, angioedema, and bronchospasm accompanied by tripling of plasma histamine levels [Moller, Brooks *et al.* 1986].

Many cases of nasal mucosa injury (inflamed mucosa, ulcerated septum, and perforated septum) have been reported in workers exposed to Cr(VI) in chrome-plating plants and tanneries [ATSDR 2000]. A 1983 study of 43 chrome-plating plants in Sweden, where workers were exposed almost exclusively to Cr(VI) acid, revealed that all workers with nasal mucosa ulceration or perforation were periodically exposed to at least 20 micrograms per cubic meter (µg/m³) when working near the plating baths (The newest U.S. permissible exposure level in the workplace for chromates and chromic acid is 5 µg/m³ as a ceiling). The period of exposure for workers experiencing nasal mucosal ulceration varied from 5 months to 10 years [Lindberg and Hedenstierna 1983]. A recent epidemiological study of U.S. workers found that the median time from date first employed to date of first diagnosis of nasal ulceration was less than a month; the median Cr(VI) concentration was similar to concentrations reported in the Swedish study [Gibb, Lees *et al.* 2000].

Occupational exposure to Cr(III) has also been associated with respiratory effects. One man developed coughing, wheezing, and decreased forced volume after an inhalation exposure to a sample of Cr(III) sulfate [Novey, Habib *et al.* 1983]. In an industrial hygiene survey of 60 ferrochromium workers exposed to Cr(III) and Cr(VI) (0.02-0.19 mg total chromium/m³) conducted in 1975, appreciably higher incidences of subjective symptoms of coughing, wheezing, and dyspnea were reported compared with controls. However, due to the tobacco smoking that cannot be excluded as a confounding factor, the increase in subjective respiratory symptoms and decreased pulmonary function parameters cannot be unequivocally be attributed to chromium exposure [Langard S 1980].

The respiratory system in animals is also a primary target for inhalation exposure to chromium. Histological examination of the lung tissue revealed alterations representing mild nonspecific irritation after exposure to 0.9 or 25 mg Cr(III) trichloride for 30 min [Henderson, Rebar *et al.* 1979].

	An extensive epidemiological survey was conducted of housewives who lived in an area of Tokyo, Japan, in which contamination from chromium slag at a construction site was discovered in 1973. The exposed population reported a higher incidence of subjective complaints of nasal irritation than the control population in the early years of the study, buy in later years the difference between the two groups became progressively less [ATSDR 2000].
Skin Effects	Dermal exposure to chromium has been demonstrated to produce irritant and allergic contact dermatitis [Polak 1983; Bruynzeel, Hennipman *et al.* 1988]. Primary irritant dermatitis is related to the direct cytotoxic properties of chromium, while allergic contact dermatitis is an inflammatory response mediated by the immune system. Allergic contact dermatitis is a cell-mediated immune response that occurs in a two-step process. In the first step (induction), chromium is absorbed into the skin and triggers the next step - an immune response (sensitization). Sensitized individuals will exhibit an allergic dermatitis response when exposed to chromium above a threshold level [Polak 1983]. Localized erythematous or vesicular lesions at points of contact or generalized eczematous dermatitis should suggest sensitization [Lewis 2004]. Chromium allergic dermatitis is characterized by symptoms of • dryness, • erythema, • fissuring, • papules, • scaling, • small vesicles, and • swelling [MacKie 1981; Adams 1990]. Solubility and pH appear to be the primary determinants of the capacity of individual chromium compounds to elicit an allergic response [Polak, Turk *et al.* 1973; Fregert and Fregert 1981]. The low solubility Cr(III) compounds are much less efficient contact allergens than Cr(VI) [Spruit, van Neer *et al.* 1966]. Penetration of the skin will cause painless erosive ulceration ("chrome holes") with delayed healing. These commonly occur on the fingers, knuckles, and forearms. The characteristic chrome sore begins as a papule, forming an ulcer with raised hard edges. Ulcers can penetrate deep into soft tissue or become the site of secondary infection, but are not known to lead to malignancy [Deng, Fleeger *et al.* 1990; Geller 2001; Lewis 2004; Meditext 2005]. In addition, occupational exposure Cr(VI) compounds has been associated with effects on the skin, nasal septum, and eardrum [Gibb, Lees *et al.* 2000]. Chromium is one of the most common skin sensitizers and often causes skin sensitizing effect in the general public. A possible source of chromium exposure is waste dumps for chromate-producing plants causing local air or water pollution.

Carcinogenic Effects

Occupational exposure to Cr(VI) compounds in a number of industries has been associated with increased risk of respiratory system cancers [ATSDR 2000].

Baetjer was one of the first to review the literature presented prior to 1950 on the occurrence of cancer in chromate-exposed workers [Baetjer 1950].

The first epidemiological study of chromate production workers in the United States that demonstrated an association with lung cancer was conducted with 1,445 workers in seven plants engaged in the extraction of chromates from ore from 1930 to 1947. The percentage death due to cancer of the respiratory system was 21.8%; the percentage expected was 1.4% [Machle and Gregorius 1948].

In another key epidemiological study involving workers at a chromate production plant who had worked at the plant for more than 1 year from 1931 to 1949, the percentage of deaths due to lung cancer was 18.2%; the percentage expected was 1.2%. For the 332 workers first employed from 1931 to 1937, the percentage of deaths due to lung cancer was close to 60% of all cancer deaths, with a latency period of approximately 30 years [Mancuso 1951; Mancuso 1975].

Studies of workers in the chromium pigment, chrome-plating, and ferrochromium industries showed a statistically significant association between worker exposure to Cr(VI) and lung cancer [Langard and Norseth 1975; Sheffet, Thind *et al.* 1982; Frentzel-Beyme 1983; Langard and Vigander 1983; Davies 1984; ATSDR 2000].

In addition to lung cancer, a number of epidemiological studies of workers in chromate industries also showed significantly increased risk for nasal and sinus cancers [ATSDR 2000].

On the basis of these and other studies, the U.S. Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC) have classified inhaled Cr(VI) as a known human carcinogen [IARC 1990; EPA 1998]. The World Health Organization (WHO) has determined that Cr(VI) is a human carcinogen. The Department of Health and Human Services (DHHS) has determined that Cr(VI) compounds are known to cause cancer in humans [ATSDR 2000].

Lung cancer risk in relation to airborne levels of Cr(VI) was analyzed for chromium chemical production workers and a dose-response relationship was observed in that long-term workers had a higher lung cancer risk than short-term workers [Hayes, Lilienfeld *et al.* 1979]. An analysis of lung cancer risk suggests a potential excess risk of death from lung cancer among U.S. workers exposed to the previous permissible exposure limit (PEL) for Cr(VI) of 52 µg/m³ [Braver, Infante *et al.* 1985]. More recent studies also disclosed excess risk of lung cancer death resulting from occupational exposure to Cr(VI) compounds [Gibb, Lees *et al.* 2000; Park, Bena *et al.* 2004].

Stratified analysis of lung cancer mortality showed a trend of increasing mortality with higher cumulative exposure levels. The analyses stratified by duration of employment and time since first exposure indicate a consistency of results among those employed the longest and with the longest elapsed time since first exposure. The latter suggests a latency period of approximately 20 -35 years, which is compatible with other research [Luippold, Mundt *et al.* 2003].

Carcinogenicity appears to be associated with the inhalation of the less soluble/insoluble Cr(VI) compounds. The toxicology of Cr(VI) does not reside with the elemental form. It varies greatly among a wide variety of very different Cr(VI) compounds [Katz and Salem 1993].

Epidemiological evidence strongly points to Cr(VI) as the agent in carcinogenesis. Solubility and other characteristics of chromium, such as size, crystal modification, surface charge, and the ability to be phagocytized, compounds might be important in determining cancer risk [Norseth 1981; Langard 1983; Gad 1989].

In addition to the occupational studies, a retrospective environmental epidemiological study was conducted in residents of a county in Sweden where two ferrochromium alloy industries are located. No indication was found that residence near these industries is associated with an increased risk of lung cancer [Axelsson, Rylander *et al.* 1980].

A number of chronic inhalation studies provide evidence that Cr(VI) is carcinogenic in animals [ATSDR 2000].

No evidence exists to indicate that Cr(III) can cause cancer in animals or humans [IARC 1990; EPA 1998].

Mechanism of Cr(VI)-induced carcinogenicity.

