

ATSDR Case Studies in Environmental Medicine



Arsenic Toxicity



ATSDR
AGENCY FOR TOXIC SUBSTANCES
AND DISEASE REGISTRY

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

CASE STUDIES IN ENVIRONMENTAL MEDICINE

Course: WBCBDV1576

Date: October 1, 2009

Expiration Date: October 1, 2011

ARSENIC TOXICITY

Key Concepts	<ul style="list-style-type: none">• Prolonged arsenic exposure causes skin and lung cancer and may cause other internal cancers as well.• Skin lesions, peripheral neuropathy, and anemia are hallmarks of chronic arsenic exposure.
---------------------	---

About This and Other Case Studies in Environmental Medicine	This educational case study document is one in a series of self-instructional modules 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 <i>and care of</i> potentially exposed patients. The complete series of <i>Case Studies in Environmental Medicine</i> is located on the ATSDR Web site at URL: www.atsdr.cdc.gov/emes/topics . 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	See Internet address: www2.cdc.gov/atsdrce/ for more information about continuing medical education credits, continuing nursing education credits, and other continuing education units.
--	---

Acknowledgements	We gratefully acknowledge the work that the medical writers, editors, and reviewers have provided to
-------------------------	--

	<p>produce this educational resource. Listed below are those who have contributed to development of this version of the <i>Case Study in Environmental Medicine</i>.</p> <p>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.</p> <p>CDC/ATSDR Author(s): Kimberly Gehle MD, MPH</p> <p>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, R; Delene Roberts, MSA; Oscar Tarrago, MD, MPH, CHES; Brian Tencza, MS</p> <p>Contributors: Selene Chou, PhD</p> <p>Peer Reviewers: William S. Beckett MD, MPH</p>
--	--

<p>Disclaimer</p>	<p>CDC, our planners, and our presenters wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters.</p> <p>Presentations will not include any discussion of the unlabeled use of a product or a product under investigational use.</p> <p>There was no commercial support received for this activity.</p>
--------------------------	--


	<p>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</p>
---	--

Table of Contents

Initial Check	5
What Is Arsenic?	11
Where Is Arsenic Found?	15
What Are Routes of Exposure for Arsenic?	23
Who Is at Risk of Overexposure to Arsenic?	29
What Are Standards and Regulations for Arsenic Exposure?	35
What Is the Biologic Fate of Arsenic in the Body?	40
How Does Arsenic Induce Pathogenic Change?	46
What Are the Physiologic Effects of Arsenic Exposure?	51
Clinical Assessment	70
How Should Patients Overexposed to Arsenic Be Treated and Managed? ...	87
What Instructions Should be Given to Patients Potentially Overexposed to Arsenic?	
Sources of Additional Information	99
Assessment and Posttest	104
Appendix: Literature Cited	113

How to Use This Course

Introduction	The goal of <i>Case Studies in Environmental Medicine</i> (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 arsenic toxicity.
---------------------	---

How to Use This Course

Availability	<p>Two versions of the Arsenic Toxicity CSEM are available.</p> <ul style="list-style-type: none"> • The HTML version http://www.atsdr.cdc.gov/csem/arsenic/ 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	<p>To make the most effective use of this course.</p> <ul style="list-style-type: none"> • Take the Initial Check to assess your current knowledge about arsenic 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	<p>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:</p>
-----------------------------	--

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

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

Area	
Overview	<ul style="list-style-type: none"> Describe arsenic.
Exposure Pathways	<ul style="list-style-type: none"> Identify where in the United States arsenic is found today. Identify the major routes of exposure to arsenic.
Who Is at Risk	<ul style="list-style-type: none"> Identify the populations most heavily exposed to arsenic.
Standards and Regulations	<ul style="list-style-type: none"> Describe U.S. standards for arsenic exposure.
Biological Fate	<ul style="list-style-type: none"> Describe what happens when arsenic enters the body.
Physiologic Effects	<ul style="list-style-type: none"> Describe the ways arsenic induces illness. Describe the health effects associated with arsenic exposure.
Clinical Assessment	<ul style="list-style-type: none"> Identify the primary focuses of the patient history (including the exposure history). Describe the most typical physical findings on patient examination. Describe the tests you would order for patients exposed to arsenic.
Treatment and Management	<ul style="list-style-type: none"> Identify primary strategies for treating arsenic associated diseases.
Patient Education and Counseling	<ul style="list-style-type: none"> Describe instructions for patient self-care.

Initial Check

Instructions	This initial check will help you assess your current knowledge
---------------------	--

	<p>about arsenic toxicity. To take the initial check, read the case below, and then answer the questions that follow.</p>
<p>Case</p>	<p>Case Study—Thirty-five-year-old carpenter</p> <p>A 35 year-old male presents because of numbness and tingling of his hands and feet.</p> <p>History of present illness: His symptoms began approximately 3 months ago, with gradual onset of numbness and tingling in his toes and fingertips, progressing over weeks to involve the feet and hands in a symmetric "stocking-glove" pattern. About 1 month ago he had an episode of nausea, abdominal pain, and diarrhea, which resolved after 3 days. In the past 2 to 3 weeks, the tingling has taken on a progressively painful, burning quality and he has noted weakness in gripping tools.</p> <p>Past medical history: non-contributory.</p> <p>Family history is unremarkable; his wife, parents, and two younger brothers are in good health.</p> <p>Social history: The patient has been a carpenter since completing high school 17 years ago. For the last 10 years, he has lived in a rural, wooded area in a home he built in the wooded foothills of the Cascade Range in Northwest Washington. Approximately 10 months ago, he married and moved with his wife, an elementary school teacher, into a newly built home on an adjacent parcel of land. The patient consumes 1 to 2 alcoholic drinks a week and quit smoking 2 years ago after a 15 pack/year history. He takes 1 multivitamin a day, but no other supplements or prescription medications.</p> <p>Review of Systems: He notes episodes of increased sweating in the last 3 months.</p> <p>Physical Examination:</p> <p>Vital signs: temperature 37. 5 degrees C; pulse 60 and regular; respirations 12; BP 124/76.</p>

Head, Eyes, Ears, Nose, and Throat are within normal limits.

Respiratory, cardiovascular, and abdominal systems are also normal to auscultation and palpation, with no hepatosplenomegaly. There is no lymphadenopathy.

Dermatologic examination reveals brown patches of hyperpigmentation, with scattered overlying pale spots in and around the axillae, groin, nipples, and neck. The palms and soles show multiple hyperkeratotic corn-like elevations 4 to 10 mm in diameter. Three irregularly shaped, sharply demarcated, erythematous, scaly plaques, measuring 2 to 3 cm, are noted on the patient's torso.

Neurologic examination reveals diminished proprioception in the hands and feet, with a hyperesthetic response to pinprick on the soles. Motor bulk and tone are normal, but there is slight bilateral muscular weakness in dorsiflexors of the toes and ankles, wrist extensors, and hand intrinsic. Reflexes are absent at the ankles and 1+ at the biceps and knees. Coordination and cranial nerve function are within normal limits. Joints have full range of motion, with no erythema, heat, or swelling.

The remainder of the physical examination is normal.

On initial laboratory evaluation, the following results came back:


- Complete blood count (CBC):
 - slight macrocytic anemia with hematocrit 35% (normal range 40% to 52%),
 - mean corpuscular volume 111 fL (normal range 80 to 100 fL),
 - white blood cell count (WBC) is 4,300/mm³ (normal range 3,900 to 11,700 /mm³);
 - the differential reveals moderate elevation of eosinophils at 9% (normal range 0% to 4%).
- Basophilic stippling of red cells was seen on blood smear.
- Liver transaminases are slightly elevated.
- Urinalysis and electrolytes, including glucose, blood

Initial Check Questions	<ol style="list-style-type: none">1. What additional laboratory testing is indicated by this patient's presentation?2. The patient's main occupational activities are framing new houses and performing renovations on existing homes. He uses "pressure treated lumber" (treated with a wood preservative) for framing and building exterior decks. He usually heats his home with a wood stove burning scrap lumber from building jobs, most of which is pressure-treated lumber. Water supply to his home is from an artesian well. What potential sources of exposure to arsenic does he have?3. A 24-hour urine collection shows 320 micrograms total arsenic per gram creatinine and a nerve conduction study shows a sensory-motor peripheral neuropathy with evidence of axon damage. What medical recommendations would you make for this patient?4. Is his wife at risk for arsenic exposure?

<p>Initial Check</p> <p>Answers</p>	<p>1. Additional evaluation should start with a 24-hour urine collection for arsenic and creatinine, and a nerve conduction study of the lower extremities.</p> <p>Where total urinary arsenic level is high the patient should be asked about recent consumption of seafood. Generally speaking, the forms of arsenic found in seafood are not toxic to humans. There are two options the clinician can take. One is to request testing for speciation of arsenic (i.e., analysis of organo-arsenicals or different inorganic species, rather than total). The other would be to wait 48 hours after last consumption of seafood and run 24 hour urine for total arsenic. Seafood arsenic should have cleared the body in 48 hours.</p> <p>Not all labs that perform arsenic levels also can perform speciation. If your laboratory does not perform this test, you may wish to consult your local Poison Control Center for this information.</p> <p>In addition, not all labs adjust the arsenic value per gram of creatinine which accounts for the dilution or concentration of the sample. This adjustment may give a more accurate measure of arsenic excretion when incomplete 24 hour or spot urine samples are analyzed.</p> <p><i>More information for this answer can be found in the "Clinical Assessment" section.</i></p>
	<p>2. He may have inhalational and dermal exposure to arsenic compounds used in pressure treating lumber as a preservative, both from inhaling sawdust and handling the lumber. He may have additional exposure to arsenic from inhaling smoke or fumes from scrap lumber burned in his home. He may have ingestion exposure from drinking artesian well water, which may contain higher-than-normal levels of arsenic from underground mineral deposits.</p> <p><i>More information for this answer can be found in the "Where is Arsenic Found?", "What are Routes of Exposure to Arsenic?", and "Who is at Risk of</i></p>

	<p><i>Overexposure to Arsenic?" sections.</i></p>
	<p>3. This is an abnormally high amount of total arsenic excretion which may indicate excessive exposure. However, a history of recent seafood ingestion should be taken and the 24 hour urine for total arsenic can be run again in 48 hours after seafood ingestion ceases. Or, a speciated arsenic testing would give information on inorganic vs. organic forms of arsenic.</p> <p>Given the chronicity of his symptoms, initial management will be to remove him from arsenic exposure and monitor his clinical course. He has normal renal function, and thus is able to excrete arsenic rapidly. Monitoring might include repeating his urine arsenic testing after an interval of time away from exposure, to assure that excretion (and thus exposure) is decreasing.</p> <p><i>More information for this answer can be found in the "Clinical Assessment" section.</i></p>
	<p>4. His wife drinks from the same well and is exposed to smoke from wood burned in the home. She is at risk for exposure and should be tested with a 24-hour urine collection, even though she is asymptomatic. The same considerations regarding seafood consumption (either repeat of total 24 hour urine arsenic 48 hours after the last seafood meal or ordering speciated arsenic testing) would apply.</p> <p><i>More information for this answer can be found in the "Where is Arsenic Found?", "What are Routes of Exposure to Arsenic?", "Who is at Risk of Overexposure to Arsenic?", and "Clinical Assessment" sections.</i></p>

What Is Arsenic?

Learning Objective	Upon completion of this section, you will be able to <ul style="list-style-type: none">• describe arsenic.
Definition	<p>Arsenic is an element and a naturally occurring mineral found widely in the environment.</p>  <p>Arsenic mineral ores, orpiment (left) and realgar (right).</p> <p>Environmental sources of arsenic exposure are</p> <ul style="list-style-type: none">• food,• water,• soil, and• air. <p>Because it is an element, arsenic persists in the environment and does not deteriorate.</p> <p>Arsenic production has greatly decreased in the United States, but imports of arsenic have increased steadily.</p>
Arsenic Compounds	Arsenic compounds can be classified into three major groups: <ol style="list-style-type: none">1. inorganic,2. organic, and

	3. arsine gas.
Classes	<p>The <i>most</i> common valence states are</p> <ol style="list-style-type: none"> 1. As(0) (metalloid arsenic, 0 oxidation state), 2. As(III) (trivalent, 3 oxidation state, such as arsenites), 3. As(V) (pentavalent, 5 oxidation state, such as arsenates), and 4. Arsine Gas (-3 oxidation state). <p>The relative toxicity of an arsenical depends primarily on</p> <ul style="list-style-type: none"> • inorganic or organic form, • valence state, • solubility, • physical state and purity, and • rates of absorption and elimination [ATSDR 2007]. <p>The toxicity of arsenic compounds can vary greatly. In general, arsenic compounds can be ranked from highest to lowest toxicity:</p> <ul style="list-style-type: none"> • inorganic trivalent compounds, • organic trivalent compounds, • inorganic pentavalent compounds, • organic pentavalent compounds, and • elemental arsenic [Gorby 1988]. <p>Inorganic arsenic is generally more toxic than organic arsenic. Forms of arsenic that are more rapidly absorbed are more toxic, while those most rapidly eliminated tend to be less toxic. Arsenite and arsenate forms are highly soluble in water.</p> <p>Although organic arsenicals are usually viewed as being less toxic than the inorganics, several methyl and phenyl derivatives of arsenic that are widely used in agriculture are of possible health concern on the basis mostly of animal studies. Chief among these are monomethylarsonic acid (MMA) and its salts and dimethyl arsinic acid (DMA) and its salts, and roxarsone [ATSDR 2007].</p> <p>Arsenobetaine and arsenocholine are the organic forms</p>

	<p>known as “fish arsenic” and are relatively nontoxic to humans.</p> <p>Arsine gas is the most toxic arsenical (acute exposure).</p>
Key Points	<ul style="list-style-type: none"> • Arsenic is an element and is a naturally occurring mineral found widely in the environment. • Arsenic exists in <i>four</i> common valence states. • Arsenic is widely used commercially, a fact that increases the risk of overexposure. Workers may be overexposed occupationally to arsenic. • Inorganic arsenic is <i>generally more toxic</i> than organic arsenic.
Progress Check Select the one best choice	<ol style="list-style-type: none"> 1. Arsenic is a <ol style="list-style-type: none"> A. Naturally occurring mineral. B. Synthetic substance. C. Commercially useless substance. D. Vegetable byproduct. 2. The toxicity of arsenic is in part related to <ol style="list-style-type: none"> A. Organic or inorganic form. B. Valence state. C. Solubility. D. Rate of absorption and elimination. E. A and D. F. All of the above.

Progress Check Answers	<p>1. The correct answer is A. Arsenic is a naturally occurring mineral often found in combination with other mineral ores. Being a mineral element, it is not synthesized and it is not a vegetable by product. Arsenic and its compounds do have beneficial uses in industry.</p> <p><i>To review relevant content, see "Definition" in this section.</i></p> <p>2. The correct answer is F, all of the above. The toxicity of arsenic is in part related to its form, valence state, solubility, rate of absorption and elimination from the body. Inorganic arsenic is generally more toxic than organic arsenic. Forms of arsenic that are more rapidly absorbed by the body are more toxic, while those most rapidly eliminated tend to be less toxic.</p> <p><i>To review relevant content, see "Classes" in this section.</i></p>
---------------------------------------	---

Where Is Arsenic Found?

Learning Objective	<p>Upon completion of this section, you will be able to</p> <ul style="list-style-type: none">• identify where in the United States arsenic is found today.
Introduction	<p>Release of arsenic in the environment is a result of both manmade and natural activity. Arsenic enters the environment naturally through</p> <ul style="list-style-type: none">• ground water,• mineral ore, and• geothermal processes.
Natural and Industrial Sources	<p>Arsenic is released into the air by volcanoes, through weathering of arsenic-containing minerals and ores, and by commercial or industrial processes.</p> <p>Arsenic occurs naturally in the earth's crust, and much of its dispersion in the environment stems from mining and commercial uses. In industry, arsenic is a byproduct of the smelting process (separation of metal from rock) for many metal ores such as</p> <ul style="list-style-type: none">• cobalt,• gold,• lead,• nickel, and• zinc. <p>In the 19th Century, arsenic was used in paints and dyes for clothes, paper, and wallpaper [Meharg 2003].</p>
Arsenic Products	<p>There has been no domestic production of arsenic since 1985. In 2003, the world's largest producer of arsenic compounds was China, followed by Chile and Peru. In 2003, the United States was the world's largest consumer of arsenic [ATSDR 2007].</p>

In the past, the United States primarily used arsenic in insecticides such as ant killers and animal dips (the concentrated liquid forms of these are most toxic to humans). However, regulatory restrictions for arsenic, especially for home products, have reduced its use and should also reduce the exposure risk to it [NAS 1977].

Other sources include

- algaecides,
- desiccants used in mechanical cotton harvesting,
- glass manufacturing,
- herbicides (such as weed killers for telephone and railroad posts and Agent Blue, which was used by U.S. troops in Vietnam), and
- nonferrous alloys [Garcia-Vargas and Cebrian 1996].

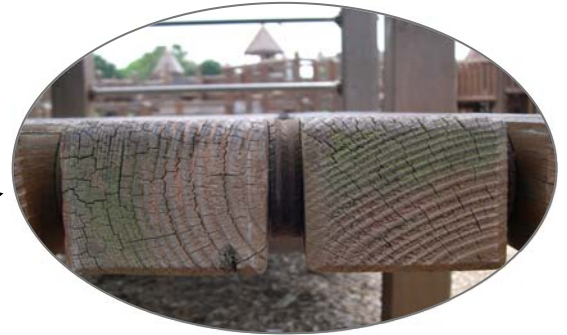
Arsenic trioxide may be found in pesticides and defoliants and as a contaminant of moonshine whiskey [Murunga and Zawada 2007].

Presently, arsenic is widely used in the electronics industry in the form of gallium arsenide and arsine gas as components in semiconductor devices.

Production of wood preservatives, primarily copper chromated arsenic (CCA), accounted for more than 90% of domestic consumption of arsenic trioxide in 2003. Wood treated with CCA is known as "pressure treated wood". In response to consumer concerns, U.S. manufacturers of arsenical wood preservative began a voluntary transition from CCA to other wood preservatives for certain residential wood products. In 2002, the U.S. Environmental Protection Agency (EPA) reached an agreement with the manufacturers of wood preservative products containing CCA to cancel the registration of CCA for use in virtually all residential applications. As of December 31, 2003, it is illegal to treat dimensional lumber used in residential applications with CCA. However, wood treated prior to this date can still be used, and CCA-treated wood products continue to be used in industrial applications [ATSDR 2007]. There are sealants that can be used to reduce the leaching of arsenic from CCA-treated wood for up to twelve months of natural weathering

[EPA 2007].

Many outdoor wood structures such as playgrounds and decks have been treated with copper-chromate-arsenate wood preservative. The photo at the left below shows one such playground. The preservative often gives wood a greenish color, as seen in the photo at the right below.



