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ARSENIC



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MEDITEXT ® - Medical Management

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0.0 OVERVIEW**0.1 LIFE SUPPORT**

- A. This overview assumes that basic life support measures have been instituted.

0.2 CLINICAL EFFECTS**0.2.1 SUMMARY OF EXPOSURE****0.2.1.1 ACUTE EXPOSURE**

- A. Arsenic compounds are absorbed mainly through the GI tract, but may be absorbed through intact skin or after inhalation. Hypovolemia from capillary leakage ('third-spacing' of fluids) is a common, serious early effect.
- B. Acute arsenic ingestion generally produces signs and symptoms within 30 minutes, but this may be delayed in onset for several hours if arsenic is ingested with food.
 - 1. Initial signs and symptoms of arsenic ingestion include burning lips, throat constriction and dysphagia, followed by excruciating abdominal pain, hemorrhagic gastritis, gastroenteritis, severe nausea, projectile vomiting, profuse "rice water-like" diarrhea, with hypovolemia that may result in hypotension and an irregular pulse.
 - 2. Muscle cramps, facial edema, bronchitis, dyspnea, chest pain, dehydration, intense thirst, and fluid-electrolyte disturbances are also common following significant exposures. A garlic-like odor of the breath and feces may occur.
 - 3. DELAYED EFFECTS - After absorption, arsenic may cause multi-organ failure by inhibiting sulfhydryl-containing enzymes within cells.
 - a. Encephalopathy, with headache, lethargy, mental confusion, hallucinations, emotional

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- lability, memory loss and delirium may occur; seizures, stupor, convulsions, coma and death may follow within 24 hours of a severe acute exposure.
- b. Dysrhythmias (particularly QTc prolongation and torsade de pointes), cardiomyopathy, ARDS, hepatitis, rhabdomyolysis, hemolysis, and renal failure may develop over several days. Peripheral polyneuropathy, bone marrow suppression, skin eruptions, depression of hematopoiesis, alopecia, and Mees' lines may develop days to weeks after acute exposure. Anemia, leukopenia and thrombocytopenia are among the hematological abnormalities resulting from exposure.
 - c. The delayed effects may lead to systemic collapse, with severe hypotension, restlessness, convulsions and coma.
- C. Many arsenic compounds are severe irritants of the skin, eye, and mucous membranes, especially of moist surfaces; some may be corrosive. Contact produces local hyperemia, followed by vesicular or pustular eruptions. Trivalent compounds are particularly caustic. Acute inhalation exposures have resulted in irritation of the upper respiratory tract.
- D. **CHRONIC POISONING** - Chronic inhalation of inorganic arsenic compounds is the most common cause of occupational poisoning.
1. The sequence of chronic poisoning involves weakness, anorexia, hepatomegaly, jaundice, and gastrointestinal complaints, followed by conjunctivitis, irritation of the throat and respiratory tract, hyperpigmentation, and eczematoid and allergic dermatitis.
 2. Other effects of chronic exposure include conjunctivitis with irritation and lacrimation; hair, skin and nail changes; hyperkeratosis of feet and hands; and melanosis, with pigment spots in corneal and conjunctival epithelium.
 3. Skin lesions are a common effect, starting as erythematous, pruritic dermatitis, followed by finely freckled hyperpigmentation with hypopigmented maculae. Melanosis also occurs. The skin lesions may sometimes be pustular, ulcerative, and gangrenous.
 4. A hoarse voice and chronic upper respiratory disease are characteristic in overexposed arsenic workers. A perforated nasal septum is a common result with prolonged inhalation of white arsenic dust or fume.
 5. Peripheral nervous system symptoms may include numbness, burning, and tingling of the hands and feet; pain; paresthesias; tenderness; muscle fasciculations; gross tremors; ataxia; incoordination; and mental confusion. Muscular weakness, limb tenderness and difficulty walking may follow. The final phase consists of peripheral sensory neuropathy of the hands and feet. That may be associated with a motor neuropathy as well.
- E. Certain arsenic compounds are known human carcinogens. Chronic exposure in either occupational settings or by drinking contaminated groundwater can cause poisoning and carries an increased risk of skin, lung, bladder, and possibly liver cancers.

0.2.3 VITAL SIGNS

0.2.3.1 ACUTE EXPOSURE

- A. Hypotension and tachycardia are common early signs. Fever and tachypnea may occur. Hypertension has been associated with chronic environmental arsenic exposure.

0.2.4 HEENT

0.2.4.1 ACUTE EXPOSURE

- A. Trivalent arsenic is corrosive to the eyes, mouth, and mucous membranes. Perforation of the nasal septum can occur.

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0.2.5 CARDIOVASCULAR

0.2.5.1 ACUTE EXPOSURE

- A. Hypovolemic or hemorrhagic shock, torsades de pointes, ventricular fibrillation or tachycardia, QTc prolongation, and T-wave changes may be seen after acute ingestion. Myocarditis has been reported in chronic arsenic poisoning.

0.2.6 RESPIRATORY

0.2.6.1 ACUTE EXPOSURE

- A. Respiratory tract irritation may occur. Cardiogenic or noncardiogenic pulmonary edema and respiratory failure may develop in severe poisonings.

0.2.7 NEUROLOGIC

0.2.7.1 ACUTE EXPOSURE

- A. Altered mental status, seizures, toxic delirium, encephalopathy, and delayed peripheral neuropathy are complications of acute arsenic poisoning.

0.2.8 GASTROINTESTINAL

0.2.8.1 ACUTE EXPOSURE

- A. Acute toxicity results in early symptoms of abdominal pain, severe vomiting and diarrhea, as well as dryness of the oral and nasal cavities.

0.2.9 HEPATIC

0.2.9.1 ACUTE EXPOSURE

- A. Hepatocellular injury occurs rarely after acute poisoning, but has occurred following chronic exposure.

0.2.10 GENITOURINARY

0.2.10.1 ACUTE EXPOSURE

- A. Hematuria and acute tubular necrosis may occur.

0.2.12 FLUID-ELECTROLYTE

0.2.12.1 ACUTE EXPOSURE

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- A. Rapid volume depletion from vomiting, diarrhea, and third spacing of fluids is common.

0.2.13 HEMATOLOGIC

0.2.13.1 ACUTE EXPOSURE

- A. Acute hemolysis and anemia may occur after acute poisoning. Pancytopenia, aplastic anemia, or leukemia may occur following chronic exposure. Bone marrow depression can occur.

0.2.14 DERMATOLOGIC

0.2.14.1 ACUTE EXPOSURE

- A. Skin findings may include hyperpigmentation, keratoses, and epidermoid carcinomas. Mees' lines of the nails are common. Trivalent arsenic compounds are corrosive to the skin. Arsenic trioxide and pentoxide are sensitizers.

0.2.15 MUSCULOSKELETAL

0.2.15.1 ACUTE EXPOSURE

- A. Muscular cramps may occur and progress to rhabdomyolysis.

0.2.20 REPRODUCTIVE HAZARDS

- A. Inorganic arsenic crosses the placenta and may result in spontaneous abortion or stillbirth with either acute or chronic poisoning.

0.2.21 CARCINOGENICITY

0.2.21.1 IARC CATEGORY

- A. IARC Carcinogenicity Ratings for CAS7440-38-2 (IARC, 2003):

Listed As	Carcinogen Rating
Arsenic and arsenic compounds	1

- 1: The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

0.2.21.2 HUMAN OVERVIEW

- A. Chronic therapeutic, occupational, and environmental arsenic exposure have been associated with lung, bladder, skin, and other cancers in humans.

- B. Exposures as little as 1 gram per year have been associated with CANCER (HSDB).

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0.2.22 GENOTOXICITY

- A. Arsenic induced DNA damage in human cells.
- B. Conflicting genetic effects have been found for arsenicals. Chromosome aberrations were elevated in the white blood cells of persons exposed to arsenic and possibly other substances (Nordenson, 1978) Burgdorf et al, 1977), but sister chromatid exchanges were not (Friberg et al, 1986). Sodium arsenite did induce sister chromatid exchanges in vitro, however (Friberg et al, 1986).