The mechanism(s) of Cr(VI)-induced carcinogenicity is not completely understood. The toxicity of chromium within the cell may result from damage to cellular components during the hexavalent to trivalent chromium reduction process, by generation of free radicals, including DNA damage [ATSDR 2000]. Recent studies indicate a biological relevance of non-oxidative mechanisms in Cr(VI) carcinogenesis [Zhitkovich, Song *et al.* 2001].

Renal Effects	Renal effects after inhalation or oral exposure to Cr(VI) compounds have been reported. Although glomerular injury has been noted in chromium workers, the predominant renal injury is tubular, with low doses acting specifically on the proximal convoluted tubules. Injury to the brush border membrane is a feature of chromate nephropathy [Kirschbaum, Sprinkel *et al.* 1981]. Severe poisoning can lead to acute tubular necrosis and acute renal failure [Sharma, Singhal *et al.* 1978]. Low-dose chronic Cr(VI) exposure typically results only in transient renal effects. Elevated urinary ß2-microglobulin levels (an indicator of renal tubular damage) have been found in chrome platers, and higher levels have generally been observed in younger persons exposed to higher Cr(VI) concentrations [Lindberg and Vesterberg 1983]. Sensitive immunochemical techniques for the measurement of specific proteins in the urine have been used for the early detection of kidney damage, a possible threshold having been indicated at exposure levels yielding 15 µg/g creatinine in urine [Franchini and Mutti 1988]. Occupational exposure to Cr(III) does not appear to be associated with renal effects (ATSDR 2000]. No renal impairment based on urinary albumin, retinol binding protein, and renal tubular antigens was found in 236 workers employed in the ferrochromium production industry [Foa, Riboldi *et al.* 1988].
Hepatic Effects	Cr(VI) has been reported to cause severe liver effects in four of five workers exposed to chromium trioxide in the chrome plating industry. The reported liver effects include derangement of the liver cells, necrosis, lymphocytic and histocytic infiltration, and increases in Kupffer cells [Pascale, Waldstein *et al.* 1952]. Cases of hepatic effects after oral exposure to Cr(VI) compounds have also been reported. Elevated liver enzyme levels were reported flowing ingestion of 150 mL solution containing 22.5 g potassium dichrome. [Kolaciski, Kostrzewski *et al.* 1999] Hepatomegaly [Michie, Hayhurst *et al.* 1991; Meert, Ellis *et al.* 1994] and hepatic failure [Loubieres, de Lassence *et al.* 1999; Stift, Friedl *et al.* 2000] have also been noted in the cases of acute poisoning. Exposure to Cr(III) has not been found to cause any liver effects in workers employed in two factories that produced Cr(III) oxide or Cr(III) sulfate [Korallus, Ehrlicher *et al.* 1974b].
Gastro-intestinal Effects	In a study of 97 workers from a chrome plant exposed to a mixture of insoluble chromite ore containing Cr(III) and soluble Cr(VI) as sodium chromate and dichromate, gastrointestinal radiography revealed that 10 of the workers had ulcer formation, and of these, six had hypertrophic gastritis. Nearly all of the workers breathed through the mouth while at work and swallowed the chromate dust, thereby directly exposing the gastrointestinal mucosa [Mancuso 1951]. Most of the previous studies reporting gastrointestinal effects, however, did not compare the workers with appropriate controls.

	Cases of gastrointestinal effects after oral exposure to Cr(VI) compounds have also been reported. In one study, a 14-year-old boy who died after ingesting 7.5 mg Cr(VI)/kg as potassium dichromate experienced abdominal pain and vomiting before death. Autopsy revealed gastrointestinal ulceration [Kaufman, DiNicola *et al.* 1970]. In another study, a 44-year-old man died of gastrointestinal hemorrhage after ingesting 4.1 mg Cr(VI)/kg as chromic acid solution [Saryan and Reedy 1988].
Cardiovascular Effects	Case reports of humans who died after ingesting Cr(VI) compounds have described cardiovascular effects as part of the sequelae leading to death. A 22-month-old boy who ingested an unknown amount of sodium dichromate died of cardiopulmonary arrest. Autopsy revealed early hypoxic changes in the myocardium [Ellis, Brouhard *et al.* 1982]. A 35-year-old woman developed cardiovascular collapse and shock within a few hours following ingestion of 50 mL chromic acid [Loubieres, de Lassence *et al.* 1999]. A woman ingested 400 ml of leather tanning solution containing 48 grams of basic chromium sulphate (CrOHSO4). The patient died of cardiogenic shock, complicated by pancreatitis and gut mucosal necrosis and hemorrhage [van Heerden, Jenkins *et al.* 1994]. A 33-year-old male developed hypotension, ventricular arrhythmias, severe respiratory distress, and metabolic acidosis after ingesting an unknown amount of a liquid wood preservative containing chromium trioxide, arsenic pentoxide, and copper oxide [Hay, Derazon *et al.* 2000].
Hematological Effects	Cases of hematological effects have been reported in humans after the ingestion of lethal or sublethal doses of Cr(VI) compounds. In a case of an 18-year-old woman who ingested a few grams of potassium dichromate, decreased hemoglobin content and hematocrit, and increased total white blood cell counts, reticulocyte counts, and plasma hemoglobin were found 4 days after ingestion. These effects were indicative of intravascular hemolysis [Sharma, Singhal *et al.* 1978]. Laboratory analysis of a 35-year-old woman, who died 12 hours after ingesting 50 ml of pure chromic acid [25 g Cr(VI)], revealed anemia (hemoglobin 56 g/L, hematocrit 17 percent) and thrombocytopenia [Loubieres, de Lassence *et al.* 1999].
Reproductive and Developmental Effects	One study showed wives of stainless steel welders were at higher risk of spontaneous abortions [Bonde, Olsen *et al.* 1992]. The more recent study [Hjollund, Bonde *et al.* 1995], however, did not corroborate those findings. No data were located regarding chromium in adverse human developmental effects. Several animal studies provide evidence that Cr(VI), after oral exposure, is a developmental toxicant in rats and mice [ATSDR 2000]. Adverse developmental effects in animals include greater incidence of post-implantation loss, decreased fetal body weight, reduced ossification, and decreased number of live fetuses.
Genotoxic and Mutagenic Effects	The mechanism of chromium-induced genotoxicity is not fully understood. In one experiment, Cr(VI) plus glutathione induced DNA damage in vitro, whereas Cr(III) with or without glutathione did not. Chromium seems to exert its genetic effects by binding directly to DNA. It can produce stable DNA-chromium complexes, DNA strand breaks, DNA-DNA cross links, and

	DNA-protein cross links. The active species for DNA binding seems to be the trivalent form [De Flora, Bagnasco *et al.* 1990; Cohen, Kargacin *et al.* 1993; Meditext 2005]. A recent clinical study reported strong DNA oxidative damage from the urinary samples of the patient who ingested 2 to 3 grams of potassium dichromate in a suicide attempt [Hantson, Van Caenegem *et al.* 2005]. Another study showed an involvement of the oxidative damage pathway in the mechanism of toxicity of chromium in occupationally exposed individuals [Goulart, Batoreu *et al.* 2005]. Cr(VI) compounds are clearly mutagenic in the majority of experimental situations [De Flora, Bagnasco *et al.* 1990; Cohen, Kargacin *et al.* 1993]. It has caused chromosome aberrations in mammalian cells and has been associated with increased frequencies of chromosome aberrations in lymphocytes from chromate production workers. Increases in sister chromatid exchanges were seen in lymphocytes from workers exposed to chromium, cobalt, and nickel dusts [WHO 1990; Meditext 2005].
Other Effects	In a chrome plating plant where poor exhaust resulted in excessively high concentration of chromium trioxide fumes, workers experienced symptoms of dizziness, headache, and weakness when working over the chromate tanks [Lieberman 1941]. Erosion and discoloration of the teeth may occur with Cr(VI) compounds exposure. In addition, papillomas of the oral cavity and larynx have been reported in workers exposed to high air concentration of Cr(VI) [Hathaway, Proctor *et al.* 1996]. Severe corneal injury may result from ocular contact with solid or concentrated solutions of chromic acid and other Cr(VI) compound [Grant 1993].
Key Points	• When inhaled, chromium compounds are respiratory tract irritants and can cause pulmonary sensitization. • Chronic inhalation of Cr(VI) compounds increases the risk of lung, nasal, and sinus cancer. • Severe dermatitis and usually painless skin ulcers can result from contact with Cr(VI) compounds. • Chromium compounds can be sensitizers as well as irritants. • DHHS, EPA, WHO, and IARC have all recognized Cr(VI) as a human carcinogen. • Occupational exposure to Cr(VI) compounds in a number of industries has been associated with increased risk of respiratory system cancers. • Latency for Cr(VI)-induced lung cancer can be greater than 20 years. • Some studies indicated that reversible renal tubular damage can occur after low-dose, chronic Cr(VI) exposure. • Occupational exposure to Cr(III) does not appear to be associated with renal effects. • Cr(VI) compounds can cause mild to severe liver abnormalities. • Some Cr(VI) compounds, such as potassium dichromate and chromium trioxide, are caustic and irritating to gastrointestinal mucosal tissue.