<p>Arsenic in Drugs</p>	<p>Arsenic is and has been used medicinally.</p> <ul style="list-style-type: none"> • Arsenic is currently used for induction and consolidation chemotherapy for acute promyelocytic leukemia and other cancers [Miller et al. 2002; Hu et al. 2005]. • Arsenic may be found in some traditional remedies from a number of Asian countries [Garvey et al. 2001; Chan 1994]. Arsenic may also be found in some naturopathic or homeopathic remedies [Kerr and Saryan 1986]. • “Fowlers solution,” which is 1% arsenic trioxide, was used historically to treat skin conditions such as psoriasis and eczema. It was also used to treat leukemia and stomatitis. When skin cancer resulted from the use of Fowler’s solution, there was a marked decrease in medicinal use of arsenic [Rossman 2007]. • Arspheamin (Salvarsan) was the first effective cure for syphilis until replaced by antibiotics after World War II [Rossman 2007].
<p>Industrial Production of Arsenic</p>	<p>Arsenic production has currently ceased in the United States. Arsenic has been phased out of domestic pesticides, but commercial use of imported arsenic is still high [ATSDR 2007].</p>
<p>Component Uses of Arsenicals</p>	<p>Discontinued arsenic-containing pesticides may still be found in some U.S. farms and homes [ATSDR 2007].</p> <p>Gallium arsenide is used in integral components of</p> <ul style="list-style-type: none"> • discrete microwave devices, • lasers, • light-emitting diodes, • photoelectric chemical cells, and • semiconductor devices. <p>Arsine gas, the most toxic arsenical (acute exposures), is used commercially in the microelectronics industry, and it is encountered accidentally in metallurgical and mining processes.</p> <p>Arsine gas is used in the production of semiconductors,</p>

	<p>although substitutes of lower toxicity such as tributylarsine have also been used.</p> <p>Arsine forms when acid or other reducing substances are added to arsenic-containing compounds, such as metals in which arsenic is a low level contaminant [ATSDR 2007].</p> <p>Arsine gas produces a clinical syndrome very different from other arsenic compounds.</p>
Use of Arsenicals in Chemical Warfare	<p>Use of arsenicals in chemical warfare.</p> <ul style="list-style-type: none"> Chlorovinyl dichloroarsine (also known as lewisite) was developed as a chemical warfare vesicant in the 1920s. It was declared obsolete in the 1950s in the United States and stockpiles were neutralized and disposed of. Unexploded ordnance containing Lewisite can still be found at U.S. former munition ranges [EPA 2008]. Lewisite is a compound from the chemical family of arsines that has different health effects than arsenic compounds. For example, it causes severe skin burns on contact at very low concentrations.
Other Industrial Processes	<p>Other industrial processes that use arsenic include</p> <ul style="list-style-type: none"> coal-fired power plants, hardening metal alloys, and purifying industrial gases (removal of sulfur)
Food	<p>Arsenic may be found in foods.</p> <ul style="list-style-type: none"> Seafood (especially bivalves [clams, oysters, scallops, mussels], crustaceans [crabs, lobsters], and certain cold water and bottom feeding finfish, and seaweed/kelp. The organic forms of arsenic found in seafood (mainly arsenobetaine and arsenocholine, also referred to as "fish arsenic") are generally considered to be nontoxic, and are excreted in urine within 48 hours of ingestion [ATSDR 2007]. However, inorganic forms of arsenic have been found in

	some types of seaweed. Recent literature suggests hijiki seaweed has very high levels of inorganic arsenic (MMA) [Rose et al. 2007].
--	--



While found in lower amounts in many foods and particularly seafoods, higher concentrations of dietary organic arsenic may be found in bivalve mollusks (clams, oysters, mussels) and crustaceans (crabs and lobsters). The organic forms of arsenic found in seafood (mainly arsenobetaine and arsenocholine, also referred to as “fish arsenic”) are generally considered to be nontoxic, and are excreted in urine within 48 hours of ingestion [ATSDR 2007].

Table 1		Arsenic Source vs. Potential Environmental Contamination	
	Arsenic Source	Environmental Contamination	
	Artesian and tube wells supplied by geologically contaminated aquifers	Drinking water	
	Mineral ore	Drinking water and soil	
	Erosion of natural land sources, discarded mine and mill tailings, arsenic-containing materials transported via rain.	Drinking water and soil	
Key Points	<ul style="list-style-type: none"> Inorganic arsenic is found in industry, in copper-chromate-arsenate treated lumber, and in private well 		

	<p>water in some parts of the country.</p> <ul style="list-style-type: none">• Organic arsenic is found in many foods and particularly in some shellfish. The organic forms and amounts of arsenic found in seafood are generally considered to be nontoxic.
<p>Progress Check</p> <p>Select the one best choice</p>	<p>3. Most of the arsenic used industrially in recent years in the United States has been for the manufacture of</p> <ul style="list-style-type: none">A. Pesticides.B. Wood preservative.C. Metal ores.D. Power.

Progress Check Answers	<p>3. The correct answer is B. Most of the arsenic used industrially in recent years in the United States has been for the manufacture of wood preservative. However, use of copper-chromate-arsenic wood preservative has now been largely phased out.</p> <p><i>To review relevant content, see "Arsenic Products" in this section.</i></p>
---------------------------------------	---

What Are Routes of Exposure for Arsenic?

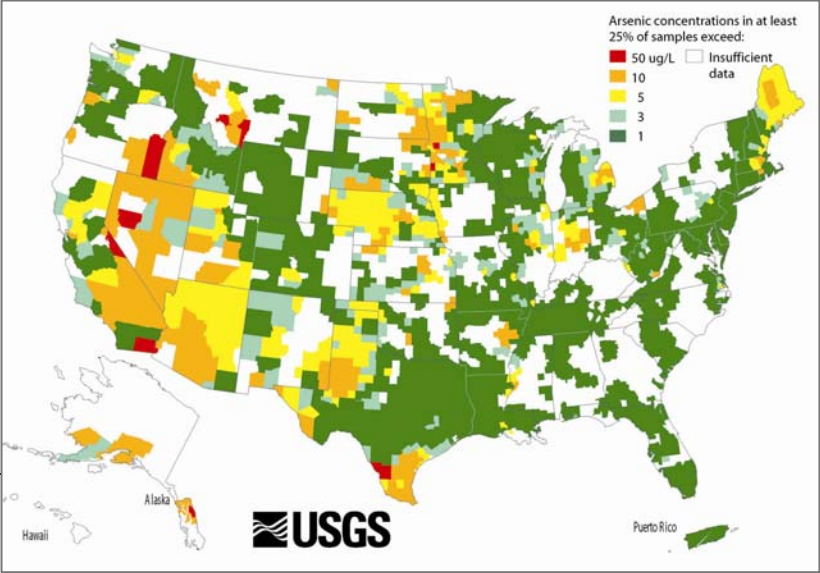
Learning Objective	<p>Upon completion of this section, you will be able to</p> <ul style="list-style-type: none"> • identify the major routes of exposure to arsenic. 				
Introduction	<p>The primary routes of arsenic entry into the body are via ingestion and inhalation. Dermal exposure can occur, but is not considered a primary route of exposure. Exposure dose is the cumulative exposure by all routes.</p>				
Ingestion	<p>In the general U.S. population, the main source of arsenic exposure is via ingestion of food containing arsenic. Intake from air, soil, and drinking water is usually much less. It has been estimated that the average daily dietary intake of arsenic by adults in the United States is 40 micrograms per day [ATSDR 2007].</p>				
Arsenic Containing Foods	<p>Meat, fish, and poultry account for 80% of dietary arsenic intake. Fish, bivalve shellfish, and algae also contain arsenic in the form of arsenobetaine and arsenocholine, sometimes referred to as "fish arsenic." Fish arsenic has low toxicity to humans and is rapidly excreted in urine [ATSDR 2007]. Recent studies have shown one form of seaweed, hijiki, to contain high levels of inorganic arsenic [Rose et al. 2007].</p>				
Arsenic from Water and Soil	<p>Well water contaminated by natural sources such as bedrock containing arsenic has been reported to be the cause of arsenic toxicity throughout the world. Arsenic in drinking-water has attracted much attention since recognition in the 1990s of its wide occurrence in well-water in Bangladesh [WHO 2001].</p> <table border="1" data-bbox="448 1671 1435 1858"> <tr> <td colspan="2" data-bbox="448 1671 1435 1787">Table 2. Countries where arsenic toxicity has been reported from natural source contamination of well water [NRC 2000].</td> </tr> <tr> <td data-bbox="448 1787 938 1858"> <ul style="list-style-type: none"> • Argentina </td> <td data-bbox="938 1787 1435 1858"> <ul style="list-style-type: none"> • India </td> </tr> </table>	Table 2. Countries where arsenic toxicity has been reported from natural source contamination of well water [NRC 2000].		<ul style="list-style-type: none"> • Argentina 	<ul style="list-style-type: none"> • India
Table 2. Countries where arsenic toxicity has been reported from natural source contamination of well water [NRC 2000].					
<ul style="list-style-type: none"> • Argentina 	<ul style="list-style-type: none"> • India 				

• Bangladesh	• Japan
• Bolivia	• Mexico
• Canada	• Mongolia
• Chile	• Romania
• China	• Spain
• Germany (Bavaria)	• Taiwan
• Ghana	• United States
• Greece	• Vietnam
• Hungary	

Areas in the United States with the highest natural groundwater concentrations of arsenic are the Southwest, Northwest, Northeast, Alaska, and other areas near geothermal activity [ATSDR 2007].

The form of ingested arsenic from drinking water sources will vary according to its exposure to air. Deep wells contain predominantly arsenite (arsenic III) and surface water will contain predominantly arsenate (arsenic V) [Rossman 2007].

Figure 1: U.S. Geological Survey Map of Arsenic in Groundwater



United States Geological Survey map of areas of the United States with arsenic in groundwater samples exceeding the specified levels in 25% or more of samples tested [USGS 2005].

Groundwater may also contain elevated concentrations of arsenic from

- agricultural runoff,
- contamination from runoff from wood preservatives containing arsenic.
- improperly disposed arsenical chemicals, or
- mining [Rossman 2007].

Instances of drinking water contamination by manmade sources has been documented at sites in the following countries:

- Brazil,
- Chile,
- India,
- Mexico,
- Nicaragua, and
- Thailand [IARC 2004].

In certain areas of the West, Midwest, Southwest, and Northeastern United States, well water may contain levels greater than 50 micrograms per liter (or 50 ppb) [Rossman 2007].

The EPA maximum contaminant level for arsenic in drinking water is 10 ppb [ATSDR 2007].

The U.S. Geological Survey has mapped arsenic distribution in soils in the United States. For the Conterminous United States, the geometric mean arsenic level in soil is 5.2 parts per million (ppm). Soil levels in the Eastern United States (east of the 96th meridian) have a geometric mean of 4.8 ppm arsenic (range <0.1 to 73 ppm). The Western United States (west of the 96th meridian) levels have a geometric mean of 5.5 ppm arsenic (range <0.10 to 97 ppm). [Shacklette and Boerngen 1984].

	<p>Elevated levels of arsenic in soil (due to either natural or man-made contamination) may be an ingestion risk, especially for children with pica and mouthing behaviors during play [Rossman 2007]. However, the bioavailability of arsenic in soil is variable, and dependent on the chemical form of arsenic.</p> <p>Arsenic uptake in plants does not appear to reach levels dangerous to human health [Rossman 2007].</p> <p>Inhalation exposure to coal fly ash may occur in some countries when coal that is contaminated with high levels of arsenic is burned [Rossman 2007].</p>
<p>Inhalation</p>	<p>Major sources of inhaled arsenic may come from air emissions from</p> <ul style="list-style-type: none"> • burning of fossil fuels that contain arsenic, • cotton gins, • glass manufacturing operations, • pesticide manufacturing facilities, • smelters, and • tobacco smoke [Rossman 2007]. <p>Airborne arsenic in the workplace is generally in the form of arsenic trioxide [Ishinishi et al. 1986]. Although measurements of arsenic concentrations in cases of occupational exposure have been rare, eight-hour averages of airborne arsenic in a U.S. copper smelter measured during 1943–1965 ranged between 6.9 and 20 milligrams/meter cubed [Welch et al. 1982]. High level occupational exposures are rare today because the current permissible exposure level is 0.01 milligrams/meter cubed.</p> <p>Exposure leading to severe arsenic toxicity may occur through inhalation of burning material containing arsenic as a wood preservative [Aposhian 1989].</p> <ul style="list-style-type: none"> • Smaller particles are deposited more deeply in the respiratory tract. • Particles deposited in the upper airways and swallowed after mucociliary clearance result in gastrointestinal

	tract absorption [Yip and Dart 2001].
Skin	Dermal contact when handling preserved wood products containing arsenic could result in arsenic exposure. However, very little is known regarding the chemical form, conditions for absorption, kinetics, or other information needed to make a statement regarding skin absorption in specific populations [NAS 1977]. Toxic effects have been reported in the occupational literature from splashes of arsenic trichloride or arsenic acid on worker's skin [Garb and Hine 1977].
Key Points	<ul style="list-style-type: none"> • Ingestion and inhalation are the most common routes of exposure to arsenic, and they are the routes that most commonly lead to illness. • Dermal exposure may lead to illness, but to a lesser extent than ingestion or inhalation routes of exposure. • The exposure dose is the cumulative exposure from all routes.
Progress Check Select the one best choice	4. The major route(s) of exposure to arsenic is/are A. Inhalation. B. Ingestion. C. Dermal contact. D. A and B. E. All are equally important.

Progress Check Answers	<p>4. The correct answer is D. The major routes of exposure to arsenic are ingestion and inhalation. Dermal exposure may lead to illness, but it is generally a minor exposure route.</p> <p><i>To review relevant content, see "Introduction", "Ingestion" and "Inhalation" in this section.</i></p>
---------------------------------------	---

Who Is at Risk of Overexposure to Arsenic?

Learning Objectives	Upon completion of this section, you will be able to <ul style="list-style-type: none">• identify the populations most heavily exposed to arsenic.
Introduction	<p>Today in the United States, the quantity of arsenic released by human activities exceeds amounts released from natural sources at least threefold.</p> <p>The major sources of arsenic release to the environment are</p> <ul style="list-style-type: none">• arsenic-treated lumber discarded in landfills, and• coal fired power plants. <p>In addition, water and soil concentrations are far higher in areas where arsenic mineral deposits have been mined. The areas in the United States with the highest natural groundwater concentrations of arsenic are the Southwest, Northwest, Northeast, Alaska, and other areas near geothermal activity [ATSDR 2007].</p> <p>Groundwater may also contain elevated concentrations of arsenic due to contamination from arsenical pesticide runoff. Groundwater is far more likely to contain high levels of arsenic than surface water. The concentration of arsenic in natural surface and groundwater is generally about 1 part per billion (ppb), but both may exceed 1,000 ppb in mining areas or where arsenic levels in soil are high [ATSDR 2007].</p> <p>The U. S. Environmental Protection Agency (EPA) maximum contaminant level for arsenic in drinking water is 10 ppb. Surveys of U.S. drinking water indicate that about 80% of water supplies have less than 2 ppb of arsenic, but 2% of supplies exceed 20 ppb of arsenic [ATSDR 2007]. Both the trivalent and pentavalent forms of inorganic arsenic can be found in drinking water.</p> <p>Low levels of naturally occurring mineral arsenic are present in soil.</p>

<p>Past Occupational Exposure</p>	<p>In the past, many occupations entailed exposures to arsenic (see Table 3). Studies have documented the scale of the problem.</p> <table border="1" data-bbox="451 386 1409 968"> <thead> <tr> <th colspan="2" data-bbox="451 386 1409 426"> Past occupational exposure to arsenic. Table 3 </th> </tr> <tr> <th data-bbox="451 426 927 466"> Trades </th> <th data-bbox="927 426 1409 466"> Occupations </th> </tr> </thead> <tbody> <tr> <td data-bbox="451 466 927 968"> <ul style="list-style-type: none"> • Construction/contracting • Ore smelting • Semiconductor manufacture </td> <td data-bbox="927 466 1409 968"> <ul style="list-style-type: none"> • Alloy manufacturing • Carpenters • Chicken and swine farming • Electronic manufacturing technicians • Pesticide, insecticide, and/or herbicide applicators • Smelter operator or engineer </td> </tr> </tbody> </table>	Past occupational exposure to arsenic. Table 3		Trades	Occupations	<ul style="list-style-type: none"> • Construction/contracting • Ore smelting • Semiconductor manufacture 	<ul style="list-style-type: none"> • Alloy manufacturing • Carpenters • Chicken and swine farming • Electronic manufacturing technicians • Pesticide, insecticide, and/or herbicide applicators • Smelter operator or engineer
Past occupational exposure to arsenic. Table 3							
Trades	Occupations						
<ul style="list-style-type: none"> • Construction/contracting • Ore smelting • Semiconductor manufacture 	<ul style="list-style-type: none"> • Alloy manufacturing • Carpenters • Chicken and swine farming • Electronic manufacturing technicians • Pesticide, insecticide, and/or herbicide applicators • Smelter operator or engineer 						
<p>Children's Exposures</p>	<p>Children may be exposed to arsenic in different ways.</p> <ul style="list-style-type: none"> • Burning plywood treated with an arsenate wood preservative in a poorly ventilated cabin has been blamed for poisoning a family in rural Wisconsin [ATSDR 2007]. • Wood treated with chromated copper arsenate (CCA) to prevent rotting due to growth of microorganisms is commonly used in marine applications, patio decks, and recreational structures for children's playgrounds. Cutting this wood or leaching of the preservative may lead to arsenic exposure. However it is not known whether, or to what extent, CCA-treated wood products may contribute to the exposure of people to arsenic [ATSDR 2007]. • Children who play on wood structures treated with CCA have increased likelihood of dermal contact or ingestion of the arsenical through normal mouthing and play activities [ATSDR 2007]. • Soil with high levels of arsenic is also an exposure risk for children due to pica or mouthing and play activities. • Drinking water contaminated with arsenic is another exposure risk for children. 						

<p>Current Occupational Exposures</p>	<p>Currently, the most heavily exposed people in the United States are in those industries that use arsenic-containing compounds, including [Rossman 2007]</p> <ul style="list-style-type: none"> • carpentry involving CCA pressure-treated lumber, and • copper or lead smelting, • electronics manufacturing industry, • pesticide application.
<p>Non-Occupational Exposures</p>	<p>Situations in which non-occupational exposure to arsenic can occur.</p> <ul style="list-style-type: none"> • Arsenic can cross the placenta, increasing the likelihood of exposure to the fetus [Lugo et al. 1969]. • Living near sources of high ambient air levels of arsenic. • Water supply containing high levels of arsenic.
<p>Exposure at School</p>	<p>Situations where students may be at risk of exposure to arsenic while attending school.</p> <ul style="list-style-type: none"> • Schools whose water supply comes from wells contaminated with high levels of arsenic • Schools that have CCA-preserved wood playground equipment/structures. • Children who play on wood structures treated with CCA have increased likelihood of dermal contact or ingestion of the arsenical through normal mouthing and play activities [USEPA 2005]. • Schools that are located near an industrial source that may emit arsenic into the air (such as a smelter).
<p>Background Exposures</p>	<p>As a naturally occurring mineral, arsenic may be found in soil and/or groundwater. The National Health and Nutrition Examination Survey (2003-2004) measured levels of total arsenic and speciated arsenic in urine of a representative sample of the US population. The data reflect relative background contributions of inorganic and seafood-related arsenic exposures in the U.S. population [Caldwell et al. 2008].</p>

<p>Exposure to Arsenicals in Unexploded Ordnance</p>	<p>Exposure of the general public to unexploded ordnance containing chlorovinyl dichloroarsine (also known as lewisite) has been reported at U.S. locations where former munitions ranges were transferred from the military to be used for other purposes. These properties are formerly used defense sites or property transferred by the past five rounds of Base Realignment and Closure (i.e., 1988, 1991, 1993, 1995, 2005). The Department of Defense is currently working to further define the inventory of sites and acreage that are potentially contaminated with military munitions and to prioritize these sites for cleanup [EPA 2008].</p>
<p>Key Points</p>	<ul style="list-style-type: none"> • Groups at risk for overexposure to arsenic may include <ul style="list-style-type: none"> ○ Industrial workers. ○ People who work with CCA treated lumber. ○ Those who drink water from private wells with high levels of arsenic in certain geographic areas. ○ The fetus of a mother exposed to arsenic.
<p>Progress Check</p> <p>Select the one best choice</p>	<p>5. Currently, occupations that may entail exposure to arsenic include which of the following?</p> <p>A. Sheet metal workers and pipe fitters. B. Workers in computer chip fabrication facilities. C. Shipyard workers and automobile mechanics. D. Carpenters cutting lumber treated with arsenic-containing preservatives. E. B and D. F. A and C.</p> <p>6. Of the following, who is <u>LEAST LIKELY</u> to be at risk of arsenic exposure and toxicity?</p> <p>A. A child attending a school with arsenic-containing wooden playground. B. An adult who works as a smelter. C. A person whose primary source of drinking water is from an artesian well. D. A suburban family receiving municipal utility</p>

	services.
--	-----------

Progress Check Answers	<p>5. The correct answer is E. Currently, occupations that may entail exposure to arsenic include workers in computer chip fabrication facilities and carpenters cutting lumber treated with arsenic-containing preservatives.</p> <p><i>To review relevant content, see "Current Occupational Exposures" in this section.</i></p> <p>6. The correct answer is D. A suburban family receiving municipal utility services is LEAST LIKELY to be at risk of arsenic exposure and toxicity.</p> <p><i>To review relevant content, see "Exposure at School," "Past Occupational Exposure," and "Non-Occupational Exposures" in this section.</i></p>
---------------------------------------	---

What Are Standards and Regulations for Arsenic Exposure?