0.3 MEDICAL SURVEILLANCE/LABORATORY

- A. Monitor CBC, serum electrolytes, urinalysis, spot urine arsenic, a 24 hour urinary arsenic collection, liver and renal function tests, and a blood arsenic level in symptomatic patients. A 24 hour urinary arsenic collection exceeding 100 mcg is usually abnormal, even after chelation.
- B. Obtain an ECG and institute continuous cardiac monitoring in symptomatic patients.
- C. An abdominal x-ray should be obtained in all patients who are suspected of having ingested arsenic because it is radiopaque. Obtain a chest radiograph in patients with severe poisoning or pulmonary effects.
- D. Initial and periodic biological monitoring and medical surveillance are required for employees exposed to arsenic.

0.4 TREATMENT OVERVIEW

0.4.2 ORAL EXPOSURE

- A. GASTRIC DECONTAMINATION - Aggressive decontamination with gastric lavage is recommended. If x-ray demonstrates arsenic in the lower GI tract, whole bowel irrigation should be considered. Activated charcoal may not bind significant amounts, but is recommended until definitive quantitative data are available. Fluid repletion should begin as soon as possible.
- B. GASTRIC LAVAGE: Consider after ingestion of a potentially life-threatening amount of poison if it can be performed soon after ingestion (generally within 1 hour). Protect airway by placement in Trendelenburg and left lateral decubitus position or by endotracheal intubation. Control any seizures first.
1. CONTRAINDICATIONS: Loss of airway protective reflexes or decreased level of consciousness in unintubated patients; following ingestion of corrosives; hydrocarbons (high aspiration potential); patients at risk of hemorrhage or gastrointestinal perforation; and trivial or non-toxic ingestion.
- C. ACTIVATED CHARCOAL: Administer charcoal as a slurry (240 mL water/30 g charcoal). Usual dose: 25 to 100 g in adults/adolescents, 25 to 50 g in children (1 to 12 years); and 1 g/kg in infants less than 1 year old.
- D. Monitor vital signs, ECG, and liver and renal function tests. Maintain high urine output 2 to 3 ml/kg/hr in patients with hemolysis or rhabdomyolysis, which may prevent red blood cell

breakdown products and myoglobin from being deposited in the renal tubules.

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E. CHELATION -

1. BAL - Symptomatic patients unable to tolerate oral medication should be treated with BAL 3 to 5 mg/kg/dose IM every 4 to 12 hours. The dose and frequency depend on the degree of toxicity seen. Higher doses of BAL invariably cause adverse effects.
2. DMSA - Dimercaptosuccinic acid (DMSA) should be used as soon as the patient is able to tolerate oral medication. DOSE: 10 mg/kg every 8 hours for 5 days, then decrease dosing to every 12 hours for 14 days. It may be more effective and causes fewer side effects than BAL.
3. PENICILLAMINE - An alternative in patients able to tolerate oral medications. DOSE: D-penicillamine 100 mg/kg/day up to 2 g daily in four divided doses.
4. ENDPOINT - In severely ill patients, combined therapy with both BAL and an oral agent should be considered. Chelation therapy should be stopped when the urinary arsenic level falls below 50 mcg per 24 hours. If renal failure exists, dose of BAL and penicillamine should be decreased after loading dose.

F. FLUID/ELECTROLYTES - Monitor volume status; establish adequate urine flow of at least 1 to 2 mL/kg/hr.

G. X-RAY - Arsenic is radiopaque. Obtain abdominal film and repeat as necessary to insure that gastric emptying maneuvers have been effective. A chest radiograph should also be obtained in patients with pulmonary symptoms.

0.5 RANGE OF TOXICITY

- A. Trivalent arsenic (arsenite) is more toxic than pentavalent arsenic (arsenate). Acute ingestion of more than 100 mg of inorganic arsenic is likely to cause significant toxicity. Acute ingestion of 200 mg or more of arsenic trioxide may be fatal in an adult.

1.0 SUBSTANCES INCLUDED/SYNONYMS

1.1 THERAPEUTIC/TOXIC CLASS

- A. Arsenic compounds are frequently used as pesticides, but are also found in a variety of occupations and as environmental contaminants.
- B. This management does NOT include recommendations for patients with ARSINE GAS exposure; refer to the document on ARSINE for more information.

1.2 SPECIFIC SUBSTANCES

- A.
1. ARSEN (German, Polish)
 2. ARSENIA
 3. ARSENIC
 4. ARSENICALS
 5. ARSENIC-75
 6. ARSENIC BLACK
 7. ARSENIC, METALLIC

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8. ARSENIC, SOLID
9. ARSENIK
10. COLLOIDAL ARSENIC
11. GRAY ARSENIC
12. GREY ARSENIC
13. INORGANIC ARSENIC
14. METALLIC ARSENIC

1.3 IDENTIFIERS

1.3.1 CAS REGISTRY NUMBER

- A. 7440-38-2 (Arsenic, inorganic)

1.3.2 NIOSH/RTECS NUMBER

- A. CG0525000

1.3.3 UN/NA NUMBER

- A. 1558 - Arsenic
- B. 1562 - Arsenical dust

1.3.4 STCC NUMBER

- A. 4923207 (Arsenic, solid, metallic)

1.3.5 DESIGNATIONS

- A. STANDARD INDUSTRIAL TRADE CLASSIFICATION NUMBER: 52499

1.3.6 MOLECULAR FORMULA

- A. As

1.7 USES/FORMS/SOURCES

A. FORMS

1. Arsenic is a silver-gray or tin-white, shiny, brittle, crystalline and metallic-looking element. It can exist in three allotropic forms: yellow (alpha), black (beta), and gray (gamma) (HSDB , 2001).
2. Arsenic is rarely found in its isolated, elemental form. More commonly, it is present in mineral species, in alloys, or as an oxide or other compound form (Budavari, 2000).
3. The amorphous metalloid form (alpha-arsenic) will darken to black (beta-arsenic) and form arsenic trioxide (As₂O₃) in moist air. When arsenic vapor is cooled suddenly, a yellow type of arsenic which has no metallic properties is formed (ACGIH, 1996; (Budavari 2000) (Hathaway et al, 1996)(Lewis, 1996)(NIOSH , 2001).
4. Arsenic is available commercially in the following grades of purity: Technical, Crude (90-95%), Refined (99%) and Semiconductor (99.999%) (Lewis, 1997).

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B. SOURCES

1. Arsenic is thought to occur throughout the universe. It is the twentieth most common element in the earth's crust, having a concentration of 1.8 ppm (Baselt, 1997)(Bingham et al, 2001)(Budavari, 2000)(Zenz, 1994).
2. Workers in art glass manufacturing can be exposed to multiple chemicals including arsenic (Apostoli et al, 1998) and may have an increased risk of developing sinonasal cancer (Battista et al, 1996).
3. Since the EPA ban on the sale of sodium arsenic-containing ant poisons, the number of arsenate related poisoning calls has decreased in Michigan (Kuslikis et al, 1991). It is unlikely that arsenic based pesticides may still be available in stores, but older formulations could potentially still be found in the home.
 - a. Arsenic poisoning has been implicated in cases of suicide or homicide for many centuries. In Spain, a recent case of arsenic poisoning was reported by a woman attempting to kill her spouse by adding arsenic (ant-killer) to his food (Navarro et al, 1996).
4. Contaminated moonshine has been found to contain up to 415 mcg/L of arsenic (Gerhardt et al, 1980).
5. Seafood, especially shellfish, have significant arsenic concentrations (Buchet et al, 1994). Concentrations range from 2 mg/kg for freshwater fish up to 22 mg/kg for lobsters. Ingestion may result in urinary arsenic levels of 0.2 - 1.7 mg/L within 4 hours (Baselt, 2000). However, the pentavalent form found in fish and shellfish (arsenobetaine) is not thought to be associated with adverse health effects (Harbison, 1998).
6. There are multiple sources of arsenic on farms. Arsenic will remain in the ash of burned arsenic-containing materials such as arsenic-treated wood (Oehme, 1987).
7. Wells in Minnesota containing up to 21,000 ppb have caused severe arsenic poisoning (Feinglass, 1973).
8. A well drilled into old mine tailings in upstate New York yielded water with arsenic concentrations of 9000 to 10,900 mcg/L; two patients were seriously poisoned (Franzblau & Lilis, 1989).
9. Chromium-copper-arsenate (CCA) used as a wood preservative was claimed to cause arsenic poisoning in a family using CCA-impregnated wood as firewood (Peters et al, 1984). Woodshop and joinery workers handling CCA (chromium-copper-arsenic) treated wood may be exposed to arsenic through airborne dust (Jensen & Olsen, 1995)(Nygren et al, 1992).
10. Patients consuming opium for long periods of time have developed arsenic neuropathy. Arsenic content of the opium has been measured to be as high as 74.1 mcg/100 g (Datta, 1977). Arsenic levels in blood, urine, hair, and nails have been shown to be higher in opium eaters in India when compared to a control population (Narang et al, 1987).
11. Homeopathic medicines have been found to contain arsenic in the following concentrations (Kerr & Saryan, 1986):