- Ingestion of a lethal dose of chromate can result in cardiovascular collapse.
- Oral exposure to Cr(VI) compounds may result in hematological toxicity.
- Potential reproductive effects of chromium in humans have not been adequately investigated.
- Data indicate that Cr(VI) compounds are teratogenic in animals.
- Cr(VI) compounds induced DNA damage, gene mutation, sister chromatid exchange, chromosomal aberrations in a number of targets, including animal cells in vivo and animal and human cells in vitro.

Progress Check

7. Which of the following is a major target of inhalation exposure to chromium compounds?

   A. Gastrointestinal tract.
   B. Respiratory tract.
   C. Cardiovascular system.
   D. Central nervous system.

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

8. Which of the following health effects from exposure to chromium is often reportedly seen in the general public?

   A. Its carcinogenicity.
   B. Its irritant effect.
   C. Its skin sensitizing effect.
   D. Its hematopoietic toxicity.

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

9. Which of following statements is **NOT** correct?

   A. Latency for Cr(VI)-induced lung cancer can be greater than 20 years.
   B. No cancers, other than lung cancer, are associated with occupational chromium exposure.
   C. No evidence exists to indicate that Cr(III) can cause cancer in animals or humans.
   D. Epidemiological evidence strongly points to Cr(VI) as the agent in carcinogenesis. Solubility and other characteristics of chromium compounds and Cr(VI) dust particles may be important in determining cancer risk.

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

Answers

7. The correct answer is B. Respiratory tract is a major target of inhalation exposure to chromium compounds.

8. The correct answer is C. Chromium is one of the most common skin sensitizers and often causes skin sensitizing effect in the general public. A possible source of chromium exposure is waste dumps for chromate-producing plants causing local air or water pollution.

9. The correct answer and false statement is B. Lung cancer is not the only cancer caused by Cr(VI) compounds. In addition to the lung cancer, a number of epidemiological studies of workers in chromate industries also showed significantly increased risk for nasal and sinus cancers.

Clinical Assessment - History, Signs and Symptoms

Learning Objectives	Upon completion of this section, you will be able to • describe characteristic clinical presentations of patients with acute and chronic chromium exposure.
Introduction	Characteristic clinical presentations of patients with Cr(VI) compound exposure include • sinusitis, nasal septum perforation, • allergic and irritant dermatitis, skin ulcers, • respiratory irritation, bronchitis, asthma, and • lung cancer [Lewis 2004].
Patient History and Physical Examination	Often, no clear diagnostic clues exist in chromium-exposed patients. A thorough history is therefore critical in evaluating a potentially exposed person. The patient's recent activities are important. Occupation, location of residence and workplace in relation to industrial facilities or hazardous waste sites, and source of drinking water supply should be investigated. In patients with known chronic chromium exposure, the physical examination should include evaluation of the respiratory system, kidneys, liver, and skin.
Signs and Symptoms	***Acute Exposure*** Acute poisoning is likely to occur through the oral route, whereas chronic poisoning is mainly from inhalation or skin contact [Meditext 2005]. Severe exposures to Cr(VI) compounds are usually accidental or intentional (suicide), and are rarely occupational or environmental. Oral intake of Cr(VI) compound may cause • intense gastrointestinal irritation or ulceration and corrosion, • epigastric pain, • nausea, • vomiting, • diarrhea, • vertigo, • fever, • muscle cramps, • hemorrhagic diathesis, • toxic nephritis, • renal failure, • intravascular hemolysis, • circulatory collapse, • liver damage, • acute multisystem organ failure, and • coma, and even death, depending on the dose [Hay, Derazon *et al.* 2000; Lewis 2004; Meditext 2005].

Acute Cr(VI) poisonings are often fatal regardless of the therapy used. The average oral lethal dose of Cr(VI) in humans is 1-3 grams (Meditext 2005).

Systemic symptoms and death have occurred after external burns, with a delay of onset of gastrointestinal symptoms of hours and days. Burns initially resemble first and second degree burns, but extend to subcutaneous tissue within a couple of days [Schiffl, Weidmann *et al.* 1982; Meditext 2005].

Signs and Symptoms

Chronic Exposure

Repeated skin contact with chromium dusts can lead to incapacitating eczematous dermatitis with edema. Chromate dusts can also produce irritation of the conjunctiva and mucous membranes, nasal ulcers and perforations, keratitis, gingivitis, and periodontitis [Cohen and Costa 1998].

When a solution of chromate contacts the skin, it can produce penetrating lesions known as chrome holes or chrome ulcers, particularly in areas where a break in the epidermis is already present. These commonly occur on the fingers, knuckles, and forearms. The characteristic chrome sore begins as a papule, forming an ulcer with raised hard edges. Ulcers can penetrate deep into soft tissue or become the sites of secondary infection, but are not known to lead to malignancy. [Geller 2001; Lewis 2004; Meditext 2005].

Lung cancer is the most serious long-term effect [Cohen and Costa 1998; Lewis 2004; Meditext 2005]. Apart from the carcinogenic potential, prolonged exposure can result in bronchitis, rhinitis, or sinusitis or the formation of nasal mucosal polyps. Besides the lungs and intestinal tract, the liver and kidney are often target organs for chromate toxicity [Rom 2007].

Reports on adverse effects from low-level environmental exposures in human populations are limited. Hudson County, NJ, was a major center for the processing of chromium ore. A study using immune-function assay described reduced production of cytokines in individuals who were exposed to chromate [Snyder, Udasin *et al.* 1996]. Long-term studies in which animals have been exposed to low levels of chromium in food or water have produced no harmful effects [ATSDR 2000].

Key Points

- Acute poisoning is likely to occur through the oral route, whereas chronic poisoning is mainly from inhalation or skin contact.
- Severe exposures to Cr(VI) compounds are usually accidental or intentional (suicide), and are rarely occupational or environmental.
- In occupational settings, the most commonly reported effects of chronic chromium exposure are contact dermatitis and irritation and ulceration of the nasal mucosa.
- Lung cancer is a potential long-term effect of chronic Cr(VI) exposure.
- Besides the lungs and intestinal tract, the liver and kidney are often target organs for chromate toxicity from chronic exposure.

Progress Check

10. Which of the following is the most serious long-term effect from chronic Cr(VI) exposure?

    A. Contact dermatitis.
    B. Nasal septum perforation.
    C. Bronchitis.
    D. Lung cancer.

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

11. Common sites for persistent ulcers ("chrome holes") include all of the following sites **EXCEPT**

    A. Finger webs.
    B. Back of hands.
    C. Forearms.
    D. Palms of hands.

    To review relevant content, see "Signs and Symptoms - Chronic Exposure" in this section

Answers

10. The correct answer is D. Although answers A-C are characteristic clinical findings of chronically exposed patients, lung cancer is the most serious long-term adverse health effect.

11. The correct answer is D. Persistent ulcers ("chrome holes") are not found on the palm of the hands. Common sites for persistent ulcers do include the finger webs, knuckles, back of the hands, and the forearms.

Learning Objectives	Upon completion of this section, you will be able to • identify laboratory tests that can assist with diagnosis of chromium exposure.
Introduction	With excessive exposure, there will be evidence of renal and hepatic damage. Proteinuria and hematuria precede anuria and uremia. A reduction in the FEV1: FVC ratio on spirometry may be seen after acute irritant exposure or in workers with chromium-induced asthma. Skin allergy can be confirmed by patch testing. Persistent cough, hemoptysis, or a mass lesion on chest radiograph in a chromium worker should prompt a thorough evaluation for possible lung cancer [Lewis 2004].
Initial Lab Exams	The following tests should be considered in the evaluation of Cr(VI) exposure [HSDB 2000] • complete blood count, • liver function tests (aspartate aminotransferase (AST) or serum glutamic-oxaloacetic transaminase (SGOT), ALT or serum glutamic-pyruvic transaminase (SGPT), and bilirubin), • blood urea nitrogen (BUN) and creatinine, and • urinalysis.
Specialized Tests	When obtaining biologic specimens for chromium analysis, care must be taken to avoid sample contamination and chromium loss during collection, transportation, and storage. For example, use of stainless steel utensils to collect tissue samples might raise tissue chromium levels, as will stainless steel grinding and homogenizing equipment. Some plastic containers contain significant amounts of leachable chromium; therefore, specially prepared acid-washed containers should be obtained from the laboratory. Considerable care also must be taken in the analysis to minimize chromium volatilization during sample washing [EPA 1984a]. ***Blood Or Serum Chromium Levels*** Several methods are available for the analysis of chromium in different biological media [ATSDR 2000]. For example, Cr(VI) and complexes of Cr(III) can be rapidly determined in plasma and other biological specimens via a high performance anion-exchange liquid chromatograph technique [Suzuki 1987]. Blood distribution of chromium appears to be divided evenly between plasma and erythrocytes. In the absence of known exposure, whole blood chromium concentrations are in the range of 2.0 µg/100 mL to 3.0 µg/100 mL; lower levels occur in rural areas, and higher levels occur in large urban centers.