Learning Objectives	<p>Upon completion of this section, you will be able to</p> <ul style="list-style-type: none"> describe U.S. standards for arsenic exposure.
Introduction	<p>We know that the toxic effects of arsenic depend on the nature and extent of exposure (dose), particularly the</p> <ul style="list-style-type: none"> concentration of arsenic involved in the exposure, frequency of exposure, duration of exposure, and type of arsenic involved in the exposure. <p>U.S. government standards for arsenic include a standard for</p> <ul style="list-style-type: none"> air levels of arsenic in the workplace, animals used as food, and arsenic in drinking water.
Workplace Standards	<p>The U.S Occupational Safety and Health Administration (OSHA) mandates permissible limits for arsenic occupational exposure.</p> <ul style="list-style-type: none"> The permissible exposure limit for arsenic is no greater than 10 micrograms of inorganic arsenic per cubic meter of air, averaged over any 8 hour period for a 40 hour workweek [OSHA 2001; NIOSH 2005]. <p>The American Conference of Governmental Industrial Hygienists has set a threshold limit value of 10 micrograms per cubic meter/ Arsenic and inorganic compounds as Arsenic [ACGIH 2005] (See Table 4).</p> <p>The recommended exposure limit set by the National Institute for Occupational Safety and Health (NIOSH) is 2 microgram per cubic meter of air for no more than a 15 minute period, based on classification of arsenic as a potential human carcinogen.</p> <p>For further information about OSHA standards, see</p>

	<p>http://www.osha.gov/SLTC/arsenic/index.html</p> <p>For further information about protection guidelines, contact NIOSH at 1-800-CDC-INFO (1-800-232-4636) or visit the Web site at http://www.cdc.gov/niosh/npg/npgname-a.html</p>
<p>Environmental Standards</p>	<p>Air</p> <p>The U.S. Environmental Protection Agency (EPA) lists arsenic under authorization of the Clean Air Act as a hazardous air pollutant, defined as a substance that may cause an increased mortality or serious illness in humans after significant exposure [EPA 2007].</p> <ul style="list-style-type: none"> • In 1986, EPA promulgated the National Emissions Standards for Hazardous Air Pollutants for three stationary source categories known to emit inorganic arsenic: <ol style="list-style-type: none"> 1. arsenic plants, 2. glass manufacturing plants, and 3. primary copper smelters [EPA 2007]. • There is no ambient air standard (i.e., no general air pollution limit) for arsenic [EPA 2007]. <p>Drinking Water</p> <p>EPA has set 10 ppb as the allowable level for arsenic in drinking water (maximum contaminant level). (EPA 2006)</p> <p>The World Health Organization recommends a provisional drinking water guideline of 10 ppb.</p> <p>Food</p> <p>Arsenic is used in some veterinary drugs, including those used to treat animals used for commercial food products.</p> <p>The U.S. Food and Drug Administration (FDA) has established tolerance levels for arsenic in byproducts of animals treated with veterinary drugs. These permissible levels range from 0.5 ppm in eggs and uncooked edible</p>

tissues of chickens and turkeys to 2 ppm in certain uncooked edible byproducts of swine.

Shellfish (especially bivalve mollusks and crustaceans) concentrate arsenic in seawater, but it exists in the organic forms, which have not been shown to produce adverse effects in humans consuming these seafoods. This type of organic arsenic is also rapidly excreted.

Pesticides

The EPA Office of Pesticide Programs (OPP) has restricted the use of inorganic arsenic in pressure-treated wood. It has also cancelled all registered uses of inorganic arsenic for non-wood preservative purposes.

For more information on EPA rules and regulations regarding arsenic, see <http://www.epa.gov/ttn/atw/hlthef/arsenic.html>.

Standards and Regulations for Inorganic Arsenic

Table 4. Standards and Regulations for Inorganic Arsenic

Agency	Focus	Level	Comments
ACGIH	Air - workplace	10 micrograms /m ³	Advisory; TLV/TWA†
NIOSH	Air - workplace	2 micrograms /m ³	Advisory; 15 minute ceiling limit
OSHA	Air - workplace	10 micrograms /m ³	Regulation; PEL over 8 hour day
EPA	Air - environment	NA	NA
	Water – drinking water	10 parts per billion	Regulation; maximum contaminant level in public drinking water supplies
FDA	Food	0.5–2 parts per million	Regulation; applies to animals treated with veterinary drugs

• ACGIH = American Conference of Governmental Industrial

	<p>Hygienists</p> <ul style="list-style-type: none"> • EPA = U.S. Environmental Protection Agency • FDA = U.S. Food and Drug Administration • NIOSH = National Institute for Occupational Safety and Health • OSHA = Occupational Safety and Health Administration <ul style="list-style-type: none"> ○ TLV/TWA (Threshold Limit Value/Time Weighted Average) = time weighted average concentration for a normal 8 hour workday or 40 hour workweek to which nearly all workers may be repeatedly exposed. ○ PEL (Permissible Exposure Limit) = highest level averaged over an 8 hour workday to which a worker may be exposed. 	
<p>Key Points</p>	<ul style="list-style-type: none"> • Occupational exposure law (OSHA standard) and environmental law (EPA standard) limit workplace airborne exposure and environmental drinking water exposures to arsenic, respectively. 	
<p>Progress Check</p> <p>Select the one best choice</p>	<p>7. Which following statement is <u>FALSE</u> regarding U.S. standards for arsenic levels?</p> <ul style="list-style-type: none"> A. There is a standard level for permissible air levels of arsenic in the workplace. B. There is a standard level for allowable arsenic in drinking water. C. There is a standard level for allowable arsenic in ambient air in the environment. D. There are permissible levels of organic arsenic set for foodstuffs by the FDA. 	

Progress Check Answers	<p>7. The correct answer identifying the <u>FALSE</u> statement is C. There is no standard level set for arsenic in ambient air in the environment. There are standards set for air levels of arsenic in the workplace, arsenic in drinking water, and permissible levels of organic arsenic set for human foodstuffs.</p> <p><i>To review relevant content, see “Workplace Standards” and “Environmental Standards” in this section.</i></p>
---------------------------------------	--

What Is the Biologic Fate of Arsenic in the Body?

Learning Objective	<p>Upon completion of this section, you will be able to</p> <ul style="list-style-type: none"> describe what happens when arsenic enters the body.
Introduction	<p>The primary routes of arsenic entry into the body are ingestion and inhalation. Dermal absorption also occurs, but to a lesser extent.</p> <p>The half-life of inorganic arsenic in humans is about 10 hours [Rossman 2007].</p> <p>Arsenic undergoes biomethylation in the liver.</p> <p>Approximately 70% of arsenic is excreted, mainly in urine [Rossman 2007].</p> <p>Arsenic is excreted in the urine; most of a single, low-level dose is excreted within a few days after ingestion.</p>
Gastro-Intestinal Tract	<p>For soluble trivalent arsenic compounds, approximately 95% of the ingested dose is absorbed from the gastrointestinal (GI) tract [Rossman 2007].</p>
Lungs	<p>Airborne arsenic in the workplace is generally in the form of arsenic trioxide [Ishinishi et al. 1986].</p> <p>The amount of arsenic absorbed by inhalation has not been determined precisely, but it is thought to be within 60% to 90% [Yip and Dart 2001].</p> <p>Smaller particles are deposited more deeply in the respiratory tract.</p>
Dermal Absorption	<p>Dermal absorption is generally negligible, although toxic systemic effects have resulted from rare occupational accidents where either arsenic trichloride or arsenic acid was splashed on workers' skin.</p>

<p>Distribution</p>	<p>After absorption through the lungs or GI tract, arsenic is widely distributed by the blood throughout the body. [ATSDR 2007]</p> <p>Most tissues rapidly clear arsenic, except for skin, hair, and nails [Lansdown 1995].</p> <p>Two to four weeks after exposure ceases, most of the arsenic remaining in the body is found in keratin-rich tissues such as</p> <ul style="list-style-type: none"> • hair, • nails, • skin, and • to a lesser extent, in bones and teeth [Yip and Dart 2001].
<p>Metabolism</p>	<p>Arsenic is absorbed into the blood stream at the cellular level and is taken up by</p> <ul style="list-style-type: none"> • red blood cells, • white blood cells, and • other cells that reduce arsenate to arsenite [Winski and Carter 1995; Wang et al. 1996]. <p>Reduction of arsenate (As V) to arsenite (As III) is needed before methylation can occur. This reaction requires glutathione (GSH) [Miller et al. 2002; Vahter et al. 1983].</p> <p>A portion of arsenite (As III) is methylated in the liver by enzymatic transfer of the methyl group from S-adenosylmethionine (SAM) to methyl arsonate (MMA V) and dimethyl arsonate (DMA V) [Aposhian et al. 2004; Styblo et al. 2002].</p> <p>The resulting metabolites are more readily excreted.</p> <p>Methylation has long been considered the main route of arsenic detoxification, but more recently there has been a growing body of literature supporting other detoxification mechanisms. For example, a number of animal species lack arsenic methylation and excrete inorganic arsenic [Vahter</p>

	<p>2002]. The implication is that there may be other more important arsenic detoxification mechanisms in mammals. Other studies have suggested additional detoxification mechanisms such as</p> <ul style="list-style-type: none"> • antioxidant defenses, • resistance to apoptosis, or • transport [Yoshida et al. 2004]. <p>There have also been studies of arsenic metabolism suggesting that methylation of inorganic arsenic may be a toxification, rather than a detoxification pathway and that trivalent methylated arsenic metabolites, particularly monomethylarsonous acid (MMA III) and dimethylarsinous acid (DMA III), are “unusually capable of interacting with cellular targets such as proteins and DNA” [Kitchin 2001].</p> <p>Methylation efficiency in humans appears to decrease at high arsenic doses. Patterns of methylated arsenic species in urine are similar between siblings and between siblings and parents, which suggests that arsenic methylation is genetically linked [Chung et al. 2002].</p> <p>When the methylating capacity of the liver is exceeded, exposure to excess levels of inorganic arsenic results in increased retention of arsenic in soft tissues.</p>
<p>Excretion</p>	<p>Arsenic is excreted in the urine primarily through the kidneys. Humans excrete a mixture of inorganic, monomethylated, and dimethylated (but not trimethylated) forms of arsenic. The pentavalent metabolites MMA V and DMA V are less toxic than arsenite or arsenate [Marafante et al. 1987].</p> <ul style="list-style-type: none"> • Approximately 50% of excreted arsenic in human urine is dimethylated and 25% is monomethylated, with the remainder being inorganic [Buchet et al. 1981]. However, there may be individual variations in percentage. According to urinary arsenic data from the National Health and Nutrition Examination Survey 2003-2004 (also described in the “<i>Clinical Assessment, Lab Testing</i>” section of this document), as urinary levels of total arsenic increase, the

	<p>percentage of methylated forms increases and at lower urinary total arsenic levels, the predominant form is inorganic [Caldwell et al. 2008].</p> <ul style="list-style-type: none"> • Fish arsenic is largely not biotransformed <i>in vivo</i>, but it is rapidly excreted unchanged in the urine. • After a single intravenous injection of radiolabeled trivalent inorganic As (III) in human volunteers, most of the arsenic was cleared through urinary excretion within 2 days, although a small amount of arsenic was found in the urine up to 2 weeks later [ATSDR 2007]. • The biologic half-life of ingested fish arsenic in humans is estimated to be less than 20 hours, with total urinary clearance in approximately 48 hours [ATSDR 2007]. • Because arsenic is rapidly cleared from the blood, blood levels may be normal even when urine levels remain markedly elevated [ATSDR 2007]. <p>Other less important routes of elimination of inorganic arsenic include</p> <ul style="list-style-type: none"> • feces, • incorporation into hair and nails, • skin desquamation, and • sweat.
Key Points	<ul style="list-style-type: none"> • The primary method of metabolizing arsenic in humans is methylation. • Although once considered the main mechanism of detoxification, studies have implied the existence of other more important arsenic detoxification mechanisms in mammals. • The main route of arsenic excretion is in the urine. • Humans excrete a combination of inorganic arsenic and its mono and dimethylated metabolites in the urine. • Fish arsenic is excreted within 48 hours of ingestion.
Progress Check Select the	<p>8. The primary method of metabolizing ingested inorganic arsenic is by</p> <p>A. Fenton reaction.</p>

one best choice	<p>B. Ubiquitination. C. Oxidation. D. Methylation.</p> <p>9. Ingested "fish arsenic" is usually completely excreted within how many hours of the last meal?</p> <p>A. 2. B. 12. C. 24. D. 48.</p>
------------------------	--

Progress Check Answers	<p>8. The correct answer is D. The primary method of metabolizing ingested inorganic arsenic is by methylation.</p> <p><i>To review relevant content, see "Introduction" and "Metabolism" in this section.</i></p> <p>9. The correct answer is D. Ingested "fish arsenic" is usually completely excreted within 48 hours of the last meal.</p> <p><i>To review relevant content, see "Excretion" in this section.</i></p>
---------------------------------------	---

How Does Arsenic Induce Pathogenic Change?

Learning Objective	<p>Upon completion of this section, you will be able to</p> <ul style="list-style-type: none"> describe the ways that arsenic induces illness.
Introduction	<p>A small molecule that can easily get into cells, arsenic can cause cell injury and death by multiple mechanisms. Interference with cellular respiration explains the potent toxicity of arsenic. In addition, arsine gas may interact directly with red cell membranes. Arsenic is a known human carcinogen, but the specific mechanisms by which it causes cancer are less well understood.</p>
Toxicity by Form	<p>Arsenic toxicity may vary by form.</p> <ul style="list-style-type: none"> Inorganic arsenic is generally more toxic than organic arsenic. The type of organic arsenic found in certain seafood (arsenobetaine and arsenocholine) appears to have low toxicity. However, animal studies have shown that other organic arsenic compounds (methyl and phenyl arsenates, for example) can produce health effects similar to those produced by inorganic arsenic [ATSDR 2007]. In vitro studies have shown that the cellular uptake of As (III) is greater than that of As (V) [Bertolero et al. 1987; Dopp et al. 2004]. Although there may be some differences in the potency of different chemical forms (e.g., arsenites tend to be somewhat more toxic than arsenates), these differences are usually minor. An exception would be arsine which is highly toxic [ATSDR 2007]. Metalloid arsenic is generally regarded as nonpoisonous due to its insolubility in water and body fluids. <p>Although the toxicity of arsenic compounds can vary greatly, in general, a listing of different compounds from highest to lowest toxicity follows:</p> <ul style="list-style-type: none"> inorganic trivalent compounds,

	<ul style="list-style-type: none"> • organic trivalent compounds, • inorganic pentavalent compounds, • organic pentavalent compounds, and • elemental arsenic [Gorby 1988].
Interaction with Cellular Macromolecules	<p>Two mechanisms of arsenic toxicity that impair tissue respiration are described below.</p> <ul style="list-style-type: none"> • Arsenic binds with sulfhydryl groups and disrupts sulfhydryl containing enzymes; As (III) is particularly potent in this regard. As a result of critical enzyme effects, there is <ul style="list-style-type: none"> ○ inhibition of the pyruvate oxidation pathway and the tricarboxylic acid cycle, ○ impaired gluconeogenesis, and ○ reduced oxidative phosphorylation. • Another mechanism involves substitution of As (V) for phosphorus in many biochemical reactions. <ul style="list-style-type: none"> ○ Arsenite does not compete with phosphate, but tends to bind to dithiol groups. ○ Replacing the stable phosphorus anion in phosphate with the less stable As (V) anion leads to rapid hydrolysis of high energy bonds in compounds such as ATP, a process that leads to loss of high energy phosphate bonds and effectively “uncouples” mitochondrial respiration [Rossman 2007]. <p>Arsenic’s affinity for thiol groups allows for the use of thiol group-containing chelators in the treatment of acute arsenic poisoning.</p> <ul style="list-style-type: none"> • Arsenite binds specifically to thiol group-containing hormone receptors, a process that prevents the binding of steroids [Lopez et al. 1990; Kaltreider et al. 2001]. • It is hypothesized that arsenic’s diabetogenic effect may be related to its ability to bind and inhibit the insulin receptor [Rossman 2007].
Controversy	<p>The present view of arsenic carcinogenesis is that there are</p>

<p>Regarding Mode of Arsenic Carcinogenesis</p>	<p>many possible chemical forms of arsenic that may be causal in carcinogenesis. In addition, arsenic induced carcinogenesis may have different mechanisms in different tissues with contributions from all species present in that tissue [ROM 2007]. Some studies in arsenic metabolism suggest that methylation of inorganic arsenic may be a toxification, rather than a detoxification pathway and that trivalent methylated arsenic metabolites, particularly monomethylarsonous acid and dimethylarsinous acid, have a great deal of biological activity [Kitchin 2001]. The evidence indicates that trivalent, methylated, and relatively less ionizable arsenic metabolites may be capable of interacting with cellular targets such as proteins and even DNA [Kitchin 2001].</p> <p>A scientific consensus has not yet been reached on the many suggested modes of arsenic carcinogenesis that exist in the literature. These include modes that are predominately genotoxic (i.e., chromosomal abnormalities, oxidative stress, and gene amplification) vs. more nongenotoxic (i.e., altered growth factors, enhanced cell proliferation and promotion of carcinogenesis, and altered DNA repair). Likewise, the dose-response relationship at low arsenic concentrations for any of these suggested modes is not known [Kitchin 2001].</p>
<p>Arsine Gas Poisoning</p>	<p>Arsine gas poisoning results in a considerably different syndrome from that caused by other forms of arsenic. After inhalation, arsine rapidly binds to red blood cells, producing irreversible cell membrane damage.</p> <ul style="list-style-type: none"> • At low levels, arsine is a potent hemolysin, causing dose-dependent intravascular hemolysis. • At high levels, arsine produces direct multisystem cytotoxicity.
<p>Key Points</p>	<ul style="list-style-type: none"> • Arsenic binds with sulfhydryl groups and disrupts sulfhydryl containing enzymes. • It replaces the stable phosphorus anion in phosphate with the less stable As (V) anion, leading to rapid hydrolysis of high energy bonds in compounds such as ATP. • The type of organic arsenic found in certain seafood appears to have low toxicity.

	<ul style="list-style-type: none"> • Studies suggest arsenic detoxification pathways other than methylation may be more important. • There is no scientific consensus on mode of arsenic carcinogenesis. • A dose response relationship at low arsenic concentrations for carcinogenesis is not known. • Arsine gas binds to red blood cells, causing hemolysis.
<p>Progress Check</p> <p>Select the one best choice</p>	<p>10. Arsenic initiates cellular injury by</p> <ul style="list-style-type: none"> A. Oxidation of lipid membranes. B. Ubiquitination. C. Methylation. D. Binding with sulfhydryl groups. <p>11. Arsine gas causes anemia by</p> <ul style="list-style-type: none"> A. Inhibiting stem cells directly. B. Inhibiting erythropoietin. C. Interference with iron metabolism. D. Hemolysis.

Progress Check Answers	<p>10. The correct answer is D. Arsenic initiates cellular injury by binding with sulfhydryl groups.</p> <p><i>To review relevant content, see "Interaction with Cellular Macromolecules" in this section.</i></p> <p>11. The correct answer is D. Arsine gas causes anemia by hemolysis.</p> <p><i>To review relevant content, see "Interaction with Cellular Macromolecules" in this section.</i></p>
---------------------------------------	---

What Are the Physiologic Effects of Arsenic Exposure?