ARSENIC IN HOMEOPATHIC PREPARATIONS		
Preparation	Calculated Arsenic*	Measured Arsenic
Alpha Homeopathic Remedy 38 (3x)	757 mcg/g	323 mcg/g, 286 mcg/g
Hyland's Homeopathic 555 (6x)	0.757 mcg/g	0.680 mcg/g
Hyland's Homeopathic Arsenicum Album (3x)	757 mcg/g	623 mcg/g, 650 mcg/g
Luyties Arsenicum Homeopathic (12x)	0.000757 mcg/g	0.005 mcg/g
Natra-Bio 519 Hay Fever (6x)	0.757 mcg/mL	0.024 mcg/mL
Pain Eased 21 Natural Homeopathic Formula		

(12x)	0.000757 mcg/mL	0.006 mcg/mL
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*Expected arsenic is calculated on the assumption that the homeopathic preparations contain the stated amount as arsenic trioxide (As₂O₃). (Elemental arsenic content of arsenic trioxide is 75.7%)

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12. Asian folk remedies have been reported to contain levels of arsenic that have resulted in arsenic poisoning with elevated arsenic levels of up to 3,334 mcg/24hr in Hmong Southeast Asian refugees (Hall & Harruff, 1989).
13. Folk remedies from China (various Chinese herbal balls) and India (chandraprabha, maya yograj guggul and others), have also been found to contain arsenic (Espinoza et al, 1995) (Kew et al, 1993)(Sheerin et al, 1994).
14. Wine produced from grapes grown in vineyards treated with an arsenical pesticide has been postulated to cause arsenic poisoning in at least one case (Houser & Vitek, 1979).
15. In Iran, an arsenic sulfide (AS₂S₃) compound with calcium oxide and starch is mixed with water to form calcium hydroxide, and then used as a depilatory (p 5).
16. Taxidermists may be exposed to preservatives which contain 3.7 to 5.4 percent arsenic (Jensen & Olsen, 1995).
17. The estimated end-use distribution of arsenic in 1990 was 70 percent in wood preservatives, 22 percent in agricultural chemicals (principally herbicides and desiccants), 4 percent in glass, 2 percent in nonferrous alloys, and 2 percent for other uses (NIH , 1996).
18. ENDEMIC HYDROARSENICISM - has been reported in Chile, Taiwan, Mexico, Argentina, Thailand and India following groundwater and drinking water contamination (Woollons & Russell-Jones, 1998)(Mazumder et al, 2001)(Rahman et al, 2001).

C. USES

1. Arsenic is used: in metallurgy for hardening copper, lead, and alloys; in the manufacture of certain types of glass; in pigment production; in pesticides (most often as arsenic trioxide), insecticides, fungicides, and rodenticides; in weed killer; in agriculture as a cotton desiccant; as a by-product in the smelting of copper ores; as a component of electrical devices and, as a dopant material in semiconductor manufacture (Bingham et al, 2001) (Budavari, 2000)(Hathaway et al, 1996)(HSDB , 2001)(Lewis, 1998)(Zenz, 1994).
2. Historically, arsenic was used in a tonic known as "Fowler's solution," to treat a variety of illnesses, such as leukemia and psoriasis (Bingham et al, 2001)(Harbison, 1998)(Zenz, 1994).
3. iT has also been used as a radioactive tracer (an artificial isotope, As) in toxicology (HSDB , 2001).

3.0 CLINICAL EFFECTS

3.1 SUMMARY OF EXPOSURE

3.1.1 ACUTE EXPOSURE

- A. Arsenic compounds are absorbed mainly through the GI tract, but may be absorbed through intact skin or after inhalation. Hypovolemia from capillary leakage ('third-spacing' of fluids) is a common, serious early effect.
- B. Acute arsenic ingestion generally produces signs and symptoms within 30 minutes, but this may be delayed in onset for several hours if arsenic is ingested with food.
 1. Initial signs and symptoms of arsenic ingestion include burning lips, throat constriction and dysphagia, followed by excruciating abdominal pain, hemorrhagic gastritis, gastroenteritis,

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- severe nausea, projectile vomiting, profuse "rice water-like" diarrhea, with hypovolemia that may result in hypotension and an irregular pulse.
2. Muscle cramps, facial edema, bronchitis, dyspnea, chest pain, dehydration, intense thirst, and fluid-electrolyte disturbances are also common following significant exposures. A garlic-like odor of the breath and feces may occur.
 3. DELAYED EFFECTS - After absorption, arsenic may cause multi-organ failure by inhibiting sulfhydryl-containing enzymes within cells.
 - a. Encephalopathy, with headache, lethargy, mental confusion, hallucinations, emotional lability, memory loss and delirium may occur; seizures, stupor, convulsions, coma, and death may follow within 24 hours of a severe acute exposure.
 - b. Dysrhythmias (particularly QTc prolongation and torsade de pointes), cardiomyopathy, ARDS, hepatitis, rhabdomyolysis, hemolysis, and renal failure may develop over several days. Peripheral polyneuropathy, bone marrow suppression, skin eruptions, depression of hematopoiesis, alopecia, and Mees' lines may develop days to weeks after acute exposure. Anemia, leukopenia and thrombocytopenia are among the hematological abnormalities resulting from exposure.
 - c. The delayed effects may lead to systemic collapse, with severe hypotension, restlessness, convulsions and coma.
- C. Many arsenic compounds are severe irritants of the skin, eye, and mucous membranes, especially of moist surfaces; some may be corrosive. Contact produces local hyperemia, followed by vesicular or pustular eruptions. Trivalent compounds are particularly caustic. Acute inhalation exposures have resulted in irritation of the upper respiratory tract.
- D. CHRONIC POISONING - Chronic inhalation of inorganic arsenic compounds is the most common cause of occupational poisoning.
1. The sequence of chronic poisoning involves weakness, anorexia, hepatomegaly, jaundice, and gastrointestinal complaints, followed by conjunctivitis, irritation of the throat and respiratory tract, hyperpigmentation, and eczematoid and allergic dermatitis.
 2. Other effects of chronic exposure include conjunctivitis with irritation and lacrimation; hair, skin and nail changes; hyperkeratosis of feet and hands; and melanosis, with pigment spots in corneal and conjunctival epithelium.
 3. Skin lesions are a common effect, starting as erythematous, pruritic dermatitis, followed by finely freckled hyperpigmentation with hypopigmented maculae. Melanosis also occurs. The skin lesions may sometimes be pustular, ulcerative, and gangrenous.
 4. A hoarse voice and chronic upper respiratory disease are characteristic in overexposed arsenic workers. A perforated nasal septum is a common result with prolonged inhalation of white arsenic dust or fume.
 5. Peripheral nervous system symptoms may include numbness, burning, and tingling of the hands and feet; pain; paresthesias; tenderness; muscle fasciculations; gross tremors; ataxia; incoordination; and mental confusion. Muscular weakness, limb tenderness and difficulty walking may follow. The final phase consists of peripheral sensory neuropathy of the hands and feet. That may be associated with a motor neuropathy as well.
- E. Certain arsenic compounds are known human carcinogens. Chronic exposure in either occupational settings or by drinking contaminated groundwater can cause poisoning and carries an increased risk of skin, lung, bladder, and possibly liver cancers.

3.3 VITAL SIGNS

3.3.2 TEMPERATURE

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- A. Loss of ability to regulate body temperature was described in a case of a 20-year-old man who remained in a persistent vegetative state after an acute sodium arsenite ingestion (Fincher & Koerker, 1987).
- B. Less acute arsenic toxicity may cause subnormal body temperatures (Hayes, 1982).

3.3.3 BLOOD PRESSURE

- A. HYPOTENSION - Patients may rapidly become hypotensive after acute arsenic poisoning from third spacing of fluids, diarrhea, or blood loss into the GI tract (Schoolmeester & White, 1980).

3.3.4 PULSE

- A. TACHYCARDIA - Patients may become tachycardic secondary to pain, hypovolemia or cardiac effects of arsenic (Shum et al, 1995).