As we have discussed in the previous section on the biologic fate of chromium, Cr(VI) enters red blood cells, but Cr(III) does not. Therefore, it is possible to distinguish sources and types of exposure (Cr(VI) versus other forms of Cr) by measuring RBC versus serum Cr. This can be especially helpful if urine Cr levels are elevated and one wants to know if this indicates a toxic (e.g., Cr[VI]) exposure or an essentially benign (e.g., Cr[III]) exposure.

Values above background levels are considered potentially toxic, but levels have not been correlated with specific physiologic effects. Chromium rapidly clears from the blood, and measurements relate only to recent exposure.

Urinary Chromium Levels

Wide individual variation in metabolism and rapid depletion of body burden limit the value of urinary chromium monitoring.

Urinary chromium excretion reflects absorption over the previous 1 or 2 days only.

In occupational settings, a urinary chromium concentration of 40 µg/L to 50 µg/L, immediately after a work shift reflects exposure to air levels of 50 µg/m³ of soluble Cr(VI) compounds, a concentration associated with nasal perforations in some studies. If sufficient time has elapsed for urinary clearance, a negative bio-monitoring result can occur even with injurious past exposure.

Assuming no source of excessive exposure, urinary chromium values are typically less than 10 µg/L for a 24-hour period [ATSDR 2000].

Urinary B2-Microglobulins Levels

Urinary β2-microglobulins were significantly higher in chromeplaters exposed to Cr(VI) than in unexposed controls [Lindberg and Vesterberg 1983].

Hair or nail analysis is of little use in evaluating an individual patient because it is impossible to distinguish chromium bound within the hair during protein synthesis from chromium deposited on the hair from dust, water, or other external sources. Populations with no known chromium exposure reportedly have hair levels ranging from 50 parts per million (ppm) to 100 ppm chromium.

The presence of chromium and chromium complexes in biologic complexes can be determined using chromatographic and colorimetric techniques; patch testing and lymphocyte proliferation testing have been used to determine chromium sensitivity [ATSDR 2000; Meditext 2005].

Other Measurements	If the patient has had possible Cr(VI) inhalation exposure, a chest radiograph and pulmonary function test should be included [Lewis 2004; Meditext 2005].

Key Points	• Chromium can be measured in blood and urine; hair or nail analysis has no clinical value. • Urinary chromium excretion is a useful index of exposure in occupational settings. However, it reflects exposure over the previous 1 or 2 days only.
Progress Check	12. To confirm chromium exposure, which of the following measurements is the most reliable? A. Chromium in blood and urine. B. Pulmonary lesion shown on radiograph. C. Elevated values of renal and liver function tests. D. Elevated values of routine laboratory tests. *To review relevant content, see "Key Points" in this section.*

Answers

12. The correct answer is A, chromium in the blood and urine. If the cause of patient symptoms is questionable, direct biologic testing, such as measuring the chromium level in blood, or urine, may be warranted to confirm chromium exposure. Keep in mind, however, that chromium rapidly clears from the blood, and measurements relate only to recent exposure. Therefore, for patients with a known history of chronic chromium exposure, a thorough evaluation including a complete exposure history, a complete blood count, chest x-ray, FVC and FEV1, urinalysis, kidney function tests, liver function tests, and dermatological examination would be appropriate for approaching an accurate diagnosis.

How Should Patients Exposed to Chromium Be Treated and Managed?

Learning Objectives

Upon completion of this section, you will be able to

- describe the principal treatment strategy for managing chromium poisoning.

Introduction

No matter what route of exposure, the initial approach to an affected individual includes a brief assessment of clinical status followed by support of basic cardiopulmonary functions.

Once the airway has been stabilized and cardiopulmonary support has been instituted as indicated, further measures can be considered [Geller 2001].

Acute Exposure

No proven antidote is available for chromium poisoning. Acute poisoning is often fatal regardless of therapy. Treatment in cases of acute high-level chromium exposure is usually supportive and symptomatic.

Fluid and electrolyte balance is critical.

Affected patients should be monitored carefully for evidence of

- gastrointestinal bleeding,
- hemolysis,
- coagulopathy,
- seizures, and
- pulmonary dysfunction [Geller 2001].

Appropriate supportive measures may include ventilatory support, cardiovascular support, and renal and hepatic function monitoring.

When renal function is compromised, maintenance of adequate urine flow is important. Progression to anuria is associated with poor prognosis [Meditext 2005].

Induction of vomiting is contraindicated, owing to the potential corrosive effects of the chromium compounds and the potential for rapid deterioration of the patient [Geller 2001; Meditext 2005].

Gastric lavage with magnesium hydroxide or another antacid might be useful in cases of chromium ingestion.

The efficacy of activated charcoal has not been proven.

Orally administered ascorbic acid was found to be protective in experimental animals and was reported beneficial in at least one patient after chromium ingestion; however, no clinical trials have been conducted to confirm the efficacy of this treatment [Bradberry and Vale 1999].

Exchange transfusion was effective in reducing blood chromium levels 67% in one case of chromium poisoning, using 10.9 L of blood [Kelly, Ackrill *et al.* 1982]. Existing evidence does not allow the conclusion that exchange transfusion generally should be employed, however [Geller 2001].

	Hemodialysis and charcoal hemoperfusion do not substantially enhance chromium removal from the body if renal function remains normal [Ellis, Brouhard *et al.* 1982]. However, if renal failure ensues, hemodialysis may be necessary for management of the renal failure itself [Schiffl, Weidmann *et al.* 1982; Geller 2001]. Chelation with ethylenediaminetetraacetic acid (EDTA) does not seem to be of clinical benefit [Geller 2001]. If the eyes and skin are directly exposed, flush with copious amounts of water. Several case reports suggest that topical ascorbic acid is effective in the management of chromium dermatitis but this has not been confirmed in controlled clinical trials [Bradberry and Vale 1999]. The ulcers heal in several weeks without specific treatment. Ethylenediaminetetraacetic acid (EDTA) ointment 10% might facilitate removal of chromate scabs [Geller 2001; Lewis 2004]. Weeping dermatitis can be treated with 1% aluminum acetate wet dressings, and chrome ulcers can be treated with topical ascorbic acid [Geller 2001; Meditext 2005].
Chronic Exposure	In most patients with chronic low-dose exposure, no specific treatment is needed. The mainstay of management is removing the patient from further exposure and relying on the urinary and fecal clearance of the body burden. Although normal urinary excretion is quite rapid, forced diuresis has been used. Except in the lungs, only small amounts of chromium are retained several weeks after exposure has ceased. Dermatitis, liver and renal injury will not progress after removal from exposure, and, in most cases, the patient will recover. If the exposure has been to high levels or lengthy, the increased risk of lung cancer should be discussed with the patient. Although no reliable tests are currently available to screen patients for lung cancer, the physician can provide advice and patient education regarding smoking cessation, avoiding or minimizing exposure to other known pulmonary carcinogens, and general preventive health measures. Annual chest radiographs might be advisable in carefully selected cases [HSDB 2000; Meditext 2005].

Key Points

- No proven antidote is available for chromium poisoning.
- Treatment in cases of acute high-level chromium exposure is usually supportive and symptomatic.
- Treatment consists of removal of the patient from further chromium exposure, reliance on the body's naturally rapid clearance of the metal and symptomatic management.
- The physician can provide advice and patient education regarding smoking cessation, how to avoid or minimize exposure to other known pulmonary carcinogens, and general preventive health measures.

Progress Check

13. Which of following measures is incorrect when managing patients with acute chromium poisoning:

    A. Ventilatory and cardiovascular support.
    B. Maintenance of adequate urine.
    C. Induction of vomiting.
    D. Hepatic function monitoring.