Learning Objective	<p>Upon completion of this section, you will be able to</p> <ul style="list-style-type: none"> describe the health effects associated with arsenic exposure.
Introduction	<p>Because it targets widely dispersed enzyme reactions, arsenic affects nearly all organ systems. The most sensitive endpoint from arsenic exposure is dermal effects. While several studies may identify effects on other endpoints at the same exposure level that produces dermal effects, the database for dermal effects is stronger than for effects on other endpoints [ATSDR 2007]</p> <p>Key physiologic effects from arsenic exposure that will be covered in detail later.</p> <ul style="list-style-type: none"> Patchy skin hyperpigmentation, small focal keratoses, and other skin lesions are common effects of heavy chronic exposure. It is difficult to establish strong associations between arsenic exposure and disease, as the prevalence and spectrum of diseases linked to chronic arsenic exposure differ not only between countries, but even within countries. Arsenic can cause lung and skin cancers and may cause other cancers. The association between chronic arsenic exposure and cancer is strongest for skin, lung, and bladder cancer. Liver (angiosarcoma), kidney, and other cancers have limited strength of association [IARC 2004; NRC 2000]. <p>Note that when strength of association (defined as the magnitude of the relative risk in the exposed group compared with that in the control group) is mentioned throughout this section, it refers to one of the five criteria used to decide whether a positive association in epidemiologic studies indicates causality. It is not absolutely</p>

	<p>required to establish causality. In addition, fulfillment of some criteria may occur when the association is a result of chance or bias. Failure to demonstrate a positive association in an epidemiologic study does not always indicate there is no association between the agent and the effects studied.</p> <p>In the United States, excess cancer mortality associated with arsenic is not generally seen [Schoen et al. 2004].</p> <p>Unlike other arsenicals, arsine gas causes a hemolytic syndrome.</p>
<p>Historical Exposure Highlighting Multiple Organ System Effects</p>	<p>The description of an historical arsenic exposure highlights its multiple organ system effects.</p> <ul style="list-style-type: none"> • Arsenic-contaminated beer resulted in 6,000 poisonings and approximately 71 deaths in Northern England in 1900. Sulfuric acid contaminated with arsenic, which was used to make sugar from sugar cane for use in brewing beer, was found to be the source of the contamination, which affected 100 breweries. <ul style="list-style-type: none"> ○ The common clinical presentation was <ul style="list-style-type: none"> ▪ anorexia, brown pigmentation, ▪ peripheral neuritis (muscular weakness, pain and paresthesias in extremities), ▪ hepatic lesions, ▪ localized edema, and ▪ fatty degeneration of the heart. ○ The concentration of arsenic in beer ranged from 2–4 parts per million (ppm) [Reynolds 1901; Aposhian 1989; Engel et al. 1994; Rosenman 2007].
<p>Gastrointestinal and Hepatic Effects</p>	<p>The gastrointestinal effects (GI) of arsenic are generally the result of ingestion; however, GI effects may also occur after heavy exposure by other routes.</p> <ul style="list-style-type: none"> • GI effects are seen acutely after arsenic ingestion, and less often after inhalation or dermal absorption. • The fundamental GI lesion appears to be increased

	<p>permeability of the small blood vessels, leading to fluid loss and hypotension.</p> <ul style="list-style-type: none"> • Extensive inflammation and necrosis of the mucosa and submucosa of the stomach and intestine may occur and progress to perforation of the gut wall. • A hemorrhagic gastroenteritis may develop, with bloody diarrhea as a presenting effect. <p>Acute arsenic toxicity may be associated with hepatic necrosis and elevated levels of liver enzymes.</p> <ul style="list-style-type: none"> • Arsenic intoxication may also result in toxic hepatitis with elevated liver enzyme levels. • Chronic arsenic ingestion may lead to cirrhotic portal hypertension [ATSDR 2007; Datta 1976]. • There is limited strength of association of chronic arsenic exposure and noncirrhotic portal hypertension [IARC 2004; NRC 2000]. • Case reports have also linked chronic high-level arsenic exposure with hepatic angiosarcoma, a rare form of liver cancer [Popper et al. 1978; Zaldivar et al. 1981; ATSDR 2007]. • There is limited strength of association, however, between chronic arsenic exposure and angiosarcoma of the liver, as determined by International Agency for Research on Cancer (IARC) and National Research Council [IARC 2004; NRC 2000].
Renal Effects	<p>Arsenic is capable of causing renal effects.</p> <ul style="list-style-type: none"> • The systemic toxicity occurring in severe acute arsenic poisoning may include acute tubular necrosis with acute renal failure. • Chronic renal insufficiency from cortical necrosis has also been reported. • The precipitating cause of renal injury may be hypotensive shock, hemoglobinuric or myoglobinuric tubular injury, or direct effects of arsenic on tubule cells. • Glomerular damage can result in proteinuria. • The kidney is not the most sensitive target organ for chronic arsenic toxicity as other organ systems may be affected at lower doses.

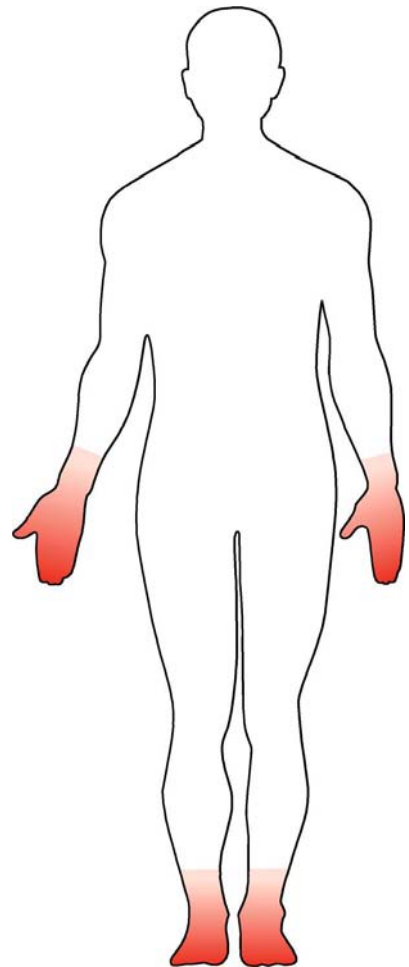
	<ul style="list-style-type: none"> • There is limited strength of association between chronic arsenic exposure and renal cancer [IARC 2004; NRC 2000]. • Arsine gas is more nephrotoxic than arsenic. However, both can cause acute tubular necrosis [Giberson et al. 1976].
Cardiovascular Effects	<p>Both acute and chronic exposure to high levels of arsenic may result in a wide range of adverse cardiovascular effects.</p> <ul style="list-style-type: none"> • There is limited strength of association between chronic arsenic exposure and peripheral vascular disease, hypertension, and cardiovascular disease [IARC 2004]. • Acute arsenic poisoning may cause both diffuse capillary leakage and cardiomyopathy, resulting in shock. • The extent of cardiovascular injury may vary with <ul style="list-style-type: none"> ○ age, ○ arsenic dose, and ○ individual susceptibility. • In acute arsenic poisoning (such as suicide attempts), diffuse capillary leakage may lead to <ul style="list-style-type: none"> ○ delayed cardiomyopathy, ○ hypotension, ○ shock, ○ transudation of plasma, and ○ vasodilation. • Arsenic ingestion from contaminated beer has been reported to cause outbreaks of cardiomyopathy [Reynolds 1901; Aposhian 1989; Rosenman 2007]. • Other reports of arsenic poisoning have resulted in peripheral vascular disease, rather than congestive heart failure [Engel et al. 1994]. • Inhibition of endothelial nitric oxide synthase, changes in coagulation and inflammation due to arsenic exposure have been shown in experimental studies to contribute to atherosclerosis [Simeonova and Luster 2004]. • Hypertension has been reported with long-term exposure to arsenic [Chen et al. 1995].

- Ingesting arsenic levels of 0.8 to 1.82 ppm in drinking water (normal concentrations of arsenic in drinking water are lower than .01 ppm) as reported in Chile and Taiwan have resulted in an increased prevalence of peripheral vascular disease and cardiovascular mortality [Rosenman 2007].
- Myocardial damage can result in a variety of electrocardiographic findings, including
 - broadening of the QRS complex,
 - prolongation of the QT interval,
 - ST depression,
 - flattening of T waves, and
 - atypical, multifocal ventricular tachycardia.
- Gangrene of the extremities, known as “blackfoot disease”, has been reported with drinking arsenic-contaminated well water in Taiwan, where the prevalence of the disease increased with increasing age and well water arsenic concentration (170–800 parts per billion) [ATSDR 2007].
 - Pathologically, blackfoot disease was due to arteriosclerotic or thromboangiitis obliterans. After the water supply was changed, the vascular and cardiovascular mortality reversed [Pi et al. 2005; Chang et al. 2004].
 - Persons with blackfoot disease also had a higher incidence of arsenic-induced skin cancers. However, investigators believe other vasoactive substances found in the water may have been contributory [ATSDR 2007].
- Vasospastic (Raynaud’s) disease in arsenic-exposed smelter workers and German vineyard workers has been reported. Smelter workers had a total exposure of 4 to 9 grams of arsenic, compared to the 20 grams of arsenic exposure reported for those with blackfoot disease [Rosenman 2007].
- Drinking arsenic-contaminated water in Chile was associated with an increase of vasospastic changes (Raynaud’s disease) and thickening of the small and medium sized arteries in autopsied children [Garcia-Vargas and Cebrian 1996].
- Arsenic ingestion affects the cardiovascular system,

	<p>altering myocardial depolarization and causing cardiac arrhythmias and hypertension in some populations [Guha 2003].</p> <ul style="list-style-type: none"> • Inorganic arsenical pesticides are now generally not used by vineyard workers, and the organic arsenicals that are used have not been associated with vasospastic changes [Rosenman 2007]. • Increased cardiovascular mortality in occupationally exposed groups may be masked by the healthy worker effect [Hertz-Picciotto et al. 2000].
<p>Neurologic Effects</p>	<p>In studies that support an association, arsenic-exposed patients may develop destruction of axonal cylinders, leading to peripheral neuropathy. This has been reported at acute high doses (>2 milligram (mg) arsenic (As)/kilogram (kg)/day) as well as from repeated exposures to lower levels (.03 – 0.1 mg As/kg/day) [Chakraborti et al. 2003a, 2003b; ATSDR 2007].</p> <ul style="list-style-type: none"> • Arsenic may cause encephalopathy at acute high doses (> 2mg As/Kg/day) [Uede and Furukawa 2003; Vantroyen et al. 2004; ATSDR 2007]. <p>Arsenic poisoning can cause peripheral neuropathy. The lesion is a sensory-motor axonopathy.</p> <ul style="list-style-type: none"> • The classic finding is a peripheral neuropathy involving sensory greater than motor neurons in a symmetrical, stocking glove distribution [Murphy et al. 1981]. • In high-level arsenic exposures, onset of neuropathy may occur after 7 to 14 days, with intense <ul style="list-style-type: none"> ○ increased sweating in the distal lower extremities, ○ muscle cramps, ○ muscle tenderness, ○ numbness, ○ paresthesia, and ○ spontaneous pain [Bleecker 2007]. • Sensory effects, particularly painful dysesthesia, occur earlier and may predominate in moderate poisoning, whereas ascending weakness and paralysis may be evident in more severe poisoning.

- Those cases may at first seem indistinguishable from Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy) [Donofrio et al. 1987].
- Cranial nerves are rarely affected, even in severe poisoning.

The most common neurologic effect of chronic arsenic intoxication is a sensory-predominant peripheral neuropathy in a “stocking-glove” pattern, as shown in the diagram to the right.




- The mechanism of arsenic neuropathy may be similar to the neuropathy of thiamine deficiency [Sexton and Gowdy 1963], whereby arsenic inhibits the conversion of pyruvate to acetyl coenzyme A and thus blocks the Krebs cycle.
- The neurotoxic forms of arsenic include inorganic trivalent (arsenite) and pentavalent (arsenate) and the

methylated metabolites, monomethyl arsonic acid and dimethylarsenic acid [Foa et al. 1984].

Encephalopathy has been reported after both acute and chronic exposures.

- Onset may begin within 24 to 72 hours following acute poisoning, but it more often develops slowly as a result of chronic exposure [Beckett et al. 1986].
- The neuropathy is primarily sensory, with chronic exposure affecting vibration and positional sense to a greater extent than other modalities. Weakness of intrinsic muscles of the extremities is mild when present in chronic arsenic exposure [Bleecker 2007].
- The neuropathy is primarily due to destruction of axonal cylinders.
- Nerve conduction and electromyography studies most frequently show a sensory-motor axonopathy and can document severity and progression. A dose response effect has been reported between environmental exposure to arsenic-containing dust and vibrotactile threshold, tremor intensity, nerve conduction studies, and standing steadiness [Gerr and Letz 2000].
- Elevated vibration threshold has been associated with a cumulative arsenic index (drinking water arsenic exposure) and urinary arsenic levels [Hafeman et al. 2005].
- Subclinical neuropathy, defined by the presence of abnormal nerve conduction, but no clinical complaints or symptoms, has been described in chronically exposed individuals [Tseng 2003; ATSDR 2007].
- Recovery from neuropathy induced by chronic exposure to arsenic compounds is generally slow, sometimes taking years, and complete recovery may not occur.
- The prognosis for recovery in mild cases of neuropathy is excellent [Bleecker 2007].
- Follow-up studies of Japanese children who chronically consumed arsenic contaminated milk revealed an increased incidence of
 - cognitive deficits,
 - epilepsy,
 - other brain damage, and
 - severe hearing loss (ATSDR 2007).

	<ul style="list-style-type: none">• Hearing loss as a sequela of acute or chronic arsenic intoxication has not been confirmed by other case reports or epidemiologic studies [ATSDR 2007].• There is limited strength of association between chronic arsenic exposure and neurologic effects, per the International Agency for Research on Cancer (IARC) and the National Research Council (NRC) [IARC 2004; NRC 2000].
Dermal Effects	<p>Pigment changes and palmoplantar hyperkeratoses are characteristic of chronic arsenic exposure.</p> <ul style="list-style-type: none">• Benign arsenical keratoses may progress to malignancy.• Delayed effects of acute or chronic exposure may be seen as Mee's lines in nails.• Mees lines are horizontal lines in the nails of digits. <div data-bbox="573 884 1122 1167" style="border: 1px solid black; padding: 5px;"><p>The patient in the photo developed severe, patchy skin hyperpigmentation after prolonged ingestion of arsenic-contaminated well water. (Photo courtesy the Arsenic Foundation).</p></div>  <p>The skin lesions occurring most frequently in arsenic-exposed humans are</p>

- hyperkeratosis,
- hyperpigmentation, and
- skin cancer.

Patchy hyperpigmentation, a pathologic hallmark of chronic exposure, may be found anywhere on the body.

- Patchy hyperpigmentation occurs particularly on the
 - axillae,
 - eyelids,
 - groin.
 - neck,
 - nipples, and
 - temples.
- The common appearance of the dark brown patches with scattered pale spots is sometimes described as "raindrops on a dusty road".
- In severe cases, the pigmentation extends broadly over the chest, back, and abdomen.
- Pigment changes have been observed in populations chronically consuming drinking water containing 400 ppb or more arsenic [ATSDR 2007].

Arsenical hyperkeratosis occurs most frequently on the palms and soles.

Arsenic keratoses (below) on the palms of a patient who ingested arsenic from a contaminated well over a prolonged period ([photo](#) courtesy Dr. Joseph Graziano).



- Keratoses usually appear as small corn-like elevations, 0.4 to 1 centimeter (cm) in diameter.
- In most cases, arsenical keratoses show little cellular atypia and may remain morphologically benign for decades [ATSDR 2007].
- In other cases, cells develop marked atypia (precancerous) and appear indistinguishable from Bowen's disease, which is an *in situ* squamous cell carcinoma discussed in Carcinogenic Effects later in this section [ATSDR 2007].
- Basal cell carcinomas have also been reported [Cohen and Moore 2007].
- Confounding factors for arsenic-induced skin cancer may include exposure to sunlight, chronic liver disease, and nutritional status [Hsueh et al. 1995].

Skin cancer (below) on the palm of a patient who ingested arsenic over a prolonged period of time from a contaminated well (photo courtesy the Arsenic Foundation).



Respiratory Effects

Inhalation of high concentrations of arsenic compounds

	<p>produces irritation of the respiratory mucosa.</p> <ul style="list-style-type: none"> • Smelter workers experiencing prolonged exposures to high concentrations of airborne arsenic at levels rarely found today had inflammatory and erosive lesions of the respiratory mucosa, including nasal septum perforation. • Lung cancer has been associated with chronic arsenic exposure in smelter workers and pesticide workers [ATSDR 2007].
<p>Hemato- poietic and Hematologic Effects</p>	<p>Bone marrow depression may result from acute or chronic arsenic intoxication and may initially manifest as pancytopenia.</p> <ul style="list-style-type: none"> • Both acute and chronic arsenic poisoning may affect the hematopoietic system. • A reversible bone marrow depression with pancytopenia may occur. • Anemia and leukopenia are common in chronic arsenic toxicity and are often accompanied by thrombocytopenia and mild eosinophilia. • The anemia may be normocytic or macrocytic, and basophilic stippling may be noted on peripheral blood smears [Kyle and Pearse 1965; Selzer 1983]. • According to the NRC and IARC, there is a suggestive association between chronic arsenic exposure and immunosuppression [NRC 2000; IARC 2004]. • Acute intoxication with arsine gas can cause fulminant intravascular hemolysis.
<p>Reproductive Effects</p>	<p>Increased frequency of spontaneous abortions and congenital malformations has been linked to arsenic exposure.</p> <ul style="list-style-type: none"> • Arsenic is a reproductive toxicant and a teratogen [Shalat 1996]. It is readily transferred across the placenta, and concentrations in cord blood are similar to those in maternal blood. • A published case report described acute arsenic ingestion during the third trimester of pregnancy, leading to delivery of a live infant that died within 12

hours. Autopsy revealed intra alveolar hemorrhage and high levels of arsenic in the brain, liver, and kidneys [ATSDR 2007].

- A study of women working at or living near a copper smelter where ambient arsenic levels were elevated reported increased frequencies of spontaneous abortions and congenital malformations [Nordstrom et al. 1979].
 - The frequency of all malformations was twice the expected rate and the frequency of multiple malformations was increased fivefold [Nordstrom et al. 1979].
 - However, a number of other chemicals, including lead, cadmium, and sulfur dioxide, were also present, and thus it is difficult to assess the role of arsenic in the etiology of these effects.

Carcinogenic Effects

The carcinogenicity of arsenic in humans has been established.

Table 5. Inorganic arsenic is a known human carcinogen [IARC 2004].