3.4 HEENT

3.4.2 EYES

- A. Conjunctivitis, photophobia, dimness of vision, diplopia, lacrimation, and sometimes hyperemia, and chemosis may occur (Grant, 1993)(Heyman et al, 1956).

3.4.4 NOSE

- A. A sensation of burning, dryness and constriction of the oral and nasal cavities may occur.
- B. PERFORATION - Chronic exposure to trivalent arsenic compounds can cause perforation of the nasal septum (OSHA, 1988)(ACGIH, 1996a).
- C. Chronic laryngitis has been reported in India following widespread arsenic contamination in water (Rahman et al, 2001).

3.4.5 THROAT

- A. A garlic-like odor may be detected on the breath.

3.5 CARDIOVASCULAR

3.5.1 ACUTE EFFECTS

- A. CONDUCTION DISORDER OF THE HEART
 1. Ventricular tachycardia, ventricular bigeminy, and ventricular fibrillation have been described after acute arsenic ingestion (Peterson & Rumack, 1977)(Goldsmith, 1980)(St Petery et al, 1970)(Brayer et al, 1997).
 2. QRS morphology of the ventricular dysrhythmia is reported consistent with torsades de pointes in 3 cases (Beckman et al, 1991)(Goldsmith, 1980)(St Petery et al, 1970).
 3. BRADYCARDIA - A 28-year-old male developed bradycardia and then asystole 16 hours after ingestion of 75 grams of arsenic trioxide and a bottle of vodka (Jolliffe et al, 1991). No dysrhythmia occurred during the previous 12 hour observation period.

4. Abrupt respiratory failure and asystole developed in a 21-year-old man who ingested 4 grams of arsenic (Moore et al, 1994).

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B. ECG ABNORMAL

1. ECG changes have included QT prolongation, left axis deviations, peaked T waves, and also deeply inverted T waves (Gousios & Adelson, 1959)(Heyman et al, 1956).
2. CASE SERIES - Of 7 patients with relapsed acute promyelocytic leukemia treated with arsenic trioxide, three developed prolongation of the QTc after an average of 1 to 3 treatments (Huang et al, 1998).

C. ATRIOVENTRICULAR BLOCK

1. CASE REPORT - complete atrial-ventricular heart block requiring a permanent pacemaker was reported in a patient given arsenic trioxide in the treatment of acute promyelocytic leukemia (Huang et al, 1998). The patient died of idiopathic interstitial pneumonitis soon after the first course of therapy; elevated arsenic levels were found in the heart and lung tissue at necropsy.

D. VENTRICULAR TACHYCARDIA

1. CASE REPORT - Refractory ventricular tachycardia, which included torsades de pointes occurred in a 29-year-old male with acute promyelocytic leukemia treated with arsenic trioxide (Olmedo et al, 1999). The patient died within 24 hours after onset of the dysrhythmias with a postmortem blood arsenic level of 69 mcg/L. No alternative cause was found by the authors to explain the cardiac effects observed.

E. CARDIOMYOPATHY

1. Interstitial myocarditis resulting in fatal ventricular arrhythmias has been reported after chronic exposure to arsenic (Hall & Harruff, 1989).
2. Myocardial congestion was found at postmortem in a 28-year-old male who ingested 75 grams of arsenic trioxide and a bottle of vodka (Jolliffe et al, 1991). Coronary circulation appeared normal.

F. HYPOTENSIVE EPISODE

1. Hypotension may develop after acute ingestion from gastrointestinal fluid loss or myocardial depression (Moore et al, 1994).

G. HYPERTENSIVE EPISODE

1. A dose-related increased incidence of hypertension was found in a Taiwanese population with chronic arsenic exposure in drinking water (Chen et al, 1995).

3.6 RESPIRATORY

3.6.1 ACUTE EFFECTS

A. APNEA

1. ACUTE TOXICITY

a. CASE REPORTS

1. A 45-year-old female developed acute respiratory distress and multiorgan failure following an intentional ingestion of between 8 and 16 g of sodium arsenite. The patient gradually improved with dimercaprol therapy and supportive care; however, residual quadriplegia occurred (Bartolome et al,

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- 1999).
2. Acute respiratory failure presumably from severe weakness of respiratory muscles was reported in a patient with severe arsenic poisoning (Greenberg et al, 1979). The problem progressed despite dimercaprol therapy and required ventilatory assistance for one month.
3. Breathlessness was associated with asymmetric bilateral phrenic nerve involvement secondary to arsenic poisoning from contaminated opium in a 35-year-old opium addict (Bansal et al, 1991).
4. Abrupt respiratory failure and asystole developed in a 21-year-old man who ingested 4 grams of arsenic (Moore et al, 1994).

B. ACUTE LUNG INJURY

1. Pulmonary edema, either noncardiogenic from capillary leaking, or cardiogenic from myocardial depression, may occur and be life threatening.

C. PLEURAL EFFUSION

1. CASE SERIES - Pleural effusion occurred in 71% (5/7) of patients treated with arsenic trioxide for acute promyelocytic leukemia (Huang et al, 1998).

D. ACUTE LUNG INJURY

1. Adult respiratory distress syndrome (ARDS) has been reported (Zaloga et al, 1970) (Schoolmeester & White, 1980) Bollinger et al, 1992).

E. BRONCHITIS

1. Acute inhalation exposure may result in irritation of the upper respiratory tract (Hathaway et al, 1996)(ACGIH, 1996a).
2. Following chronic arsenic exposure (water contamination) asthmatic bronchitis (cough, expectoration, breathlessness, restrictive asthma) has been reported in India. The causality is not well-defined (Rahman et al, 2001).

3.7 NEUROLOGIC

3.7.1 ACUTE EFFECTS

A. COMA

1. A 3-year-old male developed vomiting within 30 minutes of ingesting 3 Python brand "snakes" (fireworks) which contained arsenic, and looked like candy. He became obtunded within one hour. Neurological exam was nonfocal, and pupils were 5 mm and reactive. Blood glucose was 125 mg/dL. The patient was provided supportive care and mentation began to clear within several hours. He returned to baseline within 10 hours of ingestion. No permanent sequelae was reported (Brayer et al, 1997).

B. TOXIC ENCEPHALOPATHY

1. Toxic delirium and encephalopathy are complications of significant acute (Jenkins, 1966) (Quatrehomme et al, 1992) and chronic (Freeman & Couch, 1978)(Morton & Caron, 1989) arsenic poisoning. The encephalopathy may be permanent and result in cortical atrophy one to six months after exposure (Fincher & Koerker, 1987).
2. PREVENTION - Early institution of chelation therapy may not be successful in preventing arsenic encephalopathy (Fincher & Koerker, 1987). However, BAL has been reported to reverse the encephalopathy seen after chronic arsenic exposure (Freeman & Couch, 1978)

(Beckett et al, 1986).