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

14. Which of the following statements is incorrect?

    A. Except in the lungs, only small amounts of chromium are retained several weeks after exposure has ceased.
    B. Dermatitis, liver, and renal injury will not progress after removal from exposure.
    C. If the exposure has been lengthy (*i.e.*, 2 years to 3 years), the increased risk of lung cancer should be discussed with the patient.
    D. The mainstay of management for chronic exposure is relying on chromium clearance techniques, such as hemodialysis, exchange transfusions, or chelating agents such as dimercaprol or EDTA.

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

Answers

13. The correct answer is C. Induction of vomiting is contraindicated, due to the potential corrosive effects of the chromium compounds and the potential for rapid deterioration of the patient. Treatment in cases of acute, high-level chromium exposure is usually supportive and symptomatic.

14. The correct answer is D. Hemodialysis, exchange transfusions, or chelating agents such as dimercaprol or EDTA have not been shown to be effective in the treatment of human poisoning. The mainstay of management is removing the patient from further exposure and relying on the urinary and fecal clearance of the body burden.

What Instructions Should Be Given to Patients Exposed to Chromium?

Learning Objectives

Upon completion of this section, you will be able to

- describe patient self care, and
- describe clinical follow-up.

Introduction

Cr(VI) compounds are widely used in the chemical industry as ingredients and catalysts in pigments, metal plating and chemical synthesis. Cr(VI) can also be produced when welding on stainless steel or Cr(VI)-painted surfaces.

The major health effects associated with exposure to Cr(VI) include lung cancer, nasal septum ulcerations and perforations, skin ulcerations, and allergic and irritant contact dermatitis.

All patients exposed to chromium need some basic guidance on

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

Self Care

Effective steps patients should be advised to take to prevent and eliminate exposure.

- Wear proper personal protective equipment such as respiratory protection, protective clothing, eye protection, and gloves.
- Maintain a clean work area free of dust.
- Shower and change clothes immediately on completion of work.
- Leave or dispose of contaminated clothing at the work site.
- Do not track dust from the work area to the rest of the home.
- Do not smoke, eat, or drink in the work area.
- Wash hands well before eating, drinking, or smoking.
- Heed employer provided patient and worker education.
- If a smoker, stop smoking.

Clinical Follow-Up

Patients should be advised to call if they develop any of the following symptoms:

- symptoms of kidney dysfunction such as lower extremity swelling, reduced urine volume, changes in color of urine, etc.,
- dyspnea, cough, wheezing,
- nausea, vomiting, diarrhea,
- yellowing of the teeth,
- altered sense of smell, and
- if you suspect you have been exposed.

Key Points	• Patients should be advised to avoid exposures and conditions that might further increase their risk of disease or worsen their existing condition. • Patients should contact their physician if they develop respiratory or gastrointestinal problems or other health changes.
Progress Check	15. Patients who have been exposed to chromium should A. Seek clinical evaluation and treatment without delay. B. Learn how to avoid further exposure. C. Know when to call their doctor. D. All of the above. *To review relevant content, see "Self Care" and "Clinical Follow-up" in this section.*

Answers

15. The correct answer is D, all of the above. Patients who have been exposed to chromium should seek clinical evaluation and treatment without delay, learn how to avoid further exposure, and know when to call their primary care physician.

Sources of Additional Information

Chromium Specific Information

Please refer to the following Web resources for more information on the adverse effects of chromium, the treatment of chromium -associated diseases, and management of persons exposed to chromium.

- Agency for Toxic Substances and Disease Registry (www.atsdr.cdc.gov)
  - For chemical, emergency situations
    - **CDC Emergency Response: 770-488-7100 and request the ATSDR Duty Officer**
  - For chemical, non- emergency situations
    - CDC-INFO (www.bt.cdc.gov/coca/800cdcinfo.asp)
    - 800-CDC-INFO (800-232-4636) TTY 888-232-6348 - 24 Hours/Day
    - E-mail: cdcinfo@cdc.gov

      PLEASE NOTE
      ATSDR cannot respond to questions about individual medical cases, provide second opinions or make specific recommendations regarding therapy. Those issues should be addressed directly with your health care provider.
  - Toxicological Profile for Chromium www.atsdr.cdc.gov/toxprofiles/tp7.pdf)
  - TOXFAQs for Chromium www.atsdr.cdc.gov/tfacts7.html, or in Spanish, www.atsdr.cdc.gov/es/toxfaqs/es_tfacts7.html
- National Institute of Safety and Health (NIOSH) Safety and Health Topic - Chromium - www.cdc.gov/niosh/topics/chromium/
- National Institute of Safety and Health (NIOSH) Safety and Health Topic - Hexavalent Chromium www.cdc.gov/niosh/topics/hexchrom/
- OSHA Chemical Sampling Information - Chromium(VI) (Hexavalent Chromium) www.osha.gov/dts/chemicalsampling/data/CH_228697.html
- U.S. Environmental Protection Agency - Technology Transfer Network - Air Toxics Web Site - Chromium Compounds www.epa.gov/ttn/atw/hlthef/chromium.html

Clinical Resources

- American College of Occupational and Environmental Medicine (ACOEM) (www.acoem.org)
  - ACOEM is the nation's largest medical society dedicated to promoting the health of workers through preventive medicine, clinical care, research, and education.
  - Its members are a dynamic group of physicians encompassing specialists in a variety of medical practices is united via the

College to develop positions and policies on vital issues relevant to the practice of preventive medicine both within and outside of the workplace.

- American College of Medical Toxicologists (ACMT) (www.acmt.net)
  - ACMT is a professional, nonprofit association of physicians with recognized expertise in medical toxicology.
  - The College is dedicated to advancing the science and practice of medical toxicology through a variety of activities.

- Association of Occupational and Environmental Clinics www.aoec.org
  - The Association of Occupational and Environmental Clinics (AOEC) is a network of more than 60 clinics and more than 250 individuals committed to improving the practice of occupational and environmental medicine through information sharing and collaborative research.

- Pediatric Environmental Health Specialty Units (PEHSUs) www.aoec.org/PEHSU.htm
  - Each PEHSU is based at an academic center and is a collaboration between the pediatric clinic and the (AOEC) occupational and environmental clinic at each site.
  - The PEHSU's have been developed to provide education and consultation for health professionals, public health professionals and others about the topic of children's environmental health.
  - The PEHSU staff is available for consultation about potential pediatric environmental health concerns affecting both the child and the family. Health care professionals may contact their regional PEHSU site for clinical advice.

- Poison Control Center
  - The American Association of Poison Control Centers 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.
  - American Association of Poison Control Centers (1-800-222-1222 or www.aapcc.org).

General Environmental Health Information

Please refer to the following Web resources for general information on environmental health.

- Agency for Toxic Substances and Disease Registry (www.cdc.gov/atsdr)
  - To view the complete library of CSEMs (www.atsdr.cdc.gov/csem/).
  - Taking an Exposure History CSEM (www.atsdr.cdc.gov/csem/exphistory/)
- Centers for Disease Control and Prevention (CDC)(www.cdc.gov)
  - CDC works to protect public health and the safety of people, by providing information to enhance health decisions, and promotes health through partnerships with state health departments and other organizations.
  - The CDC focuses national attention on developing and applying disease prevention and control (especially infectious diseases), environmental health, occupational safety and health, health promotion, prevention and education activities designed to improve the health of the people of the United States.
- National Center for Environmental Health (NCEH) (www.cdc.gov/nceh/)
  - NCEH works to prevent illness, disability, and death from interactions between people and the environment. It is especially committed to safeguarding the health of populations that are particularly vulnerable to certain environmental hazards - children, the elderly, and people with disabilities.
  - NCEH seeks to achieve its mission through science, service, and leadership.
- National Institute of Health (NIH) (www.nih.gov)
  - A part of the U.S. Department of Health and Human Services, NIH is the primary Federal agency for conducting and supporting medical research.
- National Institute of Occupational Safety and Health (NIOSH) (www.cdc.gov/niosh/)
  - NIOSH is in the U.S. Department of Health and Human Services and is an agency established to help assure safe and healthful working conditions for working men and women by providing research, information, education, and training in the field of occupational safety and health.

- Association of Occupational and Environmental Clinics (www.aoec.org)

  - The Association of Occupational and Environmental Clinics (AOEC) is a network of more than 60 clinics and more than 250 individuals committed to improving the practice of occupational and environmental medicine through information sharing and collaborative research.