Agency	Carcinogenicity Classification	Description
International Agency for Research on Cancer	1	Known human carcinogen
National Toxicology Program	--	Known human carcinogen
U.S. Environmental Protection Agency	Group A	Known human carcinogen

- In humans, chronic arsenic ingestion may cause cancers of the
 - bladder,
 - kidney,
 - liver,

	<ul style="list-style-type: none"> ○ lung, ○ prostate, and ○ skin (ATSDR 2007). <ul style="list-style-type: none"> • Chronic inhalation of arsenicals has been associated with lung cancer and angiosarcoma (a rare form of liver cancer) has been reported [Falk et al. 1981]. • Several large-scale epidemiological studies of arsenic exposure have shown association and/or dose response trends for tumors of the <ul style="list-style-type: none"> ○ bladder, ○ kidney, ○ liver, ○ lung, and ○ prostate [ATSDR 2007]. • According to IARC and NRC, the association between chronic arsenic exposure and cancer is strongest for skin, lung, and bladder cancer. Liver (angiosarcoma), kidney, and other cancers have limited strength of association [IARC 2004; NRC, 2000].
Skin Cancer	<p>Latency for skin cancer associated with ingestion of arsenic may be 3 to 4 decades, while the noncarcinogenic skin effects typically develop several years after exposure [ATSDR 2007].</p> <ul style="list-style-type: none"> • An increased risk of skin cancer in humans is associated with chronic exposure to inorganic arsenic in contaminated water and the workplace. • Arsenic-induced skin cancer is frequently characterized by lesions over the entire body, mostly in unexposed areas such as the <ul style="list-style-type: none"> ○ palms, ○ soles, and ○ trunk. <p>More than one type of skin cancer may occur in a patient.</p> <ul style="list-style-type: none"> • Most of the Taiwanese who developed skin cancer in association with ingested arsenic-contaminated drinking

	<p>water had multiple cancer types [ATSDR 2007]. The most commonly reported types, in order of decreasing frequency, were</p> <ul style="list-style-type: none"> • intraepidermal carcinomas (Bowen's disease), • squamous cell carcinomas, and • basal cell carcinomas. <ul style="list-style-type: none"> • Seventy-two percent of the Taiwanese with skin cancer also had hyperkeratosis, and 90% had hyperpigmentation. • Some hyperkeratinized lesions can develop into intraepidermal carcinoma, which may ultimately become invasive. The lesions are sharply demarcated, round or irregular plaques that tend to enlarge; they may vary in size from 1 millimeter to more than 10 centimeters [ATSDR 2007]. • Arsenical basal cell carcinomas most often arise from normal tissue, are almost always multiple, and frequently occur on the trunk. The superficial spreading lesions are red, scaly, atrophic, and are often indistinguishable from Bowen's disease by clinical examination. • Arsenic-associated squamous cell carcinomas are distinguished from ultraviolet-induced squamous cell carcinomas by their tendency to occur on the extremities (especially palms and soles) and trunk, rather than on sun-exposed areas such as the head and neck. However, it may be difficult to distinguish other arsenic-induced skin lesions from those induced by other causes. • Epidemiologic studies indicate that a dose response relationship exists between the level of arsenic in drinking water and the prevalence of skin cancers in the exposed population [ATSDR 2007]. • Excessive mortality rates due to arsenic-induced skin cancer have also been observed in vineyard workers with dermal and inhalation exposure [ATSDR 2007].
Lung Cancer	<p>An association between lung cancer and occupational exposure to inorganic arsenic has been confirmed in several epidemiologic studies [Enterline et al. 1987], and arsenic is</p>

	<p>considered a cause of lung as well as skin cancer.</p> <ul style="list-style-type: none"> • In arsenic-exposed workers, there is a systematic gradient in lung cancer mortality rates, depending upon duration and intensity of exposure [ATSDR 2007]. • A higher risk of lung cancer was found among workers exposed predominantly to arsenic trioxide in smelters and to pentavalent arsenical pesticides in other settings. • Neither concomitant exposure to sulfur dioxide nor to cigarette smoke was determined to be an essential co-factor in these studies.
<p>Other Health Effects</p>	<p>There is suggestive [NRC 2000] or reasonably strong [IARC 2004] strength of association between chronic arsenic exposure and diabetes mellitus [NRC 2000; IARC 2004].</p> <p>There is limited evidence of a diabetogenic effect from long-term arsenic exposure [Tseng et al. 2002].</p>
<p>Susceptibility to Arsenic Toxicity</p>	<p>Several studies have supported the notion of susceptibility to arsenic toxicity.</p> <ul style="list-style-type: none"> • Primary human hepatocytes have exhibited interindividual variations in the rate of arsenic methylation [Drobna et al. 2004]. • Arsenite uptake into the liver (and possibly other cells) may be increased in persons with poor nutritional status, which could overtax intrinsic detoxification mechanisms such as methylation [Rossman 2007]. • Increased uptake of arsenite into the liver of malnourished animals has been shown [Carbrey et al. 2003]. • Using urinary metabolites, differences in arsenic methylation capacity between population groups and individuals have been observed in several epidemiological studies [Hopenhayn-Rich et al. 1998; Chiou et al. 1995; Concha et al. 2002; Loffredo et al. 2003]. A low rate of arsenic methylation is related to a low rate of excretion. • There is conflicting literature supporting the role of methylation in arsenic detoxification. Some literature

	<p>suggests that methylation of inorganic arsenic may be a toxification rather than detoxification pathway [Kitchin 2001]. Other studies have suggested that other detoxifying mechanisms such as transport, antioxidant defenses, or resistance to apoptosis may be more important in protecting cells than methylation [Yoshida et al. 2004].</p> <ul style="list-style-type: none">• Several studies have shown that arsenic-induced disease is increased in individuals who are undernourished or malnourished, possibly due to the decrease in arsenic methylation in such conditions [Hsueh et al. 1995; Mitra et al. 2004; Steinmaus et al. 2005].• Animal studies have shown that arsenic methylation is affected by nutritional status. A diet low in protein, choline, or methionine showed reduced rates of arsenic excretion implying reduced rates of methylation [Rossman 2007].• Methyl group donors such as folate might be important in arsenic detoxification in humans. A deficiency of folic acid promotes and supplementation of folate decreases the risk of cancers in rodents and humans [Rossman 2007]. Therefore, in cells that do not methylate arsenic, folate may be important for other reasons. Folate deficiency impairs DNA repair and alters the pattern of DNA methylation [Rossman 2007].• Arsenic and selenium might be mutually antagonistic [Zeng et al. 2005].• It has been hypothesized that low selenium levels in the soil may exacerbate arsenic toxicity and carcinogenicity in areas where there is high arsenic in the drinking water [Spallholz et al. 2004].• In Taiwan, arsenic over exposed individuals had a reduction in the percentage of inorganic arsenic in urine while the percentage of DMA was increased with the concentration of urinary selenium and serum alpha tocopherol (vitamin E) [Rossman 2007].• Since higher selenium levels in the body may promote the methylation of arsenic, it may be reasonable to suggest that a combination of selenium and Vitamin E or other antioxidants may be a safe (if taken as recommended) and possibly useful way to prevent adverse health effects in individuals with arsenic
--	---

	overexposure [Rossman 2007].
Key Points	<ul style="list-style-type: none"> • Arsenic can cause serious effects of the neurologic, respiratory, hematologic, cardiovascular, gastrointestinal, and other systems. • Arsenic is a carcinogen in multiple organ systems. • Interindividual and population differences in arsenic methylation and nutritional status may be factors in susceptibility to arsenic toxicity.
Progress Check Select the one best choice	<p>12. A patient with chronic arsenic ingestion from well water is likely to present with which of the following neurologic effects?</p> <p>A. Embolic stroke. B. Peripheral neuropathy. C. Acoustic neuroma. D. Lumbar radiculopathy.</p> <p>13. The complete blood count of a patient with chronic arsenic ingestion would show which one of the following</p> <p>A. Thrombocytosis. B. Eosinophilia C. Pancytopenia. D. Basophilia.</p>

Progress Check Answers	<p>12. The correct answer is B. A patient with chronic arsenic ingestion from well water is likely to present with peripheral neuropathy. Peripheral neuropathy is the most common neurologic effect of chronic arsenic ingestion.</p> <p><i>To review relevant content, see "Neurologic Effects" in this section.</i></p> <p>13. The correct answer is C. The complete blood count of a patient with chronic arsenic ingestion would show pancytopenia.</p> <p><i>To review relevant content, see "Hematopoietic and Hematologic Effects" in this section.</i></p>
---------------------------------------	---

Clinical Assessment

Learning Objectives	<p>Upon completion of this section, you will be able to</p> <ul style="list-style-type: none">• identify the primary focuses of the patient history (including the exposure history),• describe the most typical physical findings on patient examination, and• describe the tests you would order for patients exposed to arsenic.
Introduction	<p>Patients who have been exposed to arsenic in whom toxicity is suspected should undergo a thorough medical evaluation. Early and accurate diagnosis is important in deciding appropriate care strategies, even if the patient is not exhibiting symptoms. In cases of significant arsenic exposure, medical evaluation should include</p> <ul style="list-style-type: none">• an exposure history,• a medical history,• a physical examination, and• additional laboratory testing as indicated. <p>This section focuses on activities, which are typically conducted during the patient's visit to clinical office. Recommended tests are discussed in the next section.</p>
Clinical Presentation	<p>Arsenic-associated diseases typically have a long latency period, so that many patients exposed to arsenic are asymptomatic for years. Clinical manifestation of target organ toxicity is based on</p> <ul style="list-style-type: none">• route of exposure,• dose,• chemical form,• frequency, duration, and intensity of exposure, and• time elapsed since exposure. <p>A single patient can develop any combination of arsenic-associated diseases.</p>

Clinical Evaluation	<p>The source of arsenic exposure cannot be identified in many cases. Therefore, a careful exposure history, physical exam, lab work, and environmental testing, where appropriate, may lead to identification of the source.</p>
Exposure History and Physical Examination	<p>In chronic exposures, particular clues to arsenic poisoning may be provided by dermatologic and neurologic findings. The exposure history should include</p> <ul style="list-style-type: none"> • condition of household pets, • diet (emphasis on frequency, amount, and type of seafood ingestion), • hobbies (including use of old supplies of pesticides or herbicides in farming or gardening), • home heating methods (wood-burning stoves and fireplaces and source of fuel), • medications (including folk, imported, homeopathic or naturopathic medications), • occupational history, • residential history (proximity to former smelters, other industry, former orchards and farms, and hazardous waste sites), and • source of drinking water. <p>A sample exposure history form can be found in the ATSDR Case Study in Environmental Medicine: Taking an Exposure History http://www.atsdr.cdc.gov/csem/exphistory/ehexposure_form.html</p>
Signs and Symptoms Acute Exposure	<p>In acute arsenic poisoning, death is usually due to cardiovascular collapse and hypovolemic shock. The fatal human dose for ingested arsenic trioxide is 70 to 180 milligrams (mg) or about 600 micrograms per kilograms (kg)/day [ATSDR 2007].</p> <ul style="list-style-type: none"> • Onset of peripheral neuropathy may be delayed several weeks after the initial toxic insult. • Mee's lines may be visible in the fingernails several weeks to months after acute arsenic poisoning. Mee's lines are transverse white lines across the nails

[Rossman 2007].

Acute arsenic poisoning occurs infrequently in the workplace today; recognized poisoning more commonly results from unintentional ingestion, suicide, or homicide.

The fatal dose of ingested arsenic in humans is difficult to determine from case reports, and it depends upon many factors (e.g., solubility, valence state, etc.).

The minimal lethal dose is in the range of 1 to 3 mg/kg [ATSDR 2007].

The National Health and Nutrition Examination Survey (2003-2004) measured levels of total arsenic and speciated arsenic in urine of a representative sample of the U.S. population. The data reflect relative background contributions of inorganic and seafood-related arsenic exposures in the U.S. population [Caldwell et al. 2008]. See "*Laboratory Tests*" in this section for more details.

As a result of inorganic arsenic's direct toxicity to the epithelial cells of the gastrointestinal tract and its systemic enzyme inhibition, profound gastroenteritis, sometimes with hemorrhage, can occur within minutes to hours after ingestion.

The signs and symptoms of acute and subacute arsenic poisoning include

- Gastrointestinal
 - garlic odor on the breath,
 - severe abdominal pain,
 - nausea and vomiting,
 - thirst,
 - dehydration,
 - anorexia,
 - heartburn,
 - bloody or rice water diarrhea, and
 - dysphagia.

- Dermal

	<ul style="list-style-type: none">○ delayed appearance of Mee's lines in nail beds,○ dermatitis,○ melanosis, and○ vesiculation. ● Cardiovascular<ul style="list-style-type: none">○ hypotension,○ shock,○ ventricular arrhythmia,○ congestive heart failure,○ irregular pulse, and○ T-wave inversion and persistent prolongation of the QT interval. ● Respiratory<ul style="list-style-type: none">○ irritation of nasal mucosa, pharynx, larynx, and bronchi,○ pulmonary edema,○ tracheobronchitis,○ bronchial pneumonia, and○ nasal septum perforation. ● Neurologic<ul style="list-style-type: none">○ sensorimotor peripheral axonal neuropathy (paresthesia, hyperesthesia, neuralgia),○ neuritis○ autonomic neuropathy with unstable blood pressure, anhidrosis, sweating and flushing,○ leg/muscular cramps,○ light headedness,○ headache,○ weakness,○ lethargy,○ delirium,○ encephalopathy,○ hyperpyrexia,○ tremor,○ disorientation,○ seizure,○ stupor,○ paralysis, and
--	--

	<ul style="list-style-type: none"> ○ coma. • Hepatic <ul style="list-style-type: none"> ○ elevated liver enzymes, ○ fatty infiltration, ○ congestion, ○ central necrosis, ○ cholangitis, and ○ cholecystitis. • Renal <ul style="list-style-type: none"> ○ hematuria, ○ oliguria, ○ proteinuria, ○ leukocyturia, ○ glycosuria, ○ uremia, ○ acute tubular necrosis, and ○ renal cortical necrosis. • Hematologic <ul style="list-style-type: none"> ○ anemia, ○ leukopenia, ○ thrombocytopenia, ○ bone marrow suppression, and ○ disseminated intravascular coagulation. • Other <ul style="list-style-type: none"> ○ rhabdomyolysis and ○ conjunctivitis.
<p>Signs and Symptoms</p> <p>Hours to Days after Acute Exposure</p>	<p>Descriptions of potential signs and symptoms of subacute or delayed arsenic poisoning by time lapsed since acute exposure include</p> <ul style="list-style-type: none"> • Gastrointestinal <ul style="list-style-type: none"> ○ Symptoms may last for several days. ○ Difficulty in swallowing, abdominal pain, vomiting,

diarrhea, and dehydration may result.

- However, in subacute poisoning the onset of milder GI symptoms may be so insidious that the possibility of arsenic intoxication is overlooked.

- Cardiac and Vascular System

- As previously mentioned, arsenic has deleterious effects on the heart and peripheral vascular system.
- Capillary dilation with fluid leakage and third spacing may cause severe hypovolemia and hypotension.
- Cardiac manifestations have included
 - cardiomyopathy,
 - ventricular dysrhythmias (atypical ventricular tachycardia and ventricular fibrillation), and
 - congestive heart failure.

- Neurologic

- A delayed sensorimotor peripheral neuropathy may occur after acute arsenic poisoning.
- Symptoms are initially sensory and may begin 2 to 4 weeks after resolution of the first signs of intoxication resulting from ingestion (shock or gastroenteritis).
- Commonly reported initial symptoms include numbness, tingling, and "pins and needles" sensations in the hands and feet in a symmetrical "stocking glove" distribution, and muscular tenderness in the extremities.
- Clinical involvement spans the spectrum from mild paresthesia with preserved ambulation to
 - distal weakness,
 - quadriplegia, and,
 - in rare instances, respiratory muscle insufficiency.

- Other findings of subacute arsenic poisoning may include

- fever and
- facial edema.

<p>Signs and Symptoms</p> <p>Several Months after Acute Arsenic Exposure</p>	<p>Signs and symptoms several months after acute arsenic poisoning include.</p> <ul style="list-style-type: none"> • Transverse white striae (pale bands) in the nails called Mee’s lines (or Aldrich–Mee’s lines) may be seen, reflecting transient disruption of nail plate growth during acute poisoning. <ul style="list-style-type: none"> ○ In episodes of multiple acute exposures, several Mee’s lines may occur within a single nail. ○ In some cases, the distance of the lines from the nail bed may be used to roughly gauge the date of the poisoning episode. ○ However, Mee’s lines are not commonly seen. • Respiratory tract irritation. <ul style="list-style-type: none"> ○ Cough, laryngitis, mild bronchitis, and dyspnea may result from acute exposure to airborne arsenic dust. ○ Nasal septum perforation, as well as conjunctivitis and exfoliative dermatitis, has also been reported. • Other. <ul style="list-style-type: none"> ○ Reversible anemia and leukopenia may develop [Rosenman 2007].
<p>Signs and Symptoms</p> <p>Chronic Exposure</p>	<p>Skin lesions and peripheral neuropathy are the most suggestive effects of chronic arsenic exposure (via inhalation or ingestion). Their presence should result in an aggressive search for this etiology. In addition, neuropathy can occur insidiously in chronic toxicity without other apparent symptoms. However, careful evaluation usually reveals signs of multi organ and multi system involvement such as</p> <ul style="list-style-type: none"> • anemia, • leukopenia, and/or • elevated liver function tests. <p>Dermal</p> <ul style="list-style-type: none"> • Hyperpigmentation is the most sensitive endpoint for

arsenic exposure, but does not occur in every individual. This may suggest genetic susceptibility [Yoshida et al. 2004; Guha 2003].

- Pigment changes occur most often on the face, neck, and back [Yoshida et al. 2004; Guha 2003].
- Skin lesions are the earliest nonmalignant effect of chronic exposure [Yoshida et al. 2004; Guha 2003].
- Skin hyperpigmentation and hyperkeratosis are delayed hallmarks of chronic arsenic exposure.
- Pigment changes include areas of hyperpigmentation interspersed with smaller areas of hypopigmentation that give a "raindrop" appearance on the trunk and neck [Tseng et al. 1968; Centeno et al. 2002].
- Hyperkeratosis of the palms of the hands and soles of the feet (palmoplantar hyperkeratosis) look like small corn-like elevations and diffuse keratosis [Tseng et al. 1968; Centeno et al. 2002].
- Desquamation can also be seen.
- Skin lesions may take a long time to manifest (3 to 7 years for pigmentation changes and keratoses; up to 40 years for skin cancer) and may occur after lower doses than those causing neuropathy or anemia [ATSDR 2007].
- Hyperkeratosis and hyperpigmentation are not commonly seen in arsenic inhalation exposures [Rossman 2007].

Neural

- Neuropathy may be the first sign of chronic arsenic toxicity.
- Polyneuritis and motor paralysis, specifically of the distal extremities, may be the only symptoms of chronic arsenic poisoning [Guha 2003].
- Hearing loss, mental retardation, encephalopathy, symmetrical peripheral polyneuropathy (sensorimotor resembling Landry-Guillain-Barre syndrome), and electromyographic abnormalities.
- Both sensory and motor neuron peripheral neuropathy can be seen after chronic inhalation of arsenic and more sporadically with chronic ingestion of arsenic [Rossman 2007].

Gastrointestinal (GI)

- In chronic poisoning, GI effects are generally less severe and may include
 - esophagitis,
 - gastritis,
 - colitis,
 - abdominal discomfort,
 - anorexia,
 - malabsorption, and/or
 - weight loss.

Hepatic

- Enlarged and tender liver along with increased hepatic enzymes were found in several studies of chronically exposed individuals [Guha 2003].
- Cirrhosis
- Portal hypertension without cirrhosis.
- Fatty degeneration.

Hematological:

- Bone marrow hypoplasia.
- Aplastic anemia.
- Anemia.
- Leukopenia.
- Thrombocytopenia.
- Impaired folate metabolism.
- Karyorrhexis.
- Anemia often accompanies skin lesions in patients chronically poisoned by arsenic.

Cardiovascular

- Arrhythmias.
- Pericarditis.
- Blackfoot disease (gangrene with spontaneous amputation).
- Raynauds syndrome.
- Acrocyanosis (intermittent).
- Ischemic heart disease.
- Cerebral infarction.