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C. NEUROPATHY

1. **ONSET** - Peripheral neuropathy is common after either acute or chronic arsenic poisoning (Guha Mazmuder et al, 1992; Nazmul, 2001). After acute exposure it usually begins one to 3 weeks later (Le Quesne & McLeod, 1977)(Heyman et al, 1956)(Goebel et al, 1990)(Hahn et al, 2000).
2. **INITIAL SIGNS** - It usually begins as paresthesias of the soles of the feet, then the hands, progressing proximally over the next few days (Heyman et al, 1956). Severe muscle weakness and wasting then develops, causing severe disability (Le Quesne & McLeod, 1977)(OSHA, 1988). In one case of arsenic poisoning from burning pressure-treated wood, symptoms were limited to bilateral pain and tingling of the feet along with difficulty sleeping and walking secondary to the pain in an 11-year-old male (Hahn et al, 2000).
3. **DIFFERENTIAL** - The syndrome may initially be confused with Guillain-Barre (Donofrio et al, 1987)(Gherardi et al, 1990). Facial nerves are commonly involved in Guillain-Barre and almost never affected in arsenic poisoning (Jenkins, 1966).
4. **PAIN** - The paresthesias may be painful and are frequently described as severe burning pain in a stocking and glove distribution.
5. **PHYSICAL FINDINGS** of arsenic neuropathy usually include prominently decreased sensation to touch, pinprick, and temperature, frequently in a stocking and glove distribution (Heyman et al, 1956)(Kelafant et al, 1993); loss of vibration sense is also common; profound muscle weakness and wasting, distal more so than proximal, is also seen (Donofrio et al, 1987)(Heyman et al, 1956)(Hahn et al, 2000); wrist drop, foot drop, and fasciculations may be seen (Heyman et al, 1956).
 - a. **GAIT** may be altered by toxicity resulting in high-stepping, ataxic, waddling, or hesitation due to hyperpathia following chronic exposure (Rahman et al, 2001).
6. **ELECTRODIAGNOSTIC STUDIES** of arsenic neuropathy have shown a reduction of motor conduction velocity and marked abnormalities of sensory nerve action potentials (Le Quesne & McLeod, 1977).
 - a. Oh (1991) studied 13 victims of arsenic toxicity with peripheral neuropathy. Sensory and mixed nerve conduction was abnormal in all cases. Twelve of 13 had absent sural nerve potentials; 11 of 13 had absent median and ulnar nerve potentials. One of the cases reported suffered a steady worsening of nerve conduction until, 6 weeks later, no motor or sensory response could be found in any of the tested nerves.
 - b. A study of 43 arsenic exposed smelter workers found a negative correlation between estimated cumulative arsenic exposure and nerve conduction velocity (NCV) (Lagerkvist & Zutterlund, 1994). Seven workers had NCVs below the normal range. Workers were not assessed clinically for evidence of neuropathy.
7. **NERVE BIOPSY** may demonstrate various stages of axonal degeneration without demyelination (Le Quesne & McLeod, 1977) or with demyelination (Donofrio et al, 1987).
8. **DIMERCAPROL (BAL)** does not seem to reverse arsenic neuropathy (Donofrio et al, 1987)(Heyman et al, 1956)(Le Quesne & McLeod, 1977); recovery is usually very slow and incomplete. It has been claimed that if BAL is administered within hours of ingestion, however, that neuropathy may be prevented (Jenkins, 1966), although this is not true for all cases (Marcus, 1987).
9. **CASE REPORT** - A 35-year-old male with acute arsenic neuropathy with asymmetric bilateral phrenic nerve involvement made a significant recovery with D-penicillamine (250 mg three times daily) therapy (Bansal et al, 1991).
10. **CASE REPORT** - A patient with chronic exposure to an arsenical pesticide presented with peripheral neuropathy and macrocytosis, but without anemia (Heaven et al, 1994).
11. **CASE SERIES** - In a large survey of arsenic poisoning from various water supplies in India,

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37.3% (n=154 cases, total 413 subjects) of individuals developed clinical neuropathies. In those cases, 80.5% (n=124 cases) had a sensory neuropathy and 30 cases had a motor component (Rahman et al, 2001).

D. CEREBROVASCULAR DISEASE

1. Amongst a Taiwanese population chronically exposed to high levels of arsenic in drinking water, there was an increased prevalence of cerebrovascular disease, particularly cerebral infarction (Chiou et al, 1997).

E. QUADRIPLÉGIA

1. **CASE REPORT** - A 45-year-old female intentionally ingested between 8 and 16 g of sodium arsenite and developed multiorgan failure (i.e., respiratory, renal, hepatic and hematologic), along with neurological deterioration. During the first hospital day the patient was treated with dimercaprol (300 mg three times daily and increased to 200 mg every 4 hours) and received supportive care. The patient gradually improved, but permanent quadriplegia occurred (Bartolome et al, 1999).

3.8 GASTROINTESTINAL

3.8.1 ACUTE EFFECTS

A. GASTROENTERITIS

1. Early symptoms within hours following significant exposure to arsenic include abdominal pain, vomiting, profuse bloody or watery diarrhea (sometimes described as "rice-water like") (Gilman et al, 1985)(Quatrehomme et al, 1992)(Moore et al, 1994)(Brayer et al, 1997)(Bartolome et al, 1999), pain in the extremities and muscles, weakness, and flushing of the skin. A sensation of burning and dryness of the oral and nasal cavities may occur.
2. Stool or emesis may have a garlic like odor (Lee et al, 1995).

3.9 HEPATIC

3.9.1 ACUTE EFFECTS

A. LIVER DAMAGE

1. ACUTE TOXICITY

- a. Hepatocellular injury may occur after acute arsenic poisoning but is not common (Donofrio et al, 1987)(ACGIH, 1991). Mitotic activity of hepatocytes may be a common postmortem finding of arsenic poisoning (Mackell et al, 1985).

1. **CASE REPORT** - A 45-year-old female developed toxic hepatitis with coagulopathy and multiorgan failure following an intentional ingestion of between 8 and 16 g of sodium arsenite. The patient gradually improved with dimercaprol therapy and supportive care; however, permanent neurological damage occurred (Bartolome et al, 1999).

2. CHRONIC TOXICITY

- a. Hepatocellular damage after chronic arsenic exposure may be more common than after acute; autopsy data from patients in India known to have liver disease demonstrated higher hepatic arsenic levels than controls (Narang, 1987a):

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3.13 HEMATOLOGIC

3.13.1 ACUTE EFFECTS

A. HEMOLYSIS

1. Acute hemolysis may occur after acute arsenic poisoning (Kyle & Pease, 1965), but probably not after chronic poisoning. It is usually Coomb's negative; abnormalities of developing normoblasts are also common (Ringenberg et al, 1988).

B. PANCYTOPENIA

1. Arsenic can disturb erythropoiesis and myelopoiesis (OSHA, 1988). After either acute or chronic arsenic exposure, pancytopenia may be seen (Rezuke et al, 1991)(Kyle & Pease, 1965)(Kjeldsberg & Ward, 1972)(Bartolome et al, 1999). However, isolated leukopenia or anemia may also be seen.
2. The anemia is usually normochromic, normocytic, but may be hypochromic, microcytic (Kyle & Pease, 1965).
3. Bone marrow aspirate may demonstrate pronounced erythroid hyperplasia similar to that seen with pernicious anemia (Selzer & Ancel, 1983).
4. Basophilic stippling and rouleau formation of red cells may also be seen (Kyle & Pease, 1965).

C. ACUTE LEUKEMIA

1. CHRONIC TOXICITY - Aplastic anemia and acute myelogenous leukemia have been described after chronic arsenic exposure (Kjeldsberg & Ward, 1972).

D. ANEMIA

1. ACUTE - Decreases in the hemoglobin and hematocrit values were the only sequelae possibly associated with an acute ingestion of approximately 1.2 grams arsenic as sodium arsenate in a 44-year-old female (Chan & Mathews, 1990).
2. CHRONIC - Anemia has also been reported after chronic arsenic exposure (Guha Mazumder et al, 1992)(Rahman et al, 2001).

E. MACROCYTOSIS

1. CASE REPORT - A patient presented with macrocytosis and peripheral neuropathy but without anemia after chronic exposure to an arsenical pesticide (Heaven et al, 1994).

3.13.3 ANIMAL STUDIES

A. ANIMAL STUDIES

1. LYMPHOCYTES ATYPICAL

- a. IN VITRO - Tests of human whole blood lymphocytes exposed to arsenite and arsenate in concentrations similar to those found in the blood of exposed humans, revealed a dose-related inhibition of proliferation (Gonsebatt et al, 1992).

3.14 DERMATOLOGIC

3.14.1 ACUTE EFFECTS

A. GENERALIZED EXFOLIATIVE DERMATITIS

1. Common skin findings after either acute or chronic arsenic poisoning may include flushing,

diaphoresis, diffuse pigmentation, hyperkeratosis of palms and/or soles, peripheral edema, hyperpigmentation, brawny desquamation (Heyman et al, 1956), and exfoliative dermatitis (Zaloga et al, 1970)(Schoolmeester & White, 1980)(Hutton & Christians, 1983)(Huang et al, 1998) Nazmul Ahasan, 2001).