ATSDR Division of Regional Operations

The Division of Regional Operations fulfills the Agency's directives at the regional level by staffing an ATSDR Regional Office within each of the 10 EPA Regional Offices.

The regional representatives are essential liaisons with all NCEH/ATSDR divisions and offices and facilitate the implementation of ATSDR specific programs in the regions. Through the working relationships they have established with EPA, other federal and state agencies, individual citizens, and community groups, regional representatives are able to maintain current and historic knowledge of the hazardous sites and issues in their regions. This information enables ATSDR to address regional issues with appropriate sensitivity and make informed decisions.

ATSDR's Regional Offices, along with the states and territories that they cover as well as contact information, can be found at:

www.atsdr.cdc.gov/DRO/dro_contact.html

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.

Accrediting Organization	Credits Offered
Accreditation Council for Continuing Medical Education (ACCME)	The Centers for Disease Control and Prevention is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The Centers for Disease Control and Prevention designates this educational activity for a maximum of **2.0** *AMA PRA Category 1 Credits*. Physicians should only claim credit commensurate with the extent of their participation in the activity.
American Nurses Credentialing Center (ANCC), Commission on Accreditation	The Centers for Disease Control and Prevention is accredited as a provider of Continuing Nursing Education by the American Nurses Credentialing Center's Commission on Accreditation. This activity provides **2.0** contact hours.
National Commission for Health Education Credentialing, Inc. (NCHEC)	The Centers for Disease Control and Prevention is a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is a designated event for the CHES to receive **2.0** Category I contact hours in health education, CDC provider number GA0082.
International Association for Continuing Education and Training (IACET)	The CDC has been approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), 1760 Old Meadow Road, Suite 500, McLean, VA 22102. The CDC is authorized by IACET to offer **0.2** CEU's for this program.

Disclaimer	In compliance with continuing education requirements, all presenters must disclose any financial or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters as well as any use of unlabeled product(s) or product(s) under investigational use. CDC/ATSDR, our planners, and the presenters for this seminar do not have financial or other relationships with the manufacturers of commercial products, suppliers of commercial services or commercial supporters. This presentation does not involve the unlabeled use of a product or product under investigational use.

Instructions	To complete the assessment and posttest, go to www2.cdc.gov/atsdrce/ and follow the instructions on that page. You can immediately print your continuing education certificate from your personal transcript online. No fees are charged.
Posttest	1. Which of the following statements is NOT true? A. Chromium is excreted in urine and bile as Cr(III). B. Cr(III) is generally more toxic than Cr(IV). C. Cr(VI) is absorbed more quickly than Cr(III). D. Cr(VI) is carcinogenic when inhaled. 2. Which of the following statements is correct? A. Naturally occurring chromium is usually present as hexavalent Cr(VI). B. Cr(III) and Cr(VI) are released to the environment primarily from stationary point sources resulting from human activities. C. Cr(VI) in the air does not undergo any reaction. D. Tobacco smoke is a source of chromium intake. 3. Which of the following statements is incorrect? A. Due to the actions of gastric acid and other components within the gastrointestinal tract, most of ingested Cr(VI) dosage is converted to Cr(III) B. Cr(VI) is reduced to Cr(III) in the lower respiratory tract. C. Absorption of Cr(VI) compounds can not occur through intact skin. D. The general population is exposed most often by ingestion through chromium content in soil, food, and water. 4. EPA's MCL for chromium in drinking water is which of the following? A. 50 g/L. B. 100 g/L. C. 500 g/L. D. None of the above. 5. Which of the following is **NOT** true? A. Chromium deficiency may result in glucose intolerance. B. Cr(VI) compounds are irritating and corrosive. C. Cr(III) readily passes through cell membranes. D. Chromium compounds may be skin and pulmonary sensitizers. 6. Significant chromium uptake occurs in all of the following **EXCEPT** A. Lung. B. Kidneys. C. Muscle. D. Liver.

7. Dermal signs of chromium exposure may include all of the following **EXCEPT**

   A. Penetrating, painless, and persistent ulcers.
   B. Papule-like lesions.
   C. Dermatitis with eczema and edema.
   D. Erythema nodosum.

8. Effects of chronic chromium exposure may include all of the following **EXCEPT**

   A. Pancreatitis.
   B. Nasal mucosal irritation.
   C. Chromium-induced asthma.
   D. Lung cancer.

9. Because Cr(VI) is a powerful oxidizing agent, it does all of the following **EXCEPT**

   A. Causes gastrointestinal hemorrhage as a result of ingestion.
   B. Causes skin necrosis on dermal contact.
   C. Appears to be much more toxic systemically than Cr(III) compounds, given similar amounts and solubilities.
   D. Is eliminated in the urine.

10. Which of the following tests is of little use in evaluating a chromium-exposed individual?

    A. Urinary β2-microglobulins level.
    B. Urinary chromium level.
    C. Chromium level in the hair.
    D. Chest x-ray.

11. Treatment recommendations for patients with chronic chromium poisoning may include all of the following **EXCEPT**

    A. Prolonged chelation therapy with dimercaprol.
    B. Cessation of further exposure.
    C. Surveillance for lung cancer.
    D. Topical ascorbic acid treatment for chrome ulcers.

12. Patients who have been exposed to chromium should contact their physician if they develop all of the following **EXCEPT**

    A. Respiratory problems.
    B. Yellowing of teeth.
    C. Altered sense of smell.
    D. Difficulty sleeping.

Relevant Content	To review content relevant to the posttest questions, see
Question	**Location of Relevant Content**
1	What is chromium?
2	Where is chromium found?
3	What are the routes of exposure to chromium?
4	What are the standards and regulations for chromium exposure?
5	What is the biologic fate of chromium in the body?
6	What is the biologic fate of chromium in the body?
7	What are the physiologic effects of chromium?
8	What are the physiologic effects of chromium?
9	Clinical assessment - history, signs and symptoms
10	Clinical assessment - laboratory tests
11	How should patients exposed to chromium be treated and managed?
12	What instructions should be given to patients?

Literature Cited

References

- Adams, R. M. (1990). "In: Occupational Skin Disease, 2nd ed., Adams, RM, ed." Philadelphia: W.B. Saunders, pp. 26-31.
- Agency for Toxic Substances and Disease Registry (2000). "Toxicological Profile for Chromium." http://www.atsdr.cdc.gov/toprofiles/tp7.html.
- Aitio, A., J. Jarvisalo, *et al.* (1984). "Urinary excretion of chromium as an indicator of exposure to trivalent chromium sulphate in leather tanning." International Archives of Occupational & Environmental Health **54**(3): 241-9.
- Axelsson, G., R. Rylander, *et al.* (1980). "Mortality and incidence of tumours among ferrochromium workers." British Journal of Industrial Medicine **37**(2): 121-7.
- Baetjer, A. M. (1950). Pulmonary carcinoma in chromate workers. 1. A review of the literature and report of cases, A. M. A. Archives of Industrial Hygiene & Occupational Medicine. 2(5):487-504, 1950 Nov.
- Baranowska-Dutkiewicz, B. (1981). "Absorption of hexavalent chromium by skin in man." Archives of Toxicology **47**(1): 47-50.
- Bonde, J. P., J. H. Olsen, *et al.* (1992). "Adverse pregnancy outcome and childhood malignancy with reference to paternal welding exposure." Scandinavian Journal of Work, Environment & Health **18**(3): 169-77.
- Bradberry, S. M. and J. A. Vale (1999). "Therapeutic review: is ascorbic acid of value in chromium poisoning and chromium dermatitis?" Journal of Toxicology - Clinical Toxicology **37**(2): 195-200.
- Braver, E. R., P. Infante, *et al.* (1985). "An analysis of lung cancer risk from exposure to hexavalent chromium." Teratogenesis, Carcinogenesis, & Mutagenesis **5**(5): 365-78.
- Bruynzeel, D. P., G. Hennipman, *et al.* (1988). "Irritant contact dermatitis and chrome-passivated metal." Contact Dermatitis **19**(3): 175-9.
- Cohen, M. D. and M. Costa (1998). In: Rom WN, ed. Environmental and Occupational Medicine, Third Edition. Philadelphia, Lipponcott-Raven Publishers: pp.1045-1052.
- Cohen, M. D., B. Kargacin, *et al.* (1993). "Mechanisms of chromium carcinogenicity and toxicity." Critical Reviews in Toxicology **23**(3): 255-81.
- Davies, J. M. (1984). "Lung cancer mortality among workers making lead chromate and zinc chromate pigments at three English factories." British Journal of Industrial Medicine **41**(2): 158-69.
- Dayan, A. D. and A. J. Paine (2001). "Mechanisms of chromium toxicity, carcinogenicity and allergenicity: review of the literature from 1985 to 2000." Human & Experimental Toxicology **20**(9): 439-51.
- De Flora, S., G. S. Badolati, *et al.* (1987). "Circadian reduction of chromium in the gastric environment." Mutation Research **192**(3): 169-74.
- De Flora, S., M. Bagnasco, *et al.* (1990). "Genotoxicity of chromium compounds. A review." Mutation Research **238**(2): 99-172.
- De Mattia, G., M. C. Bravi, *et al.* (2004). "Impairment of cell and plasma redox state in subjects professionally exposed to chromium."