	<ul style="list-style-type: none"> • Carotid atherosclerosis. • Hypertension. • Microcirculation abnormalities. <p>Respiratory</p> <ul style="list-style-type: none"> • Rhino-pharyngo-laryngitis. • Tracheobronchitis. • Pulmonary insufficiency (emphysematous lesions). • Chronic restrictive/obstructive diseases. <p>Endocrine</p> <ul style="list-style-type: none"> • Diabetes mellitus. <p>Other</p> <ul style="list-style-type: none"> • Lens opacity. • Cancer. <p>Lung cancer and skin cancer are serious long-term concerns in cases of chronic arsenic exposure.</p>
<p>The Toxicity of Arsine Gas</p>	<p>The toxicity of arsine gas is quite different from toxicity of other arsenicals, requiring different emphases in</p> <ul style="list-style-type: none"> • the medical history, • physical examination, and • patient management. <p>It is important to recognize that although arsine is an arsenical, it has distinct differences from other arsenicals.</p> <p>Arsine is a powerful hemolytic poison in both acute and chronic exposures. Massive hemolysis with hematuria and jaundice may persist for several days [Rossman 2007].</p> <p>The clinical signs of hemolysis may not appear for up to 24 hours after acute exposure, thereby obscuring the relationship between exposure and effect.</p> <p>Initial symptoms of arsine poisoning may include</p>

	<ul style="list-style-type: none"> • headache, • nausea, • abdominal pain, and • hematuria. <p>Direct effects on the myocardium may occur, resulting in</p> <ul style="list-style-type: none"> • high peaked t-waves, • conduction disorders, • various degrees of heart block, and • asystole [Rossman 2007]. <p>Death is most often due to renal failure from arsenic acid damage, but can also result from cardiac failure [Rossman 2007].</p>
<p>Laboratory Tests</p>	<p>Early clinical diagnosis of arsenic toxicity is often difficult; a key laboratory test in recent exposures is urinary arsenic excretion.</p> <p>Clinical diagnosis of arsenic intoxication is often difficult because both acute and chronic poisoning present a wide spectrum of signs and symptoms, which are largely dependent upon</p> <ul style="list-style-type: none"> • route of exposure, • chemical form, • dose, and • time elapsed since exposure. <p>In many cases, the patient or person providing the history may suppress information, or the source of exposure may not be apparent. By integrating laboratory results with history and clinical findings, it is often possible to confirm a diagnosis.</p> <p>Immediately after patient stabilization, laboratory tests should be performed to obtain baseline values, with periodic monitoring as indicated.</p> <p>Because urinary levels of arsenic may drop rapidly in the first 24–48 hours after acute exposure, a urine specimen for</p>

arsenic analysis should be obtained promptly.

Depending on the patient's clinical state, general tests for biomarkers of effect, specific tests for biomarkers of exposure, and specific biomarkers of effect may be warranted.

- General Tests for Biomarkers of Effect.
 - Complete Blood Count (CBC) with peripheral smear.
 - BUN and creatinine.
 - Liver enzymes.
 - Nerve conduction studies (if peripheral neurologic symptoms are present).
 - Electrocardiogram.
 - Abdominal x-ray.
 - Chest X-ray.

- Specific Tests for Biomarkers of Exposure.
 - The key diagnostic laboratory test for recent exposure is urinary arsenic measurement.
 - The best specimen is a 24-hour urine collection for arsenic and creatinine as it more accurately reflects the true amount of arsenic excretion. (Not all labs adjust the arsenic value per gram of creatinine which accounts for the dilution and concentration of the sample).
 - Spot urine specimens (also for arsenic and creatinine) can be helpful in an emergency. A spot urine should be sent for arsenic and creatinine. Dividing the arsenic concentration by grams creatinine adjusts for urine dilution or concentration.
 - Total arsenic values in excess of 100 micrograms (μg) per liter (L) ($\mu\text{g}/\text{L}$) are considered abnormal [ATSDR 2007].
 - However, total arsenic measurement in human urine assesses the combined exposure from all routes of exposure and all species of arsenic.
 - Therefore, when total urinary arsenic is measured, it is important to inquire about recent seafood (bivalve mollusks, crustaceans) and seaweed in the diet in the last 48 hours as seafood or seaweed arsenic can significantly increase total urinary arsenic levels

	<p>(sometimes by several thousands of ug/L after seafood ingestion.) [Kales et al. 2006]</p> <ul style="list-style-type: none">○ Where total urinary arsenic level is high and seafood is considered a possible contributor, a request for speciation of arsenic (i.e., analysis of organo-arsenicals or different inorganic species, rather than total) may be a consideration.○ Not all labs that perform arsenic level measurement also perform speciation. If your laboratory does not perform this test, you may wish to consult your local Poison Control Center for this information.○ If speciation is not available, cessation of seafood ingestion with a repeat of the total urinary arsenic test in 2 or 3 days can be done.○ The National Health and Nutrition Examination Survey (NHANES) (2003-2004) measured levels of total arsenic and speciated arsenic in urine of a representative sample of the U.S. population. The data reflect relative background contributions of inorganic and seafood-related arsenic exposures in the U.S. population. Biomonitoring results since the 2005 publication of the Third National Report on Human Exposure to Environmental Chemicals can be found at: http://www.cdc.gov/exposurereport/ [CDC 2009, Caldwell et al. 2008].○ NHANES 2003-2004 data show that as total urinary arsenic levels increase from <20 to 20-50 micrograms per liter and to >50 µg/L, the percentage of the total urinary arsenic is increasingly due to arsenobetaine (fish arsenic), with median percentages being 62.7% for total urinary arsenic levels >50 µg/L [CDC 2009].○ Some studies suggest that slight health risks may be associated with total urinary levels > 50 µg/L [ACGIH 2001; WHO 2001; Tseng et al. 2005, Valenzuela et al. 2005].○ Conclusions from the NHANES 2003-2004 data indicate that a urine sample of < 20 µg/L is likely to have little contribution from organic arsenic species [CDC 2009].○ For all participants aged > or equal to 6 years, the 95th percentile for total urinary arsenic and the sum of inorganic-related arsenic were 65.4 and 18.9 µg/L respectively [CDC 2009].
--	--

	<ul style="list-style-type: none">○ The 95th percentile of the NHANES 2003-2004 subsample for the sum of inorganic arsenic species (18.9 µg/L) is below the ACGIH Biologic Exposure Index (BEI) for workers of 35 µg arsenic per liter (inorganic plus methylated metabolites in urine) measured at end of a work week. (Note that the BEI is not a value for the onset of toxicity, but a screening value based on non-cancer health effects. They were developed for individuals trained in industrial hygiene to use, interpret and apply as applicable.) [ACGIH 2005]○ The sum of the inorganic-related species is an important upper benchmark for the U.S. population as it represents a dose of the more toxic inorganic arsenic most likely incurred from drinking water [Caldwell et al. 2008].○ If 18.9 micrograms is considered an approximate daily exposure, (0.27 µg/kg/per day) then about 95% of the adult US population is likely to be below the U.S. Environmental Protection Agency reference dose [EPA 2001] for inorganic arsenic intake (0.3 µg/kg/per day) [Caldwell et al. 2008].○ Long after urine levels have returned to baseline, the arsenic content of hair and nails may be the only clue of arsenic exposure.○ However, because the arsenic content of hair and nails may be increased by external contamination, caution must be exercised in using the arsenic content of these specimens to diagnose arsenic intoxication.○ Arsenic blood levels, normally less than 1 µg per deciliter (µg/dL) in nonexposed individuals, are less useful than urinary arsenic measurements in following the clinical course of an acute poisoning case because of the rapid clearance of arsenic from the blood [ATSDR 2007]. <ul style="list-style-type: none">● Biomarkers of Effect<ul style="list-style-type: none">○ If arsenic toxicity is suspected, several tests can be performed to assess clinical status. If abnormal, these may help to confirm clinical suspicion.○ The CBC can provide evidence of
--	---

- arsenic induced anemia,
- leukopenia,
- thrombocytopenia, or
- eosinophilia.

Although basophilic stippling on the peripheral smear is not specific for arsenic poisoning, it is consistent with the diagnosis.

Laboratory Findings

CBC: pancytopenia; basophilic stippling* may be seen on peripheral smear



arsenic poisoning



normal red blood cells

*** Also seen in lead poisoning**



Liver transaminases are frequently elevated in acute and chronic arsenic exposure and can help confirm clinical suspicion.

If arsenic neuropathy is suspected, nerve conduction velocity tests should be performed. Such tests may show a decrease in amplitude initially, as well as slowed conduction.

Skin lesions in patients with chronic arsenic exposure may require biopsy to evaluate for skin cancer.

Some arsenic compounds, particularly those of low solubility, are radio opaque, and if ingested may be visible on an abdominal radiograph.

<p>Key Points</p>	<ul style="list-style-type: none"> • Evaluation for arsenic toxicity requires a detailed history, including environmental and occupational exposure history, physical examination, and laboratory testing. • For recent and chronic exposure, the 24-hour urine collection for arsenic is the most useful laboratory test. • Organic arsenic from recent seafood ingestion (last 48 hours) may produce a positive urine test for total arsenic. • Arsenic Speciation testing can be requested, but may not be readily available. • A repeat 24 hour total urinary arsenic test can be done 48 hours after cessation of seafood consumption.
<p>Progress Check</p> <p>Select the one best choice</p>	<p>14. What is the significance of reporting urinary arsenic levels as micrograms arsenic per gram creatinine?</p> <ul style="list-style-type: none"> A. To adjust for concentration or dilution of urine by variation in fluid intake. B. To adjust for adverse effects of arsenic on kidney function. C. Because of the chronic muscle-wasting effect of arsenic. D. To adjust for the creatinine content in seafood. <p>15. Abnormal laboratory tests in arsenic toxicity include</p> <ul style="list-style-type: none"> A. Elevated amylase. B. Reduced serum B12. C. Elevated liver enzymes. D. White blood cell casts on urinalysis.

Progress Check Answers	<p>14. The correct answer is A. Urinary arsenic levels are often reported in micrograms arsenic per gram creatinine to adjust for concentration or dilution of urine by variation in fluid intake.</p> <p><i>To review relevant content, see "Laboratory Tests" in this section.</i></p> <p>15. The correct answer is C. Abnormal laboratory tests in arsenic toxicity include elevated liver enzymes.</p> <p><i>To review relevant content, see "Laboratory Tests" in this section.</i></p>
---------------------------------------	--

How Should Patients Overexposed to Arsenic Be Treated and Managed?

Learning Objectives	<p>Upon completion of this section, you will be able to</p> <ul style="list-style-type: none"> • identify primary strategies for treating arsenic-associated diseases.
Introduction	<p>Patients presenting to their primary care providers with a history of arsenic exposure will vary widely in their clinical condition.</p> <ul style="list-style-type: none"> • Some will be asymptomatic. • Some will just be beginning to show signs of arsenic-associated disease, and others will have more established disease. • The care provided, including any referrals made, will depend on the clinical status of the patient. • Patients who demonstrate excessive occupational exposure (urinary arsenic greater than 35 microgram per liter) may benefit from early workplace intervention to prevent future hazardous exposure.
Treatment and Management –Acute Over Exposure	<p>Gut decontamination and hemodynamic stabilization are key factors in the initial management of acute arsenic intoxication.</p> <p>Patients with suspected acute arsenic poisoning generally require rapid stabilization with fluid and electrolyte replacement in an intensive care setting.</p> <ul style="list-style-type: none"> • Aggressive intravenous fluid replacement therapy may be life-saving in severe poisoning. • Gastric lavage may be useful soon after an acute ingestion to prevent further absorption. • The efficacy of activated charcoal is controversial, but its administration together with a cathartic (such as sorbitol) is frequently recommended. • If profuse diarrhea is present, cathartics should be withheld.

	<ul style="list-style-type: none"> • Hemodialysis may be beneficial in a patient with concomitant renal failure. <p>Chelating agents administered within hours of arsenic absorption may successfully prevent the full effects of arsenic toxicity.</p> <p>Dimercaprol (2, 3 dimercaptopropanol, also known as British anti Lewisite or BAL), was previously the most frequently recommended chelating agent for arsenic. The currently recommended treatment is 2-3-dimercapto-1-propanesulfonate (DMPS) or meso 2, 3-dimer-captosuccinic acid (DMSA). These are more water soluble than BAL, and can be administered orally with lower toxicity [Mazumder et al. 2001].</p> <p>All known chelating agents have adverse side effects and should be used with caution.</p> <ul style="list-style-type: none"> • In animal models, the efficacy of chelation therapy generally declines as the time elapsed since exposure increases. • If patients are treated within several hours after arsenic ingestion, chelation is <i>likely to be beneficial</i>. Therefore, even if arsenic ingestion is only suspected, but not confirmed, consultation with a clinical specialist with expertise in the treatment and management of arsenic poisoning is key. <p>Data supporting duration of treatment are limited, and regimens may warrant adjustment. If acute renal insufficiency develops, hemodialysis may be of value.</p> <p>If the source of arsenic exposure has not been determined, the patient may be at risk for further arsenic intoxication.</p>
<p>Treatment and Management –Chronic Over Exposure</p>	<p>Identification and removal of the toxic source and supportive measures are primary concerns for the treatment of chronically exposed patients.</p> <ul style="list-style-type: none"> • Studies suggest that the use of vitamin A analogs (retinoids) may be useful in treating pre-cancerous arsenical keratoses [Elmariah et al. 2008]

	<ul style="list-style-type: none"> • Recovery from chronic arsenic toxicity, particularly from the resulting peripheral neuropathy, may take months and may not be complete. • An established arsenical neuropathy is not improved by chelation therapy. • Significant improvement of symptoms and signs of chronic arsenic poisoning has been demonstrated in a prospective single blind, placebo-controlled trial with DMPS [Mazumder et al. 2001]. <p>Patients demonstrating excessive exposure on urine testing or clinical effects of arsenic exposure, and whose source of exposure is unclear, may require environmental testing (such as of drinking water), attention to exposure from malicious intent, or workplace investigation.</p>
Clinical Follow-up	<p>After an intervention has been made, follow-up urine testing may be necessary to confirm a reduction in exposure, and follow-up clinical testing may be necessary to verify a resolution of clinical and lab test abnormalities.</p>
Occupational Over Exposure—Ensuring a Healthy Workplace	<p>Patients whose excessive arsenic exposure occurred in the workplace can be medically removed from exposure while remediation of the workplace is undertaken.</p> <ul style="list-style-type: none"> • This requires prompt notification of the employer of a hazard that requires corrective action. • Often an industrial hygienist familiar with the industrial processes can be consulted by the employer. • If an imminent hazard exists that the employer has not addressed, the Occupational Safety and Health Administration (OSHA) can require the employer to take appropriate corrective action. OSHA is the federal regulatory agency responsible for enforcing federal workplace health standards. <p>OSHA's standard for arsenic also requires that medical examinations be provided for all employees exposed to levels of inorganic arsenic above the action level of 5 micrograms per meter cubed for at least 30 days per year. For more information on the OSHA standard for arsenic, see</p>

	http://www.osha.gov/SLTC/arsenic/index.html
Nutrition in Prevention	Nutritional status may play a role in preventing arsenic health effects. For example, arsenic and selenium may be mutually antagonistic [Zeng et al. 2005]. There have been recent reports that a diet rich in selenium and other antioxidants (such as vitamin E) helps promote methylation of arsenic which leads to increased excretion [Verret et al. 2005; Rossman 2007; Son et al. 2008]. Methyl donors such as folate may also be of help in arsenic metabolism and excretion in humans [Rossman 2007]. Arsenic-induced disease has been shown to increase in individuals who are mal- or under-nourished, possibly due to the decrease in arsenic methylation [Hsueh et al. 1995; Mitra et al. 2004; Steinmaus et al. 2005].
Arsine Gas Poisoning	<p>Arsine gas poisoning requires careful monitoring of hematocrit/hemoglobin and renal function.</p> <ul style="list-style-type: none"> • Therapy is supportive and is primarily aimed at maintaining renal function. Red cell transfusion may be necessary to replace the patient's hemolyzed red cells. • Patients with significant hemolysis may require folate or iron supplementation.
Key Points	<ul style="list-style-type: none"> • Most frequently, removal from exposure is the key management intervention for arsenic effects due to overexposure. • Gut decontamination and hemodynamic stabilization are key factors in the initial management of acute arsenic intoxication. • In severe acute arsenic over exposure such as heavy ingestion, chelation with DMSA or DMPS may reduce morbidity. This should be done in consultation with a clinical expert in arsenic poisoning treatment. • Patients occupationally over exposed to arsenic may want to discuss with employers their concerns regarding ways to prevent this hazardous exposure. • Arsine gas poisoning requires careful monitoring of hematocrit/hemoglobin and renal function.

Progress Check Select the one best choice	<p>16. Use of the chelating agents DMSA or DMPS should be considered when</p> <ul style="list-style-type: none">A. The patient has had a remote exposure to fish arsenic.B. The patient has had a recent exposure to fish arsenic.C. The patient has an established arsenical neuropathy.D. The patient has had a very recent and very high dose exposure. <p>17. The role of OSHA for a patient with a toxic, occupational arsenic exposure is to</p> <ul style="list-style-type: none">A. Investigate the workplace to remediate an imminent health hazard for the patient and other workers.B. Perform routine urine testing in all exposed workers.C. Perform routine, weekly air monitoring of arsenic in the workplace.D. Evaluate the role of arsenic in the patient's diet.

Progress Check Answers	<p>16. The correct answer is D. Use of the chelating agents DMSA or DMPS should be considered when the patient has had a very recent and very high dose exposure. This should be done in consultation with a clinical expert with experience in treating arsenic toxicity. Chelation treatment is not needed for exposure to fish arsenic, recent or remote. Chelation treatment has not been shown to be effective for patients with an established arsenical neuropathy.</p> <p><i>To review relevant content, see "Treatment and Management of Acute Overexposure" in this section.</i></p> <p>17. The correct answer is A. The role of OSHA for a patient with a toxic, occupational arsenic exposure is to investigate the workplace to remediate an imminent health hazard for the patient and other workers. OSHA evaluates workplaces to enforce existing federal exposure standard (Permissible Exposure Limits and other standards) for workplace health and safety.</p> <p><i>To review relevant content, see "Occupational Overexposure - Ensuring a Healthy Workplace" in this section.</i></p>
---------------------------------------	--

What Instructions Should Be Given to Patients Potentially Overexposed to Arsenic?