- a. ACUTE - A 45-year-old female intentionally ingested between 8 and 16 g of sodium arsenite and developed multiorgan failure along with an erythroderma with vesicles and pustules. Skin biopsies showed multiple small pigment granules inside and outside the histiocytes. Prednisone was started on hospital day 12 with improvement of the cutaneous lesions. At two month follow-up, cutaneous lesions were absent (Bartolome et al, 1999).
 - b. CHRONIC - In one small study of individuals chronically exposed to well water which contained arsenic, the duration of skin lesions lasted from 2 to 8 years (Nazmul Ahasan, 2001).
2. ENDEMIC ARSENISM - Outbreaks of arsenic poisoning from water are common in the West Bengal and Bangladesh countries, it was found that clinical symptoms often did not manifest until 6 months to 10 years after exposure. The first signs and symptoms of chronic exposure were related to dermatologic changes. Arsenical skin lesions included the following: melanokeratosis, diffuse melanosis, spotted melanosis (raindrop pigmentation), leucomelanosis and keratosis. Minor dermatological changes included: buccal mucous membrane pigmentation, nonpitting edema, and red eyes (without signs or symptoms of inflammation) (Rahman et al, 2001).
 3. INCIDENCE - In a review of 648 cases of patients with cutaneous lesions, 17 (2.6%) had cutaneous lesions associated with long-term arsenic exposure. Of those patients, 15 patients (88%) had asthma, of whom 14 (93%) ingested Chinese proprietary medicines which contained inorganic arsenic and the remaining patients had a history of ingesting well water contaminated with arsenic (Wong et al, 1998).
 - a. Bowen's disease (precancerous dermatosis) and palmar arsenical keratoses were reported in all 17 patients, 14 (82%) had plantar arsenical keratoses, four (24%) had arsenical keratoses on the arms, and four (24%) had arsenical keratoses at other sites. Eleven patients had macular hypopigmentation; no patient developed hyperpigmentation.

B. NEOPLASM OF SKIN

1. Basal cell and squamous cell cancers of the skin may also be seen years after exposure (Renwick et al, 1981)(Jackson & Grainge, 1975)(Wagner et al, 1979)(Sass et al, 1993) Nazmul Ahasan, 2001). Merkel cell carcinoma has also been associated with chronic arsenism in a small number of patients (Lien et al, 1999).
 - a. LATENCY - The latency period is at least 10 years and the carcinomas usually occur on unexposed areas of the body (Parish & Burnett, 1987), and are usually multifocal and randomly distributed (Shannon & Strayer, 1989).
 1. In one study, the mean age at presentation of skin cancer was 63.6 years with a latency period of 40.6 years (Wong et al, 1998).

C. MEE'S LINE

1. Transverse white striae of the nails (Mees' lines) may be seen after acute or chronic exposure (Sass et al, 1993). Mees' lines commonly take 5 weeks to appear above the cuticle and advance 1 mm per week afterwards, allowing the approximation of the time of acute exposure (Heyman et al, 1956).

D. HERPES ZOSTER

1. Shingles have been reported following arsenic poisoning (Jenkins, 1966).

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1. SENSITIZATION - Arsenic trioxide and pentoxide can cause contact dermatitis (OSHA, 1988).
2. CASE REPORT - The organic arsenical pesticide cacodylic acid has caused airborne contact dermatitis (Bourrain et al, 1998).

F. ALOPECIA

1. ALOPECIA may occur.

G. STEVENS-JOHNSON SYNDROME

1. Stevens Johnson syndrome developed in a 42-year-old woman 4 days after the application of arsenic trioxide for devitalization of a gangrenous tooth pulp (Vassileva et al, 1990).

3.15 MUSCULOSKELETAL**3.15.1 ACUTE EFFECTS****A. RHABDOMYOLYSIS**

1. CASE REPORT - After ingestion of 20 g of arsenic trioxide, a 23-year-old man developed rhabdomyolysis and multi-organ failure and died 80 hours after ingestion (Sanz et al, 1989). Autopsy demonstrated loss of striation and centralization of the nuclei in pectoral muscles.
2. Fernandez-Sola et al (1991) found on muscle biopsy disruption of the normal oxidative intermyofibrillar network (involving type I fibers), perifascicular hypercontracted fibers, increased vacuolization in approximately 30% of fibers, abnormally enlarged mitochondria with loss of cristae, and abundant lipid vacuoles separating the myofibrils.
3. CASE REPORT - Mild rhabdomyolysis (CPK 1200 U/Liter) developed in a 21-year-old man who ingested 4 grams of arsenic (Moore et al, 1994).

B. MUSCLE PAIN

1. CHRONIC TOXICITY - Myalgia and myopathy have been reported following chronic exposure, and are considered rare events (Rahman et al, 2001).

3.16 ENDOCRINE**3.16.2 CHRONIC EFFECTS****A. DIABETES MELLITUS**

1. A dose-related increase in prevalence of diabetes mellitus has been seen in residents of areas where arsenism is hyperendemic and in workers exposed to arsenic at a copper smelter (Lai et al, 1994)(Rahman et al, 1998)(Rahman & Axelson, 1995).
2. However, there was no increased incidence of diabetes mellitus amongst Swedish art glass workers with chronic arsenic exposure (Rahman et al, 1996).

3.20 REPRODUCTIVE HAZARDS**3.20.1 TERATOGENICITY****A. LACK OF INFORMATION**

1. HUMANS - There is no evidence that adverse effects on human reproduction will occur at permissible exposure limits (Council on Scientific Affairs, 1985).

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B. CONGENITAL ANOMALY

1. ANIMAL STUDIES

- a. Arsenic (inorganic) is teratogenic in rodents at doses of 20 mg/kg or greater.
- b. In mice, the combination of maternal restraint stress and arsenic (in the form of sodium arsenate at 20 mg/kg IP on day 9) produced roughly twice the incidence of exencephaly than either agent alone (Rasco & Hood, 1994).
- c. There have been many studies on the reproductive effects of arsenic and its compounds in laboratory animals. Typically they can cause birth defects at high doses which may have been toxic to the mothers. Birth defects have been found in chickens (sodium ortho arsenate) (Ridgway & Karnofsky, 1952), in hamsters (disodium arsenate) (Ferm, 1971), in mice (sodium arsenate and sodium arsenite) (Baxley, 1981) (Hood & Bishop, 1972), and in rats (sodium arsenate) (Beaudoin, 1974).
- d. IP injection of 40 mg/kg arsenate on days 7 and 8 of gestation induced 90 to 100 percent neural tube defects in the susceptible strain LM Bc of mice. Analysis of gene expression showed increased transcription of bcl-2 and p53 on day 9, compared with controls. This result suggests that arsenic induces neural tube defects in mice via inhibition of cell proliferation, rather than by inducing apoptosis. Whether or not arsenic can induce neural tube defects in humans is controversial (Wlodarczyk et al, 1996).
- e. Generally the maximum activity for inducing birth defects in animals was at doses which were equally toxic to the mothers (OTA, 1985). Arsenite was more active than arsenate, but both were less active orally than when injected (OTA, 1985).
- f. The teratogenicity of arsenate was antagonized by sodium selenite in hamsters (Barlow & Sullivan, 1982), a finding consistent with the general antagonism between these two families of compounds. Heat was synergistic with arsenic in hamsters. Chelating agents which are known to remove arsenic from the body, such as BAL (2,3-dimercaptopropanol), reduced the teratogenicity of sodium arsenate in mice (Barlow & Sullivan, 1982).

2. HUMANS

- a. Birth defects of the cardiovascular system tended to be elevated in areas with high levels of arsenic in the drinking water, as determined in a survey of 30 US counties from 1968 to 1984 (Engel & Smith, 1994).
- b. From clinical experience there were five cases of arsenic poisoning during pregnancy which resulted in normal offspring (Kantor & Levin, 1948). Organic arsenicals have been used during pregnancy to treat congenital syphilis in the fetus with apparently no ill effect on the unborn (Barlow & Sullivan, 1982).
- c. A critical analysis of literature concluded that in environmentally relevant exposure scenarios (such as 100 ppm in soil), inorganic arsenic is unlikely to pose a risk to pregnant women and their offspring (DeSesso et al, 1998).

3.20.2 EFFECTS IN PREGNANCY

A. HUMANS

1. STILLBIRTH

- a. Acute ingestion of arsenic in a female with a 30-week pregnancy has been reported to result in the death of the infant born 4 days after the poisoning (Lugo et al, 1969). The child apparently died of hyaline membrane disease but did have elevated tissue levels of arsenic. It seems apparent that arsenic can cross the placenta.
- b. Associations between arsenic exposure in populations living near or working in smelters and an increased incidence of spontaneous abortions and stillbirths have been reported, but the studies are difficult to interpret because multiple chemical

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exposures were involved (Golub et al, 1998) Sholot et al, 1996).