American Journal of Industrial Medicine **46**(2): 120-5.
- Deng, J. F., A. K. Fleeger, *et al.* (1990). "An outbreak of chromium ulcer in a manufacturing plant." Veterinary & Human Toxicology **32**(2): 142-6.
- Donaldson, R. M., Jr. and R. F. Barreras (1966). "Intestinal absorption of trace quantities of chromium." Journal of Laboratory & Clinical Medicine **68**(3): 484-93.
- Ellis, E. N., B. H. Brouhard, *et al.* (1982). "Effects of hemodialysis and dimercaprol in acute dichromate poisoning." Journal of Toxicology - Clinical Toxicology **19**(3): 249-58.
- EPA (1984a). "Health assessment document for chromium." Research Triangle Park, NC: Environmental Assessment and Criteria Office, U.S. Environmental Protection Agency. EPA 600/8-83-014F.
- EPA (1998). "Toxicological Review of Trivalent Chromium. CAS No. 16065-83-1. In support of Summary Information on the Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, D.C."
- EPA (1999 h). "U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.32."
- Fagliano, J. A., J. Savrin, *et al.* (1997). "Community exposure and medical screening near chromium waste sites in New Jersey." Regulatory Toxicology & Pharmacology **26**(1 Pt 2): S13-22.
- Federal Register (2006). "**Occupational Exposure to Hexavalent Chromium; Final Rule**" **Vol. 71, No. 39**(Tuesday, February 28, 2006 / Rules and Regulations
- Foa, V., L. Riboldi, *et al.* (1988). "Effects derived from long-term low-level chromium exposure in ferro-alloy metallurgy. Study of absorption and renal function in workers." Science of the Total Environment **71**(3): 389-400.
- Franchini, I. and A. Mutti (1988). "Selected toxicological aspects of chromium(VI) compounds." Science of the Total Environment **71**(3): 379-87.
- Fregert, S. and S. Fregert (1981). "Chromium valencies and cement dermatitis." British Journal of Dermatology **105 Suppl 21**: 7-9.
- Frentzel-Beyme, R. (1983). "Lung cancer mortality of workers employed in chromate pigment factories. A multicentric European epidemiological study." Journal of Cancer Research & Clinical Oncology **105**(2): 183-8.
- Gad, S. C. (1989). "Acute and chronic systemic chromium toxicity.[erratum appears in Sci Total Environ 1990 Jun;95:295]." Science of the Total Environment **86**(1-2): 149-57.
- Geller, R. (2001). "Chromium." In:Clinical Environmental Health and Toxic Exposures. Sullivan, JB, Jr. and Krieger, GR, editors. 2nd Ed. Lippincott Williams & Wilkins, Philadelphia, PA.
- Gibb, H. J., P. S. Lees, *et al.* (2000). "Clinical findings of irritation among chromium chemical production workers." American Journal of Industrial Medicine **38**(2): 127-31.
- Gibb, H. J., P. S. Lees, *et al.* (2000). "Lung cancer among workers in chromium chemical production.[see comment]." American Journal of Industrial Medicine **38**(2): 115-26.
- Goulart, M., M. C. Batoreu, *et al.* (2005). "Lipoperoxidation products and thiol antioxidants in chromium exposed workers." Mutagenesis **20**(5): 311-5.

- Grant, W. M. (1993). "Toxicology of the Eye." **34th ed, Charles C Thomas, Springfield, IL.**: pp 398.
- Hantson, P., O. Van Caenegem, *et al.* (2005). "Hexavalent chromium ingestion: biological markers of nephrotoxicity and genotoxicity." Clinical Toxicology: The Official Journal of the American Academy of Clinical Toxicology & European Association of Poisons Centres & Clinical Toxicologists **43**(2): 111-2.
- Hathaway, G. J., N. H. Proctor, *et al.* (1996). **Chemical Hazards of the Workplace, 4th ed, Van Nostrand Reinhold Company, New York, NY.**
- Hay, E., H. Derazon, *et al.* (2000). "Suicide by ingestion of a CCA wood preservative." Journal of Emergency Medicine **19**(2): 159-63.
- Hayes, R. B., A. M. Lilienfeld, *et al.* (1979). "Mortality in chromium chemical production workers: a prospective study." International Journal of Epidemiology **8**(4): 365-74.
- HazDat (2000.). "Hazardous substances database." Agency for Toxic Substances and Disease Registry (ATSDR), Atlanta, GA.
- Henderson, R. F., A. H. Rebar, *et al.* (1979). "Early damage indicators in the lungs. IV. Biochemical and cytologic response of the lung to lavage with metal salts." Toxicology & Applied Pharmacology **51**(1): 129-35.
- Hjollund, N. H., J. P. Bonde, *et al.* (1995). "Male-mediated risk of spontaneous abortion with reference to stainless steel welding." Scandinavian Journal of Work, Environment & Health **21**(4): 272-6.
- HSDB (2000). "Hazardous Substances Data Bank." National Library Of Medicine. Bethesda, MD, Thomson Micromedex, CO.
- International Agency for Research on Cancer (1990). "Chromium, Nickel and Welding." IARC Monograph on the Evaluation of Carcinigenic Risks to Human, **49, Lyon.**
- Katz, S. A. and H. Salem (1993). "The toxicology of chromium with respect to its chemical speciation: a review." Journal of Applied Toxicology **13**(3): 217-24.
- Kaufman, D. B., W. DiNicola, *et al.* (1970). "Acute potassium dichromate poisoning. Treated by peritoneal dialysis." American Journal of Diseases of Children **119**(4): 374-6.
- Kelly, W. F., P. Ackrill, *et al.* (1982). "Cutaneous absorption of trivalent chromium: tissue levels and treatment by exchange transfusion." British Journal of Industrial Medicine **39**(4): 397-400.
- Kiilunen, M., H. Kivisto, *et al.* (1983). "Exceptional pharmacokinetics of trivalent chromium during occupational exposure to chromium lignosulfonate dust." Scandinavian Journal of Work, Environment & Health **9**(3): 265-71.
- Kirschbaum, B. B., F. M. Sprinkel, *et al.* (1981). "Proximal tubule brush border alterations during the course of chromate nephropathy." Toxicology & Applied Pharmacology **58**(1): 19-30.
- Kolaciski, Z., P. Kostrzewski, *et al.* (1999). "Acute potassium dichromate poisoning: a toxicokinetic case study." Journal of Toxicology - Clinical Toxicology **37**(6): 785-91.
- Korallus, U., H. Ehrlicher, *et al.* (1974b). "Trivalent chromium compounds - results of a study in occupational medicine. Part 2. Disease status analysis." Arb Soz Prev **9**: 76-79. (German).
- Langard, S. (1983). "The carcinogenicity of chromium compounds in man and animals." In: Burrow, C., Ed. Chromium: Metabolism and

Toxicity. CRC Press, Inc., Boca Raton, FL, pp. 13-30.