Learning Objective	Upon completion of this section, you will be able to <ul style="list-style-type: none"> describe instructions for patient self care. 	
Introduction	Primary health care providers should insure that their patients understand applicable clinical follow-up instructions as well as preventive strategies to stop over exposure to harmful substances (self care).	
Self Care	Preventive messages that allow patients to take action to avoid over exposure to arsenic are essential to preventing or decreasing the progression of arsenic-related illness.	
Preventive Messages to Avoid or Reduce the Risk of Over Exposure to Arsenic	Message: <ul style="list-style-type: none"> Patients who may have been over exposed to arsenic through drinking water should be advised to have their well tested. They should use bottled water for drinking until their well is shown not to be a source of arsenic exposure or until appropriate water filtration systems are put in place to remove the arsenic. 	Rationale: <ul style="list-style-type: none"> By law, water from public supplies must be tested for arsenic. Please see drinking water standards. In areas with known high arsenic in ground or well water, private wells should be checked to determine if they are a source of arsenic exposure. Information on how to obtain testing for arsenic in well water is often available from the local health department.
	Message: <ul style="list-style-type: none"> Patients should be advised when using Chromated Copper Arsenate (CCA)-treated lumber in nonresidential 	Rationale: <ul style="list-style-type: none"> Avoiding over exposure to known sources of arsenic in the environment is prudent. There should be a warning label with the

	<p>applications to follow the warnings regarding the wearing of personal protective equipment such as gloves, eye, and respiratory protection.</p>	<p>CCA-treated lumber (if at a store or lumber yard for consumers) or at a designated place at the worksite (for employees).</p>
	<p>Message:</p> <ul style="list-style-type: none"> • Parents should be advised to have children wash their hands after playing on playground equipment made with CCA-treated lumber. 	<p>Rationale:</p> <ul style="list-style-type: none"> • Avoiding over exposure to known sources of arsenic in the environment is prudent. Research is ongoing as to whether there are health risks from contact with CCA-treated lumber now in use. Children who play on playground equipment made of CCA-treated lumber may have higher than normal background levels of arsenic on their hands. Hand washing after playground visits is recommended.
	<p>Message:</p> <ul style="list-style-type: none"> • Patients should be advised to consider applying a sealant on existing exposed CCA-treated lumber surfaces annually. 	<p>Rationale:</p> <ul style="list-style-type: none"> • Prevention of the release of arsenic from CCA-treated lumber already in place may be accomplished by annual application of a sealant. The U.S. Environmental Protection Agency (EPA does not currently recommend the removal of CCA-treated lumber. EPA has more information on this on its Website,

		provided in the next section.
	<p>Message:</p> <ul style="list-style-type: none"> • The patient should contact the health department for assistance if a source of arsenic over exposure is not identified. 	<p>Rationale:</p> <ul style="list-style-type: none"> • Where the source of arsenic over exposure is not identified, a concerted effort must be made to identify it. Assistance may be obtained from the local health department.
<p>Preventive Messages to Help Avoid or Minimize Potential Health Effects from Over Exposure to Arsenic.</p>	<p>Message:</p> <ul style="list-style-type: none"> • Patients should be advised to maintain a well-balanced diet rich in selenium, other antioxidants, and folate. 	<p>Rationale:</p> <ul style="list-style-type: none"> • There is evidence that mal- or undernourishment affects arsenic metabolism. There is also evidence that selenium is antagonistic to arsenic. Methyl donors such as folate may help in arsenic metabolism and excretion. Therefore, a diet rich in selenium and other antioxidants may prevent arsenic toxicity.
	<p>Message:</p> <ul style="list-style-type: none"> • Avoid ingestion of Hijiki seaweed as it has been found to have high levels of inorganic arsenic. 	<p>Rationale:</p> <ul style="list-style-type: none"> • Avoiding dietary sources of inorganic arsenic is prudent toward avoiding arsenic toxicity.
	<p>Message:</p> <ul style="list-style-type: none"> • Patients should contact their doctor if they 	<p>Rationale:</p> <ul style="list-style-type: none"> • Early detection and treatment may improve

	develop signs of health changes	prognosis.
General preventive messages to reduce the risk of cancer	<p>Message:</p> <ul style="list-style-type: none"> • Patients should be advised to stop smoking. They should also be informed that smoking along with arsenic over exposure increases the risk for developing lung cancer. 	<p>Rationale:</p> <ul style="list-style-type: none"> • Smoking causes lung cancer. Studies have shown that smoking coupled with arsenic inhalation or ingestion can increase the risk of developing lung cancer. Smoking cessation may help reduce lung cancer risk.
	<p>Message:</p> <ul style="list-style-type: none"> • Limit sun exposure. • Use sunscreen. 	<p>Rationale:</p> <ul style="list-style-type: none"> • Limiting sun exposure and use of sunscreen may decrease the risk of skin cancer. Arsenic-induced skin cancers and the probable combined roles of arsenic exposure and UVB radiation in producing skin lesions has been reported [Yu et al. 2006].
Preventive Messages for Avoidance of Over Exposure to Arsenic in the Workplace	<p>Message:</p> <ul style="list-style-type: none"> • Patients should be encouraged to discuss their concerns regarding prevention of hazardous exposures at the workplace with their employer and/or workplace health and safety representative. 	<p>Rationale:</p> <ul style="list-style-type: none"> • OSHA's health hazard risk communication standard requires covered employers to educate their employees on health hazards in the workplace and how to prevent them. See OSHA Website for more specifics on the health hazard risk

		communication standard.URL: http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=standards&p_id=10099
ATSDR Patient Education Care Instruction Sheet	ATSDR has developed a patient education, care instruction sheet on arsenic toxicity that you might find useful. It can be found at www.atsdr.cdc.gov/csem/arsenic/patient_education.html	
Key Points	<ul style="list-style-type: none"> • Patients should be instructed on ways to protect themselves from over exposure to arsenic that might increase their risk of disease or worsen their existing health condition. 	
Progress Check Select the one best choice	<p>18. Patients who have been over exposed to arsenic should be advised to</p> <ul style="list-style-type: none"> A. Stop smoking. B. Contact their doctor if they develop signs of health changes. C. Stay well nourished with a diet rich in selenium, antioxidants, and folate. D. All of the above. 	

Progress Check Answers	<p>18. The correct answer is D. All of the recommendation options presented as answers to this question are appropriate protective measures the health care provider should advocate. These patient instructions include recommending the patient: stop smoking, contact their doctor if they develop signs of health changes, and stay well nourished with a diet rich in selenium, antioxidants, and folate.</p> <p><i>To review relevant content, "Self Care" in this section.</i></p>
---------------------------------------	---

Sources of Additional Information

Arsenic Specific Information	<p>Please refer to the following Web resources for more information on the adverse effects of arsenic, the treatment of arsenic-associated diseases, and management of persons exposed to arsenic.</p> <ul style="list-style-type: none">• Agency for Toxic Substances and Disease Registry (ATSDR) (www.cdc.gov/atsdr)<ul style="list-style-type: none">○ For <u>chemical</u>, emergency situations<ul style="list-style-type: none">▪ CDC Emergency Response: 770-488-7100 and request the ATSDR Duty Officer○ For <u>chemical</u>, non-emergency situations<ul style="list-style-type: none">▪ 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<p>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 a health care provider.</p><ul style="list-style-type: none">○ Toxicological Profile for Arsenic (www.atsdr.cdc.gov/toxprofiles/tp2.html)○ TOXFAQs for Arsenic (www.atsdr.cdc.gov/tfacts2.html)○ TOXFAQs Chemical Agent Briefing Sheets (CABS) for Arsenic (www.atsdr.cdc.gov/cabs/arsenic/index.html)○ ATSDR Minimal Response Levels (www.atsdr.cdc.gov/mrls/index.html)○ ATSDR Medical Management Guidelines—Arsenic Trioxide (www.atsdr.cdc.gov/MHMI/mmg168.html)<ul style="list-style-type: none">• Centers for Disease Control and Prevention
-------------------------------------	---

	<ul style="list-style-type: none"> ○ Third National Report on Human Exposure to Environmental Chemicals. Population Biomonitoring Results ○ www.cdc.gov/exposurereport/ ● National Institute of Safety and Health (NIOSH) <ul style="list-style-type: none"> ○ NIOSH Safety and Health Topic Arsenic (www.cdc.gov/niosh/topics/arsenic/) ○ NIOSH's Workplace Health Hazard Evaluation Program (http://www.cdc.gov/niosh/hhe/) ● Occupational Safety and Health Administration (OSHA) <ul style="list-style-type: none"> ○ For urgent issues regarding workplace exposures, please contact OSHA at www.osha.gov/html/Feed_Back.html or 1-800-321-OSHA (6742). ○ OSHA Safety and Health Topics—Arsenic (www.osha.gov/SLTC/arsenic/index.html) ● U.S. Environmental Protection Agency (EPA) <ul style="list-style-type: none"> ○ EPA Arsenic in Drinking Water (www.epa.gov/safewater/arsenic/index.html)
Clinical Resources	<ul style="list-style-type: none"> ● American College of Occupational and Environmental Medicine (ACOEM) (www.acoem.org) <ul style="list-style-type: none"> ○ 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, 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)

	<p>(www.acmt.net)</p> <ul style="list-style-type: none"> ○ 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. <ul style="list-style-type: none"> ● Association of Occupational and Environmental Clinics www.aoec.org <ul style="list-style-type: none"> ○ 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/pesu <ul style="list-style-type: none"> ○ Each PEHSU is based at an academic center and there is collaboration between the pediatric clinic and the (AOEC) occupational and environmental clinic at each site. ○ The PEHSUs 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 <ul style="list-style-type: none"> ○ American Association of Poison Control Centers (1-800-222-1222 or www.aapcc.org).
General Environ-	Please refer to the following Web resources for general

<p>mental Health Information</p>	<p>information on environmental health.</p> <ul style="list-style-type: none"> • Agency for Toxic Substances and Disease Registry (www.cdc.gov/atsdr) <ul style="list-style-type: none"> ○ To view the complete library of the Case Studies in Environmental Medicine (CSEM) (www.atsdr.cdc.gov/csem/). ○ Taking an Exposure History CSEM (http://www.atsdr.cdc.gov/csem/exphistory) ○ ATSDR Division of Regional Operations. <ul style="list-style-type: none"> ▪ Through the working relationships they have established with EPA, other federal and state agencies, individual citizens, and community groups, regional representatives are able to maintain current and historic knowledge of the sites and issues in their regions. ▪ 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 • Centers for Disease Control and Prevention (CDC)(www.cdc.gov) <ul style="list-style-type: none"> ○ CDC works to protect public health and the safety of people by providing information to enhance health decisions, and CDC promotes health through partnerships with state health departments and other organizations. ○ 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/) <ul style="list-style-type: none"> ○ NCEH works to prevent illness, disability, and death from interactions between people and the
---	---

	<p>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.</p> <ul style="list-style-type: none">○ NCEH seeks to achieve its mission through science, service, and leadership.● National Institute of Health (NIH) (www.nih.gov)<ul style="list-style-type: none">○ 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/)<ul style="list-style-type: none">○ NIOSH is part of the U.S. Department of Health and Human Services.○ It helps 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.● National Library of Medicine<ul style="list-style-type: none">○ Environmental Health and Toxicology National Library of Medicine TOXNET http://sis.nlm.nih.gov/enviro.html
--	--

Assessment and Posttest

Introduction	<p>ATSDR seeks feedback on this course so we can assess its usefulness and effectiveness. We ask you to complete the assessment questionnaire online for this purpose.</p> <p>You can receive continuing education credits as follows:</p>
Accrediting Organization	Credits Offered
Accreditation Council for Continuing Medical Education (ACCME)	<p>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.</p> <p>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.</p>
American Nurses Credentialing Center (ANCC), Commission on Accreditation	<p>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.</p> <p>This activity provides 1.8 contact hours.</p>
National Commission for Health Education Credentialing, Inc. (NCHEC)	<p>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.</p>
International Association for Continuing Education and Training	<p>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 IACET CEU's for this program.</p>

(IACET)	
Instructions	<p>To complete the assessment and posttest, go to www2.cdc.gov/atsdrce/ and follow the instructions on that page.</p> <p>You can immediately print your continuing education certificate from your personal transcript online. No fees are charged.</p>
Online Assessment Questionnaire	<ol style="list-style-type: none"> 1. The learning outcomes (objectives) were relevant to the goal(s) of the course <ul style="list-style-type: none"> A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree. 2. The content was appropriate given the stated objectives of the course <ul style="list-style-type: none"> A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree. 3. The content was presented clearly <ul style="list-style-type: none"> A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree. 4. The learning environment was conducive to learning <ul style="list-style-type: none"> A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree.

	<p>5. The delivery method (e.g., web, video, DVD, etc.) helped me learn the material</p> <p>A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree.</p> <p>6. The instructional strategies helped me learn the material.</p> <p>A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree.</p> <p>7. Overall, the quality of the course materials was excellent</p> <p>A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree.</p> <p>8. The difficulty level of the course was</p> <p>A. Much too difficult. B. A little difficult. C. Just right. D. A little easy. E. Much too easy.</p> <p>9. Overall, the length of the course was</p> <p>A. Much too long. B. A little long. C. Just right. D. A little short. E. Much too short.</p> <p>10. The availability of CE credit influenced my decision to</p>
--	---

	<p>participate in this activity</p> <p>A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree. F. Not applicable.</p> <p>11. As a result of completing this educational activity, it is likely that I will make changes in my practice</p> <p>A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree. F. Not applicable.</p> <p>12. I am confident I can better provide appropriate clinical care for patients exposed to environmental hazards as described in this course</p> <p>A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree. F. Direct patient care is not provided.</p> <p>13. I intend to apply recommendations from this course in my clinical practice</p> <p>A. Strongly agree. B. Agree. C. Undecided. D. Disagree. E. Strongly disagree. F. Direct patient care is not provided.</p> <p>14. The content expert(s) demonstrated expertise in the subject matter</p> <p>A. Strongly agree.</p>
--	---

	<p>B. Agree. C. Undecided. D. Disagree. E. Strongly disagree.</p> <p>15. Do you feel this course was commercially biased? If yes, please explain</p> <p>16. Please describe any technical difficulties you experienced with the course.</p> <p>17. What could be done to improve future offerings?</p> <p>18. Do you have any further comments?</p>
--	--

<p>Posttest</p> <p>Select the one best answer</p>	<p>1. What is arsenic?</p> <p>A. A naturally occurring mineral. B. An element. C. Commercially useful. D. All of the above.</p> <p>2. Most of the arsenic used industrially in recent years in the United States has been for the manufacture of</p> <p>A. Pesticide. B. Wood preservative. C. Metal ores. D. Power plants</p> <p>3. The major route(s) of exposure to arsenic is/are</p> <p>A. Inhalation. B. Ingestion. C. Dermal contact. D. A and B E. All are equally important.</p> <p>4. Of the following, the U. S. population most at risk of exposure to arsenic today is</p>
---	---

	<p>A. People who work in farming. B. People who work in copper smelting or cutting and sawing of CCA pressure-treated lumber. C. People in the Mississippi river valley. D. People who live in major urban areas.</p> <p>5. Which of the following is FALSE regarding U.S. standards for arsenic levels?</p> <p>A. There is a standard level for permissible air levels of arsenic in the workplace. B. There is a standard level for allowable arsenic in drinking water. C. There is a standard level for allowable arsenic in ambient air in the environment. D. There are permissible levels of organic arsenic set for foodstuffs by the FDA.</p> <p>6. After ingestion, most arsenic is</p> <p>A. Retained in the kidneys. B. Retained in the bones. C. Rapidly excreted in the urine. D. Stored in the liver.</p> <p>7. Arsenic initiates cellular injury by</p> <p>A. Oxidation of lipid membranes. B. Ubiquitination. C. Methylation. D. Binding with sulfhydryl groups.</p> <p>8. Of the neurologic effects associated with arsenic exposure, the most common one is</p> <p>A. Peripheral neuropathy in a stocking-glove pattern. B. Pseudotumor cerebri. C. Thrombotic stroke. D. Autonomic neuropathy.</p> <p>9. Which dermatologic condition(s) may occur from chronic arsenic ingestion?</p> <p>A. Psoriasis.</p>
--	---

	<p>B. Hyperpigmentation and hyperkeratosis C. Verucca vulgaris. D. Melanoma.</p> <p>10. Abnormal laboratory tests in arsenic toxicity include</p> <p>A. Elevated amylase. B. Reduced serum B12. C. Elevated liver enzymes. D. White blood cell casts on urinalysis.</p> <p>11. A 64-year-old male who worked in a copper smelter in the United States in the 1960s and 1970s presents complaining of hemoptysis, 30 lb weight loss, and constant chest pain. He says his symptoms began several months ago. Of the arsenic-associated diseases, the <u>MOST LIKELY</u> culprit is</p> <p>A. Bronchial irritation from acute inhalation. B. Cardiomyopathy. C. Lung carcinoma. D. Pleural mesothelioma.</p> <p>12. As part of the exposure history, you should explore</p> <p>A. Possible occupational exposures to arsenic. B. Possible home environmental exposures to arsenic. C. Use of personal protective equipment. D. All of the above.</p> <p>13. In a patient with an occupational exposure to arsenic several years ago, urinary arsenic is likely to show</p> <p>A. Persistently high levels. B. No arsenic. C. Low levels consistent with normal population dietary intake of arsenic. D. None of the above.</p> <p>14. On peripheral blood smear, basophilic stippling of red cells is suggestive of</p> <p>A. Arsenic or lead toxicity. B. Chronic liver disease.</p>
--	---

	<p>C. Promyelocytic leukemia. D. Chronic renal disease.</p> <p>15. In caring for a patient who has been exposed to arsenic, it is important to</p> <p>A. Identify the source or sources of exposure. B. Take steps to avoid further exposure to arsenic. C. Monitor the patient to assure that exposure has ceased. D. All of the above</p> <p>16. Patients who have been diagnosed with an arsenic-associated disease should be instructed to</p> <p>A. Consider the possibility of exposure both from home or workplace. B. Inquire with employer if there is any possibility of workplace exposure. C. If drinking from a private well, have the well tested for arsenic D. All of the above.</p>
--	--

Relevant Content	To review content relevant to the post-test questions, see:		
	Question	Location of Relevant Content	Learning Objective (s) Met
	1	What is arsenic? Where is arsenic found?	<ul style="list-style-type: none"> • Describe arsenic • Identify where arsenic is found in the United States today.
	2	Where is arsenic found?	<ul style="list-style-type: none"> • Identify where arsenic is found in the United States today.
	3	What are routes of exposure for arsenic?	<ul style="list-style-type: none"> • Identify the major routes of exposure to arsenic.
	4	Who is at risk of arsenic	<ul style="list-style-type: none"> • Identify the populations most

		overexposure?	heavily exposed to arsenic.
5		What are standards and regulations for arsenic?	<ul style="list-style-type: none"> Describe standards for arsenic exposure.
6		What is the biological fate of arsenic in the body?	<ul style="list-style-type: none"> Describe what happens when arsenic enters the body.
7		How does arsenic induce pathogenic change?	<ul style="list-style-type: none"> Describe the ways arsenic induces illness.
8, 9, 11		What are the physiologic effects of arsenic exposure?	<ul style="list-style-type: none"> Describe the health effects associated with arsenic exposure.
10, 12, 13, and 14		Clinical assessment	<ul style="list-style-type: none"> Identify the primary focuses of the exposure and medical history. Describe the most typical findings on physical exam Describe the tests you would order for patients exposed to arsenic.
15		How should patients exposed to arsenic be treated and managed?	<ul style="list-style-type: none"> Identify primary strategies for treating and managing arsenic associated diseases.
16		What instructions should be given to patients exposed to arsenic?	<ul style="list-style-type: none"> Describe instructions for patient self care.

Appendix: Literature Cited

References	<p>[ACGIH] American Conference of Governmental Industrial Hygienists. 2005. TLVs and BEIs. Cincinnati, OH: Signature Publications.</p> <p>[ATSDR] Agency for Toxic Substances and Disease Registry. 2007. Toxicological profile for arsenic. Draft for Public Comment. Atlanta GA [updated 2007 August; accessed 2008 January 14]. Available from: http://www.atsdr.cdc.gov/toxprofiles/tp2.html.</p> <p>Aposhian, HV. 1989. Biochemical toxicology of arsenic. 1989. Rev Biochem Toxicol. New York, NY: Elsevier/North Holland. 10:265–299.</p> <p>Aposhian HV, Zakharyan RA, Avram MD, Sampayo-Reyes A, Wollenberg ML. 2004. A review of the enzymology of arsenic metabolism and a new potential role of hydrogen peroxide in the detoxication of the trivalent arsenic species. Toxicol Appl Pharmacol 198:327–335.</p> <p>Armstrong CW, Stroube RB, Rubio T, Siudyla EA, Miller GB Jr. 1984. Outbreak of fatal arsenic poisoning caused by contaminated drinking water. Arch Environ Health 39:276–9.</p> <p>Beckett WS, Moore JL, Keogh JP, Bleecker ML. 1986. Acute encephalopathy due to occupational exposure to arsenic. Br J Indust Med 43:66–67.</p> <p>Bleecker M. 2007. Toxic Peripheral Neuropathy. In: Rom W and Markowitz S eds. Environmental and Occupational Medicine, 4th ed. Hagerstown, MD: Lippincott Williams & Wilkins. p. 643.</p> <p>Bertolero F, Pozzi G, Sabbioni E, Saffiotti U. 1987. Cellular uptake and metabolic reduction of pentavalent to trivalent arsenic as determinants of cytotoxicity and morphological transformations. Carcinogenesis 8:803–808.</p> <p>Buchet JP, Lauwerys R, Roels H. 1981. Comparison of the urinary excretion of arsenic metabolites after a single dose of sodium arsenite, monomethylarsonate or dimethylarsinate in</p>
-------------------	---

man. In Arch Occup Environ Health 48: 71–179.

Caldwell KL, Jones RL, Verdon, CP, Jeffery M, Jarrett JM, Caudill SP, Osterloh JD. 2008. Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003-2004. Journal of Exposure Science and Environmental Epidemiology. 1–10.

Carbrey JM, Gorelick-Feldman DA, Kozono D, Praetorius J, Nielsen S, Agre P. 2003. Aquaglyceroporin AQP9: solute permeation and metabolic control of expression in liver. Proc Natl Acad Sci U S A. 100: 2945–2950.

Centeno JA, Mullick FG, Martinez L, Page NP, Gibb H, Longfellow D, et. al. 2002. Pathology related to chronic arsenic exposure. Environ Health Perspect 110: 883–886.