- c. There was an increased incidence of stillbirths in an Hispanic population in central Texas where arsenical agricultural products had been produced for 60 years (Ihrig et al, 1998).
2. PREGNANCY DISORDER
 - a. Early chelation therapy is thought to have abrogated the toxic effect of an acute arsenic ingestion in a woman and her 20-week fetus (Daya et al, 1989).
 3. LABORATORY TEST ABNORMAL
 - a. In a study of women living near a copper smelter, placental arsenic levels increased with increasing arsenic levels in the environment (Tabacova et al, 1994). Higher levels of arsenic exposure were associated with a lower percentage of reduced compared with total glutathione levels in maternal and cord blood, suggesting reduced antioxidant protection.
 - b. A similar study did not find increased arsenic body burdens in pregnant Swedish women (Jakobsson-Lagerkvist et al, 1993).

3.20.3 EFFECTS DURING BREAST-FEEDING

A. BREAST MILK

1. HUMANS

- a. In a population of women living in an area of the Argentinean Andes where drinking water contains about 200 mcg/L of arsenic, the average breast milk arsenic concentration was 2.3 mcg/kg fresh weight (range: 0.83 to 7.6 mcg/kg). Urinary arsenic concentrations in 2 nursing infants were low (17 and 47 mcg/L), indicating that inorganic arsenic is not secreted to any significant extent in breast milk, as maternal blood and urine arsenic levels were 10 and 320 mcg/L, respectively (Concha et al, 1998).
- b. Arsenic is transferred across the placenta and into breast milk (Barlow & Sullivan, 1982). There may be some risk to nursing infants of mothers exposed to arsenic from evidence in Japanese children who drank arsenic-contaminated powdered milk and who may have suffered problems in later brain development (Barlow & Sullivan, 1982).

3.20.4 FEMALE REPRODUCTIVE HAZARDS

A. HUMANS

1. There is evidence that arsenic can have reproductive effects in both humans and animals. There were increased miscarriages and birth defects in employees and women living near a metal smelter in Sweden (Nordstrom, 1979), but in this study the exposures were mixed with other metals and toxic gases. Finnish women metal workers also experienced miscarriages (Hemminki, 1980), but again the exposures were mixed.
2. One review of the reproductive effects of arsenic has concluded that inorganic arsenic should be regarded as a probable human reproductive hazard (Shalat et al, 1996).

3.20.5 MALE REPRODUCTIVE HAZARDS

A. ANIMAL STUDIES

1. Potassium arsenate was not teratogenic in ewes at the relatively low dose of 0.5 mg/kg (James, 1966). There was no effect on fertility in a multi-generation study in mice at 0.025 to 215 mg/kg in the diet (Barlow & Sullivan, 1982), but sperm production and fertility were affected in mice and pigs (Barlow & Sullivan, 1982). Post-implantation losses were

increased in rats at 0.0025 mg/kg (sic) over 7 months (Barlow & Sullivan, 1982).

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3.21 CARCINOGENICITY

3.21.1 IARC CATEGORY

A. IARC Carcinogenicity Ratings for CAS7440-38-2 (IARC, 2003):

Listed As	Carcinogen Rating
Arsenic and arsenic compounds	1

1. 1: The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans. This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent (mixture) may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity.

3.21.2 SUMMARY/HUMAN STUDIES

- A. Chronic therapeutic, occupational, and environmental arsenic exposure have been associated with lung, bladder, skin, and other cancers in humans.
- B. Exposures as little as 1 gram per year have been associated with CANCER (HSDB).

3.21.4 HUMAN STUDIES

A. CARCINOMA

1. The Occupational Safety and Health Administration has linked arsenic to cancer of the skin, lungs, lymph glands, and bone marrow (Anon, 1979).
2. A study of a population in Taiwan with high-arsenic artesian well water found a dose-response relationship between the amount of arsenic in the water and the incidence of mortality from bladder, kidney, skin, prostate, lung, and liver cancer (Chen et al, 1988).
 - a. Another study found a dose response relationship between the amount of arsenic in well water and the mortality rate from kidney, bladder, liver and lung cancer (Chen et al, 1992).
 - b. Another study of populations in Taiwan exposed to high concentrations of arsenic in artesian well water found a dose response relationship between the estimated cumulative arsenic exposure and the incidence of lung and bladder cancers and of all cancers combined (Chiou et al, 1995). Patients with Blackfoot disease (dry gangrene postulated to be associated with chronic arsenic exposure) had an increased risk of cancer.
3. CASE REPORTS - Epithelioid angiosarcoma of the adrenal gland was described in a 59-year-old vineyard cultivator who was exposed to arsenic-containing insecticides for 20 years and in a 60-year-old man treated with potassium arsenite for psoriasis for 10 years (Livaditou et al, 1991) Duenas et al, 1988).
4. SINONASAL CANCER - Three cases of sinonasal cancer (adenocarcinoma, melanoma, squamocellular carcinoma) have been reported amongst arsenic-exposed art glass workers (Battista et al, 1996).

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5. An epidemiological study in Belgium of persons exposed to 0.3 nanograms/cubic meter of arsenic in air or 20 to 50 micrograms of arsenic per liter in drinking water did not find any increased cancer mortality, suggesting a non-linear dose-response relationship (Buchet & Lison, 1998).
 6. Arsenic is a known human carcinogen for lung and skin cancers (IARC, 1973)(Hathaway et al, 1991) and possibly for angiosarcoma of the liver and stomach cancer (EOSH, 1982). Typically there is a 15 to 30 year latency before development of the cancers (EOSH, 1982).
 7. The association between arsenic and respiratory cancer was stronger after adjusting in various ways for the healthy worker effect (Arrighi & Hertz-Picciotto, 1996).
 8. In a group of arsenic miners exposed to insoluble arsenic in the form of arsenopyrite, levels of arsenic in the lungs averaged 51.4 mcg/g dry tissue, and correlated with duration of exposure as well as incidence of lung cancer. Metabolites formed (arsenous acid, arsenic acid, methyl arsenate and dimethyl arsenate) were identical to those formed from arsenic trioxide. Arsenopyrite should therefore be considered a human carcinogen (Liu & Chen, 1996).
 9. Arsenic is one of the rare cases where the evidence in humans for its carcinogenic effects is much stronger than in animals. It has not produced cancer in animals except by implantation (RTECS). The role of ingested arsenic in cancers has been reviewed (Engel & Receveur, 1993).
 10. Critics have pointed out that both the Argentine and Taiwan studies show a dose-response relationship between inorganic arsenic exposure and mortality from bladder cancer, but neither study has sufficient data to allow specific risks to be related to specific exposures (Brown & Beck, 1996).
 11. The authors of the Taiwanese study have concluded that application of the cancer risk estimates from Taiwanese farmers may overestimate American risks from arsenic, because their diet of rice and yams contains high amounts of inorganic arsenic, and their daily intake of arsenic-contaminated water is higher than the US average (Slayton et al, 1996). Estimates of arsenic exposure and the role of arsenic methylation in cancer risk estimates from the Taiwanese study are controversial (Mushak & Crocetti, 1996).
 12. Arsenic is an INDIRECT CARCINOGEN. It induces cancer by a mechanism of generalized induction of genes (Appel et al, 1984), rather than inducing mutations in specific genes. The question of whether or not there is a threshold for induction of cancer by arsenic has been a matter of much debate. A recent review of the literature has concluded that the threshold for arsenic-induced cancer is the same as that for arsenical skin disease: 400 mcg per day; a further conclusion is that the development of hyperpigmentation may be a sensitive indicator of risk for subsequent development of cancer in the same individual (Stohrer, 1991).

B. SKIN CARCINOMA

1. Basal cell and squamous cell carcinomas of the skin have been described after both acute (Renwick et al, 1981) and chronic (Jackson & Grainge, 1975)(Wagner et al, 1979) Nazmul Ahasan, 2001) arsenic exposure.
 - a. CASE SERIES - In a review of 648 patients with cutaneous lesions associated with long-term arsenic exposure, 7 patients developed squamous cell carcinoma (SCC). One patient had a history of carcinoma of the larynx before skin lesions appeared. The authors observed the following risk factors: ingestion of arsenic at an older age and were more likely to have palmar arsenical keratoses compared with those without SCC (Wong et al, 1998).
2. Two patients with arsenic-induced basal cell carcinomas of the skin also developed malignancies of other organs (breast and colon) (Jackson & Grainge, 1975).
3. In a small study of patients who developed Merkel cell carcinoma an association with

chronic arsenism was observed (Lien et al, 1999).