- Langard S (1980). "A survey of respiratory symptoms and lung function in ferrochromium and ferrosillicon workers." Int Arch Occup Environ Health(46): 1-9.
- Langard, S. and T. Norseth (1975). "A cohort study of bronchial carcinomas in workers producing chromate pigments." British Journal of Industrial Medicine **32**(1): 62-5.
- Langard, S. and T. Vigander (1983). "Occurrence of lung cancer in workers producing chromium pigments." British Journal of Industrial Medicine **40**(1): 71-4.
- Lewis, R. (2004). "Occupational Exposures: Metals. In: Current Occupational & Environmental Medicine. LaDou, J. editor. 3rd Ed." Lange Medical Books/McGraw-Hill Companies, Inc.: pp. 439-441.
- Lieberman, H. (1941). "Chrome ulcerations of the nose and throat." New Engl J Med(225): 132-133.
- Lindberg, E. and G. Hedenstierna (1983). "Chrome plating: symptoms, findings in the upper airways, and effects on lung function." Archives of Environmental Health **38**(6): 367-74.
- Lindberg, E. and O. Vesterberg (1983). "Monitoring exposure to chromic acid in chromeplating by measuring chromium in urine." Scandinavian Journal of Work, Environment & Health **9**(4): 333-40.
- Lindberg, E. and O. Vesterberg (1983). "Urinary excretion of proteins in chromeplaters, exchromeplaters and referents." Scandinavian Journal of Work, Environment & Health **9**(6): 505-10.
- Loubieres, Y., A. de Lassence, *et al.* (1999). "Acute, fatal, oral chromic acid poisoning." Journal of Toxicology - Clinical Toxicology **37**(3): 333-6.
- Luippold, R. S., K. A. Mundt, *et al.* (2003). "Lung cancer mortality among chromate production workers." Occupational & Environmental Medicine **60**(6): 451-7.
- Machle, W. and F. Gregorius (1948). "Cancer of the respiratory system in the United States chromate-producing industry." Public Health Rep **63**: 114-127.
- MacKie, R. M. (1981). "Clinical dermatology." New York, Toronto: Oxford University Press.
- Mancuso, R. F. (1951). "Occupational cancer and other health hazards in a chromate plant: a medical appraisal. II. Clinical and toxicologic aspects." Industrial Medicine & Surgery **20**(9): 393-407.
- Mancuso, T. F. (1975). "Consideration of chromium as an industrial carcinogen." In: Hutchinson TC, ed. Preceedings of the international conference on heavy metals in the environment. **Toronto, Canada: Toronto Institute for Environmental Studies,** : pp 343-356.
- Medeiros, M. G., A. S. Rodrigues, *et al.* (2003). "Elevated levels of DNA-protein crosslinks and micronuclei in peripheral lymphocytes of tannery workers exposed to trivalent chromium." Mutagenesis **18**(1): 19-24.
- Meditext - Medical Management (2005). "Chromium Hexavalent Salts." TOMES Information System. Denver, CO: Micromedex, Inc.
- Meert, K. L., J. Ellis, *et al.* (1994). "Acute ammonium dichromate poisoning." Annals of Emergency Medicine **24**(4): 748-50.
- Mertz, W. (1969). "Chromium occurrence and function in biological systems." Physiological Reviews **49**(2): 163-239.
- Mertz, W. (1993). "Chromium in human nutrition: a review." J.

Nutr(123): 626-633.
- Michie, C. A., M. Hayhurst, *et al.* (1991). "Poisoning with a traditional remedy containing potassium dichromate." Human & Experimental Toxicology **10**(2): 129-31.
- Moller, D. R., S. M. Brooks, *et al.* (1986). "Delayed anaphylactoid reaction in a worker exposed to chromium." Journal of Allergy & Clinical Immunology **77**(3): 451-6.
- NIOSH (2005). "Online pocket guide to chemical hazards. Septemvber 2005." http://www.cdc.gov/niosh/npg/nengapdx.html#c.
- Norseth, T. (1981). "The carcinogenicity of chromium." Environmental Health Perspectives **40**: 121-30.
- Novey, H. S., M. Habib, *et al.* (1983). "Asthma and IgE antibodies induced by chromium and nickel salts." Journal of Allergy & Clinical Immunology **72**(4): 407-12.
- OSHA (2006). "OSHA Issues Final Standard on Hexavalent Chromium." National News Release: 06-342-NAT(February 27, 2006).
- Park, R. M., J. F. Bena, *et al.* (2004). "Hexavalent chromium and lung cancer in the chromate industry: a quantitative risk assessment." Risk Analysis **24**(5): 1099-108.
- Pascale, L. R., S. S. Waldstein, *et al.* (1952). Chromium intoxication, with special reference to hepatic injury, Journal of the American Medical Association. 149(15):1385-9, 1952 Aug 9.
- Petrilli, F. L., G. A. Rossi, *et al.* (1986). "Metabolic reduction of chromium by alveolar macrophages and its relationships to cigarette smoke." Journal of Clinical Investigation **77**(6): 1917-24.
- PHS (1953). "Health of workers in chromate producing industry: A study." Washington, DC: U.S. Public Health Service. Publication no.192.
- Polak, L. (1983). "Immunology of chromium. In: Chromium: metabolism and toxicity." Burrows, D, ed. Boca Raton, FL: CRC Press,: pp. 51-135.
- Polak, L., J. L. Turk, *et al.* (1973). "Studies on contact hypersensitivity to chromium compounds." Progress in Allergy **17**: 145-226.
- Rom, W. N. (2007). "Environmental and Occupational Medicine. 4th Ed. 2007 by Lippincott Williams & Wilkins."
- Samitz, M. H. (1970). "Ascorbic acid in the prevention and treatment of toxic effects from chromates." Acta Dermato-Venereologica **50**(1): 59-64.
- Saryan, L. A. and M. Reedy (1988). "Chromium determinations in a case of chromic acid ingestion." Journal of Analytical Toxicology **12**(3): 162-4.
- Schaffer, A. W., A. Pilger, *et al.* (1999). "Increased blood cobalt and chromium after total hip replacement." Journal of Toxicology - Clinical Toxicology **37**(7): 839-44.
- Schiffl, H., P. Weidmann, *et al.* (1982). "Dialysis treatment of acute chromium intoxication and comparative efficacy of peritoneal versus hemodialysis in chromium removal." Mineral & Electrolyte Metabolism **7**(1): 28-35.
- Sharma, B. K., P. C. Singhal, *et al.* (1978). "Intravascular haemolysis and acute renal failure following potassium dichromate poisoning." Postgraduate Medical Journal **54**(632): 414-5.
- Sheffet, A., I. Thind, *et al.* (1982). "Cancer mortality in a pigment

plant utilizing lead and zinc chromates." Archives of Environmental Health **37**(1): 44-52.
- Sluis-Cremer, G. and R. du Toit (1968). "Pneumoconiosis in chromite miners in South Africa." Br J Ind Med **25**: 63-67.
- Snyder, C. A., I. Udasin, *et al.* (1996). "Reduced IL-6 levels among individuals in Hudson County, New Jersey, an area contaminated with chromium." Archives of Environmental Health **51**(1): 26-8.
- Spruit, D., F. C. van Neer, *et al.* (1966). "Penetration rate of Cr (3) and Cr (VI)." Dermatologica **132**(2): 179-82.
- Stift, A., J. Friedl, *et al.* (2000). "Successful treatment of a patient suffering from severe acute potassium dichromate poisoning with liver transplantation." Transplantation **69**(11): 2454-5.
- Suzuki, Y. (1987). "Anion-exchange high-performance liquid chromatography of water-soluble chromium (VI) and chromium (III) complexes in biological materials." Journal of Chromatography A **415**(2): 317-24.
- Suzuki, Y. and K. Fukuda (1990). "Reduction of hexavalent chromium by ascorbic acid and glutathione with special reference to the rat lung." Archives of Toxicology **64**(3): 169-76.
- U.S. Environmental Protection Agency (1998). "Toxicological Review of Hexavalent Chromium.
- ." **National Center for Environmental Assessment, Office of Research and Development, Washington, DC.**
- U.S. Environmental Protection Agency (1998). "Toxicological Review of Trivalent Chromium.
- ." National Center for Environmental Assessment, Office of Research and Development, Washington, DC.
- U.S. Environmental Protection Agency (2002). "Common Chemicals Found at Superfund Sites." Available at: http://www.epa.gov/superfund/resources/chemicals.htm.
- van Heerden, P. V., I. R. Jenkins, *et al.* (1994). "Death by tanning--a case of fatal basic chromium sulphate poisoning." Intensive Care Medicine **20**(2): 145-7.
- Wiegand, H. J., H. Ottenwalder, *et al.* (1984). "Disposition of intratracheally administered chromium(III) and chromium(VI) in rabbits." Toxicology Letters **22**(2): 273-6.
- World Health Organization (1990). "Chromium (Environmental Health Criteria 61) International Programme on Chemical Safety,." Geneva, Switzerland.
- World Health Organization (1990). "Chromium (Environmental Health Criteria 61) International Programme on Chemical Safety,." Geneva, Switzerlands.
- Zhitkovich, A., Y. Song, *et al.* (2001). "Non-oxidative mechanisms are responsible for the induction of mutagenesis by reduction of Cr(VI) with cysteine: role of ternary DNA adducts in Cr(III)-dependent mutagenesis." Biochemistry **40**(2): 549-60.