[CDC] Centers for Disease Control and Prevention. Third National Report on Human Exposure to Environmental Chemicals. Biomonitoring Results since the Third Report. Atlanta GA [updated 2009 March; accessed 2009 April]. Available from: <http://www.cdc.gov/exposurereport/>

Chakraborti D, Mukherjee SC, Saha KC, Chowdhury UK; Rahman MM; Sengupta MK. 2003a. Arsenic toxicity from homeopathic treatment. J Toxicol Clin Toxicol 41(7): 963–967.

Chakraborti D, Hussam A, Alauddin M. 2003b. Arsenic: Environmental health aspects with special reference to ground water in South Asia. J Environ Sci Health Part A 38(1): xi–xv.

Chan TYK. 1994. The prevalence, use and harmful potential of some Chinese herbal medicines in babies and children. Vet Hum Toxicol 36(3): 238–240.

Chang CC, Ho SC, Tsai SS, Yang CY. 2004. Ischemic heart disease mortality reduction in an arsenosis-endemic area in southwestern Taiwan after a switch in the tap-water supply system. J Toxicol Environ Health 67: 1353–1361.

Chen CJ, Hsueh YM, Lai MS, Shyu MP; Chen SY; Wu MM; et. al. 1995. Increased prevalence of hypertension and long-

term arsenic exposure. *Hypertension* 25:53–60.

Chiou HY, Hsueh YM, Liaw KF, [Horng SF](#), [Chiang MH](#), [Pu YS](#). 1995. Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. *Cancer Res* 55:1296–1300.

Chung JS, Kalman DA, Moore LE, Kosnett, MJ, Arroyo AP, Beeris M, et al. 2002. Family Correlations of Arsenic Methylation Patterns in Children and Parents Exposed to High Concentrations of Arsenic in Drinking Water. *Environmental Health Perspectives* Vol 110, number 7, 729–733.

Cohen D and Moore M. Occupational Skin Disease. 2007. In: Rom W and Markowitz S eds. *Environmental and Occupational Medicine*, 4th ed. Hagerstown, MD: Lippincott Williams & Wilkins. p. 635.

Concha G, Vogler G, Nermell B, [Vahter M](#). 2002. Intra-individual variation in the metabolism of inorganic arsenic. *Int Arch Occup Environ Health* 75:576–580.

Datta DV. 1976. Arsenic and non-cirrhotic portal hypertension. *Lancet* 1:433.

Donofrio PD, Wilbourne AJ, Albers JW, Do, LR, Salanga, V, Greenberg, HS. 1987. Acute arsenic intoxication presenting as Guillain Barré like syndrome. *Muscle Nerve* 10:114–120.

Dopp E, Hartmann LM, Florea AM, [von Recklinghausen U](#), [Pieper R](#), [Shokouhi B](#). 2004. Uptake of inorganic and organic derivatives of arsenic associated with induced cytotoxic and genotoxic effects in Chinese hamster ovary (CHO) cells. *Toxicol Appl Pharmacol* 201(2): 156–165.

Drobna Z, Waters SB, Walton FS, Lecluyse EL Thomas DJ; Styblo M. 2004. Interindividual variation in the metabolism of arsenic in cultured primary human hepatocytes. *Toxicol Appl Pharmacol* 201:166–177.

Elmariah SB, Anolik R, Walters RF, Rosenman K, Pomeranz MK, Sanchez MR, 2008. Invasive squamous-cell carcinoma and arsenical keratoses. *Dermatol Online J.* 14(10):24.

Engel RR, Hopenhayn-Rich C, Recheveur O, Smith AH. 1994. Vascular effects of chronic arsenic exposure: a review. *Epidemiol Rev* 16: 184–209.

Enterline PE, Henderson VL, Marsh GM. 1987. Exposure to arsenic and respiratory cancer: a reanalysis. *Am J Epidemiol* 125: 929–38.

[EPA] U.S. Environmental Protection Agency. Arsenic in drinking water. Washington DC [updated 2006, September 14; accessed 2009 March]. Available from: <http://www.epa.gov/safewater/arsenic/index.html>.

[EPA] U.S. Environmental Protection Agency. Arsenic compounds hazard summary. Technology transfer network air toxics website. Washington DC [updated 2007 November 6; accessed 2009 March]. Available from: <http://www.epa.gov/ttn/atw/hlthef/arsenic.html>.

[EPA] U.S. Environmental Protection Agency. Recommendations for management of lumber treated with arsenic-containing pesticides used in homes. "Questions & answers on CCA-treated wood sealant studies (interim results)." Washington DC [updated April 7 2008; accessed 2009 September 14]. Available from: http://www.epa.gov/oppad001/reregistration/cca/sealant_qa.htm

[EPA] U.S. Environmental Protection Agency. Federal Facilities Restoration and Reuse. Military munitions/unexploded ordnance. Washington DC [updated 2008 November 10; accessed 2009 April]. Available from: <http://www.epa.gov/fedfac/documents/munitions.htm>.

Falk H, Caldwell GG, Ishak KG, Thomas LB, Popper H. 1981. Arsenic related hepatic angiosarcoma. *Am J Ind Med* 2: 43–50.

Foa V, Colombi A, Maroni M. 1984. The speciation of the chemical forms of arsenic in the biological monitoring of exposure to inorganic arsenic. *Sci Total Environ.* 34: 241–259.

Garb LG, Hine CH. 1977. Arsenical neuropathy: residual

effects following acute industrial exposure. *J Occup Med* 19567–568.

Garcia-Vargas GG, Cebrian ME. 1996. Health effects of arsenic. In: Wang LW, ed. *Toxicology of metals*. Boca Raton FL: CRC Press. p. 423–438.

Garvey GJ, Hahn G, Lee RV, [Harbison RD](#). 2001. Heavy metal hazards of Asian traditional remedies. *Int J Environ Health Res* 11(1):63–71.

Gerr F, Letz R. 2000. Epidemiological case definitions of peripheral neuropathy: experience from two neurotoxicity studies. *Neurotoxicity* 21:761–768.

Giberson A, Vaziri ND, Mirahadi K, [Rosen SM](#). 1976. Haemodialysis of acute arsenic intoxication with transient renal failure. *Arch Intern Med* 136:1303–1304.

Gorby MS. 1988. Arsenic poisoning. *West J Med* 149:308–315.

Guha Mazumder DN. 2003. Chronic arsenic toxicity: clinical features, epidemiology, and treatment: experience in West Bengal. *J Environ Sci Health A Tox Hazards Subst Environ Eng* A38:141–163.

Hafeman DM, Ahsan H, Louis ED, Siddique AB, Slavkovich V, Zhongqi C, et al. 2005. Association between arsenic exposure and a measure of subclinical sensory neuropathy in Bangladesh. *Occup Environ Med* 47:778–784.

Hertz-Picciotto I, Arrighi HM, Hu SW. 2000. Does arsenic exposure increase the risk for circulatory disease? *Am J Epidemiol* 151:174–181.

Hopenhayn-Rich C, Biggs ML, Smith AH. 1998. Lung and kidney cancer mortality association with arsenic in drinking water in Cordoba Argentina. *Int Epidemiol Assoc* 27:561–569.

Hsueh YM, Cheng GS, Wu MM, [Yu HS](#), [Kuo TL](#), [Chen CJ](#). 1995. Multiple risk factors associated with arsenic-induced skin cancer: effects of chronic liver disease and

malnutritional status. *Br J Cancer* 71:109–114.

Hu J, Fang J, Dong Y, Chen, SJ, Chen, Z. 2005. Arsenic in cancer therapy. *Anti-Cancer Drugs* 16:119–127.

[IARC] International Agency for Research on Cancer. 2004. IARC monograph on the evaluation of carcinogenic risk to humans. Some drinking water disinfectant and contaminants, including arsenic. Vol. 84. Lyon, FR: International Agency for Research on Cancer.

Ishinishi N, Tsuchiya K, Vahter M, Fowler BA. 1986. Arsenic. In: Friberg L, Nordberg GF, Vouk V, eds. *Handbook on the toxicology of metals*. Amsterdam, NL: Elsevier Science.

Kales, SN; Huyck, KL; Goldman, RH. 2006. Elevated urine arsenic: un-specified results lead to unnecessary concern and further evaluations. *J Anal Toxicol* 30(2):80–85.

Kaltreider RC, Davis AM, Lariviere JP, Hamilton JW. 2001. Arsenic alters the function of the glucocorticoid receptor as a transcription factor. *Environ Health Perspect* 109:245–251.

Kerr HD, Saryan LA. 1986. Arsenic content of homeopathic medicines. *Clin Toxicol* 24(5): 451–459.

Kitchin, KT. 2001. Recent advances in arsenic carcinogenesis: Modes of action, animal model systems, and methylated arsenic metabolites. *Toxicology and Applied Pharmacology* 172:49–261.

Kyle RA, Pease GL. 1965. Hematologic aspects of arsenic intoxication. *N Engl J Med* 273:18–23.

Lansdown AB. 1995. Physiological and toxicological changes in the skin resulting from the action and interaction of metal ions. *Crit Rev Toxicol* 25:397–462.

Lasngerkvist BJ, Zetterlund B. 1994. Assessment of exposure to arsenic among smelter workers: a five year follow-up. *Am J Ind Med* 25:377–88.

Lauwerys R, Hoet P. 1993. *Industrial Chemical Exposure. Guidelines for Biological Monitoring*. Second Edition. Boca

Raton, FL: CRC Press.

Loffredo CA, Aposhian HV, Cebrian ME, Yamauchi H, Silbergeld EK. 2003. Variability in human metabolism of arsenic. *Environ Res* 92:85–91.

Lopez S, Miyashita Y, Simons SS. 1990. Structurally based, selective interaction of arsenic with steroid receptors. *J Biol Chem* 265:16039–16042.

Lugo G, Cassady G, Palmisano P. 1969. Acute maternal arsenic intoxication with neonatal death. *Am J Dis Child* 117:328–330.

Marafante E, Vahter M, Norin H, Envall J, Sandström M, Christakopoulos A. 1987. Biotransformation of dimethylarsinic acid in mouse, hamster and man. *J Appl Toxicol* 7:111–117

Mazumder DG, De BK, Santra A, Ghosh N; Das S; Lahiri S. 2001. Randomized placebo-controlled trial of 2,3-dimercapto-1-propanesulfonate (DMPS) in therapy of chronic arsenicosis due to drinking arsenic-contaminated water. *Clin Toxicol* 39:665–674.

Meharg, A. 2003. The arsenic green. *Nature* 423:688.

Miller WH Jr, Schipper HM, Lee JS, Singer J, Waxman S. 2002. Mechanisms of action of arsenic trioxide. *Cancer Res* 62:3893–3903.

Mitra SR, Guha Mazumder DN, Basu A, Block G, Haque R, Samanta S, et al. 2004. Nutritional factors and susceptibility to arsenic-caused skin lesions in West Bengal, India. *Environ Health Perspect* 112:1104–1109.

Murphy MJ, Lyon LW, Taylor JW. 1981. Subacute arsenic neuropathy: clinical and electrophysiological observations. *J Neurol Neurosurg Psychiatry* 44:896–900.

Murunga E, Zawada E. 2007. Environmental and occupational causes of toxic injury to the kidneys and urinary tract. In: Rom W and Markowitz S eds. *Environmental and occupational medicine*, 4th ed. Hagerstown, MD: Lippincott

Williams & Wilkins. p. 810.

[NAS] National Academy of Sciences. 1977. Medical and biologic effects of environmental pollutants, arsenic. Washington, DC: National Research Council, National Academy of Sciences.

[NIOSH] National Institute of Occupational Safety and Health. 2005. NIOSH pocket guide to chemical hazards: arsenic. NIOSH publication no. Washington, DC: NIOSH. p. 149.

[NRC] National Research Council. 2000. Arsenic in drinking water. Washington, DC: National Academy Press.

Nordstrom S, Beckman L, Nordenson I. 1979 Occupational and environmental risks in and around a smelter in northern Sweden. V. Spontaneous abortion among female employees and decreased birth weight in their offspring. VI. Congenital malformations. *Hereditas* 90:291–302.

[OSHA] Occupational Safety and Health Administration. Safety and health Topics. Arsenic. Washington, DC [updated 2008 June; accessed September 2009]. Available from: <http://www.osha.gov/SLTC/arsenic/index.html>

Pi J, Yamauchi H, Sun G, Yoshida T, Aikawa H, Fujimoto W, et. al. 2005. Vascular dysfunction in patients with chronic arsenosis can be reversed by reduction of arsenic exposure. *Environ Health Perspect* 113:339–341.

Popper H, Thomas LB, Telles NC, Falk H, Selikoff IJ. 1978. Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast and arsenic. *Am J Pathol* 92:349–376.

Ratnaike RN. 2003. Acute and chronic arsenic toxicity. *Postgraduate Medical Journal* 79:391–396.

Reynolds ES. 1901. An account of the epidemic outbreak of arsenical poisoning occurring in beer drinkers in the north of England and midland countries in 1900. *Lancet* 1:166-170.

Rose M, Lewis J, Langford N, Baxter M, Origgi S, Barber M,

et al. 2007. Arsenic in seaweed—forms, concentration and dietary exposure. *Food and Chemical Toxicology* Volume 45, Issue 7: 1263–1267.

Rosenman K. 2007. Occupational heart disease. In: Rom W and Markowitz S eds. *Environmental and occupational medicine*, 4th ed. Hagerstown, MD: Lippincott Williams & Wilkins. p. 688.

Rossmann T. 2007. Arsenic. In: Rom W and Markowitz S eds. *Environmental and occupational medicine*, 4th ed. Hagerstown, MD: Lippincott Williams & Wilkins. p. 1006–1017.

Schoen A, Beck B, Sharma R, Dube E. 2004. Arsenic toxicity at low doses: epidemiological and mode of action considerations. *Toxicol Appl Pharmacol* 198:253–267.

Selzer PM, Ancel MA. 1983. Chronic arsenic poisoning masquerading as pernicious anemia. *West J Med* 139(2):219–220.

Sexton GB, Gowdey CW. 1963. Relation between thiamine and arsenic toxicity. *Arch Dermatol Syph* 56:634–647.

Shacklette, HT, Boerngen, JG. 1984. Element concentrations in soils and other surficial materials of the conterminous United States: Reston, VA: U.S. Geological Survey. Professional Paper 1270. p. 6.

Shalat SL, Walker DB, Finnell RH. 1996. Role of arsenic as a reproductive toxin with particular attention to neural tube defects. *J Toxicol Env Hlth* 48(3):253–72.

Simeonova PP, Luster MI. 2004. Arsenic and atherosclerosis. *Toxicol Appl Pharmacol* 198:444–449.

Son SB, Song HJ, Son SW. 2008. Successful treatment of palmoplantar arsenical keratosis with a combination of keratolytics and low dose acitretin. *Clin Exp Dermatol* 33(2): 202–4.

Spallholz JE, Boylan LM, Rhaman MM. 2004. Environmental hypothesis: is poor dietary selenium intake an underlying

factor for arsenicosis and cancer in Bangladesh and West Bengal, India? *Sci Total Environ* 323:21–32.

Steinmaus C, Carrigan K, Kalman D, Yuan Y, Smith AH. 2005. Dietary intake and arsenic methylation in a U.S. population. *Environ Health Perspect* 113:1153–1159.

Styblo M, Drobna Z, Jaspers I, Lin S, Thomas DJ. 2002. The role of biomethylation in toxicity and carcinogenicity of arsenic: a research update. *Environ Health Perspect* 110:767–771.

Tseng WP, Chu HM, How SW, Fong JM, Lin CS, Yeh S. 1968. Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. *J Natl Cancer Inst* 40:453–463.

Tseng CH, Huang YK, Huang YL, Chung CJ, Yang MH, Chen CJ, et al. 2005. Arsenic exposure, urinary arsenic speciation, and peripheral vascular disease in blackfoot disease-hyperendemic villages in Taiwan [published erratum appears in *Toxicol Appl Pharmacol* 2006; 211 (2):175] *Toxicol Appl Pharmacol* 206(3):299–308.

Tseng CH, Tseng CP, Chiou HY, Hsueh YM, Choon-Khim Chong CK, Chen CJ. 2002. Epidemiologic evidence of diabetogenic effect of arsenic. *Toxicol Lett* 133:69–76.

Tseng CH. 2003. Abnormal current perception thresholds measured by neurometer among residents in blackfoot disease-hyperendemic villages in Taiwan. *Toxicol Lett* 146:27–36.

Uede K, Furukawa F. 2003. Skin manifestations in acute arsenic poisoning from the Wakayama curry-poisoning incident. *British Journal of Dermatology* 149 (4):757–762.

[USGS] United States Geological Survey. 2005. Arsenic in ground water in the United States. Reston, VA [updated 2009 June 16; accessed 2009 September 14]. Available from: http://water.usgs.gov/nawqa/trace/pubs/geo_v46n11/fig3.html

Vahter M. 2002. Mechanisms of arsenic biotransformation.

Toxicology 181:211–217.

Vahter M, Marafante E, Dencker L. 1983. Metabolism of arsenobetaine in mice, rats and rabbits. *Sci Total Environ* 30:197–211.

Valentine JL, Kang HK, Spivey G. 1979. Arsenic levels in human blood, urine, and hair in response to exposure via drinking water. *Environ Res* 20:24–32.

Valenzuela OL, Borja-Aburto VH, Garcia-Vargas GG, Cruz-Gonzalez MBB, Garcia-Montalvo EA, Calderon-Aranda ES et al. 2005. Urinary trivalent methylated arsenic species in a population chronically exposed to inorganic arsenic. *Environ Health Perspect* 113(3):250–254.

Vantroyen B, Heilier JF, Meulemans A, Michels A, Buchet J-P, Vanderschueren S, et al. 2004. Survival after a lethal dose of arsenic trioxide. *J Toxicol Clin Toxicol* 42(6): 889–895.

Verret WJ, Chen Y, Ahmed A; Islam T, Parvez F, Kibriya MG et al. 2005. A randomized, double-blind placebo-controlled trial evaluating the effects of vitamin E and selenium on arsenic-induced skin lesions in Bangladesh. *J Occup Environ Med* 47(10):1026–35.

Wang Z, Dey S, Rosen BP, Rossman TG. 1996. Efflux mediated resistance to arsenicals in arsenic-resistant and hypersensitive Chinese hamster cells. *Toxicol Appl Pharmacol* 137:112–119.

Welch, K., Higgins, I., Oh, M. and Burchfiel, C. 1982. Arsenic exposure, smoking and respiratory cancer in copper smelter workers. *Arch Environ Health* 37 325–335.

[WHO] World Health Organization (WHO). Arsenic and arsenic compounds, 2nd edn. *Environmental Health Criteria* 224. Geneva CH [updated 2001; accessed 2008 April 2]. Available from:

<http://www.inchem.org/documents/ehc/ehc/ehc224.htm>

Winski SL, Carter DE. 1995. Interactions of rat red blood cell sulfhydryls with arsenate and arsenite. *J Toxicol Environ*

Health 46: 379–397.

Yeh S, How SW, Lin CS. 1968. Arsenical cancer of skin—histologic study with special reference to Bowen's disease. *Cancer* 21(2): 312–39.

Yip L, Dart R. 2001. Arsenic. In: Sullivan J and Kreiger G, eds. *Clinical environmental health and toxic exposures*, Second Edition. Philadelphia, PA: Lippincott Williams & Wilkins. p. 858-865.

Yoshida T, Yamauchi H, Sun GF. 2004. Chronic health effects in people exposed to arsenic via the drinking water: dose-response relationships in review. *Toxicol Appl Pharmacol* 198: 243–252.

Yu HS, Liao WT, Chai CY. 2006. Arsenic carcinogenesis in the skin. *J Biomed Sci* 13(5): 657–66.

Zaldivar R, Prunes L, Ghai GL. 1981. Arsenic dose in patients with cutaneous carcinomata and hepatic haemangioma after environmental and occupational exposure. *Arch Toxicol* 47: 145–154.

Zeng H, Uthus EO, Combs GF Jr. 2005. Mechanistic aspects of the interaction between selenium and arsenic. *J Inorg Biochem* 99: 1269–1274.