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C. BLADDER CARCINOMA

1. In a cohort study of 478 patients treated with Fowler's solution (potassium arsenite) during the period 1945-1969, a significant excess of bladder cancer mortality occurred. It has been suggested that persons who have ingested arsenic may be at risk of developing bladder cancer and may be suitable for regular screening, especially if signs of arsenic exposure, such as palmar keratoses, are present (Cuzick et al, 1992).
2. An historical cohort study of a Japanese population that consumed well water with high arsenic concentrations (>1 ppm) for five years found an excess mortality from kidney and bladder cancer (standardized mortality ratio 31.2) (Tsuda et al, 1995).
3. A marked increased incidence of bladder cancer was found in a population in northern Chile chronically exposed by drinking groundwater with high arsenic levels (Smith et al, 1998).
4. A Taiwanese population exposed to high levels of arsenic in drinking water had an increased incidence of bladder, kidney, ureter, and urethral cancers, although there was no increased incidence of some specific types (i.e., nephroblastomas, renal cell carcinomas, or bladder adenocarcinomas) (Guo et al, 1997).
5. An Argentinean population with chronic arsenic exposure in drinking water had a dose-related increased incidence of bladder cancer (Hopenhayn-Rich et al, 1996).

D. PULMONARY CARCINOMA

1. Analysis of worker exposure to arsenic and the incidence of lung cancer has yielded conflicting results. In Sweden and China, a positive dose-response relationship has been found (Jarup & Pershagen, 1991)(Jarup et al, 1989)(Weiai, 1988) Liu & Chan, 1996); this has not confirmed in one study (Sobel et al, 1988), but was in agreement with two others (Enterline et al, 1987)(Lee-Feldstein, 1989).
2. The histologic types of lung cancer among smelter workers developing lung cancer does not appear to be different from that seen in smokers, even among workers who have never smoked (Pershagen et al, 1987). The incidence of lung cancer among women residing near a smelter was not different than for controls (Frost et al, 1987).
3. Jarup & Pershagen (1991) reported lung cancer risks were positively related to cumulative arsenic exposure after control of smoking in a case-control study of 3,916 Swedish copper smelter workers. An updated study of 2802 copper smelter workers found a positive relationship between airborne exposures and cancers of the respiratory tract, bone, and kidney (Enterline et al, 1995).
4. An historical cohort study of a Japanese population that consumed well water with high arsenic concentrations (greater than 1 ppm) for five years found an excess mortality from lung cancer (standardized mortality ratio 15.7) and a synergistic effect from smoking (Tsuda et al, 1995). Bronchogenic carcinoma (one case) was also diagnosed in a study of individuals (n=11) exposed to well water in India which contained arsenic (Nazmul Ahasan, 2001).
5. A study of French workers in gold mines and refineries exposed to arsenic, radon and silica found an excess mortality from lung cancer (Simonato et al, 1994).
6. A marked increased incidence of lung cancer was found in a population in northern Chile chronically exposed to arsenic in drinking water (Smith et al, 1998).
7. There seems to be a synergistic effect between occupational exposure to airborne arsenic and smoking (Hertz-Piccioto et al, 1992; (Tsuda et al, 1995) Japup & Pershagen, 1991).

3.22 GENOTOXICITY

3.22.1 SUMMARY

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- A. Arsenic induced DNA damage in human cells.
- B. Conflicting genetic effects have been found for arsenicals. Chromosome aberrations were elevated in the white blood cells of persons exposed to arsenic and possibly other substances (Nordenson, 1978) Burgdorf et al, 1977), but sister chromatid exchanges were not (Friberg et al, 1986). Sodium arsenite did induce sister chromatid exchanges in vitro, however (Friberg et al, 1986).

3.22.2 DNA DAMAGE/REPAIR

- A. When tested in an A(L) cell assay, arsenite causes both intragenic and multilocus mutations, at least partly through generation of reactive oxygen species (Hei et al, 1998).
- B. Arsenic (in the form of sodium arsenite) has been shown to induce DNA-protein cross-links at low concentrations (1 to 5 mcM) in cultured human fetal lung fibroblasts. DNA strand breaks were associated with these DNA-protein cross-links. DNA-protein cross-links may be part of the mechanism of arsenic-induced chromosome aberrations, sister chromatid exchanges, and carcinogenesis (Dong & Luo, 1993).
- C. Arsenic (as sodium arsenite at concentrations up to 10 mcM) induced unscheduled DNA synthesis in cultured human fetal lung cells, a result consistent with the above finding (Dong & Luo, 1994). Trivalent and pentavalent arsenic compounds stimulated DNA synthesis in human lymphocytes at low concentrations, but inhibited it at high ones (Meng, 1993).
- D. Sodium arsenite was also shown to enhance the DNA damage induced by methyl methanesulfonate in Chinese hamster ovary cells, by increasing the number of alkali-labile sites in the DNA (Leechen et al, 1993). This finding is consistent with the work of Dong et al (1993), in that these alkali-labile sites in DNA may be related to DNA-protein cross-links induced by arsenic.
- E. Arsenic was not mutagenic in Salmonella, E. coli, or hamster cells (Friberg et al, 1986) but was positive in the rec assay in B. subtilis (a test for inhibition of DNA repair) (Friberg et al, 1986). It did not induce dominant lethal mutations in male mice (OTA, 1985) but did transform hamster embryo cells into cancer cells in culture (Friberg et al, 1986).

3.22.3 MUTAGENICITY

- A. MICRONUCLEI - Elevated in exfoliated bladder cells from persons living in areas of endemic arsenism, compared with a control group with low arsenic exposure. This result is consistent with reported increased risk for bladder cancer with arsenic in the drinking water (Smith et al, 1994).
- B. Trivalent arsenic causes significant increases in micronuclei in human lymphocytes in vitro (Schaumloffel & Gebel, 1998).
- C. Micronuclei were elevated in exfoliated bladder, but not buccal, cells from persons living in areas with high levels of arsenic in well water (average 1312 mcg/L), compared with a control group with low levels of well-water arsenic (average 16 mcg/L). This result is consistent with the genotoxic effect of arsenic on bladder cells (Smith et al, 1994). Frequencies of micronuclei were elevated in exfoliated bladder cells from persons exposed to arsenic in the drinking water; the levels of micronuclei were positively correlated with levels of urinary arsenic and its metabolites (Moore et al, 1996).

- D. Excessive endoreduplication was seen in Chinese hamster ovary cells cultured in trivalent arsenic, but not with pentavalent arsenic (Kochhar et al, 1996).

3.22.4 CHROMOSOME ABERRATIONS

- A. SISTER CHROMATID EXCHANGES - Significantly elevated in lymphocytes of persons who had consumed drinking water containing greater than 0.13 ppm arsenic; mean SCE's 10.46/cell in 282 exposed persons, 7.49/cell in 155 controls, with dose responses to levels of arsenic in both drinking water and urine (Lerda, 1994). Chinese hamster ovary cells had an increase in chromosomal aberrations when exposed to trivalent arsenic in vitro; therefore, trivalent arsenic compounds should be considered more potent genotoxicants than pentavalent arsenic compounds (Kochhar et al, 1996).
- B. Arsenic (in the form of arsenite) increased chromosome aberrations, but not sister chromatid exchanges, induced by 1,3-butadiene diepoxide (Yager & Wiencke, 1993).
- C. A variety of arsenic compounds can induce chromosomal aberrations (particularly chromatid gaps and breaks) in cultured human fibroblasts (Oya-Ohta et al, 1996).
- D. In one study on persons exposed to arsenic in the drinking water, urine from highly-exposed individuals was not positive in the B. subtilis rec assay, nor were sister chromatid exchanges elevated. Complex chromosome aberrations and HGPRTase mutations were higher in a highly-exposed group compared with a low-exposed group, but these differences were not statistically significant (Ostrosky-Wegman et al, 1991). Frequencies of sister-chromatid exchanges did not differ between arsenic-exposed persons and healthy controls, but they were more inducible by mitomycin C (Liou et al, 1996).
- E. Increases in sister chromatid exchanges were not seen in peripheral lymphocytes of persons after ingesting arsenic, except at the highest dose of 20 grams (in the form of arsenic trioxide) (Hantson et al, 1996).
- F. Of various arsenicals tested, the rank order for inducing chromosome aberrations in cultured human fibroblasts was arsenite > arsenate > dimethylarsinic acid > methylarsonic acid > trimethylarsine oxide. Glutathione protected against damage by arsenite, arsenate and methylarsonic acid (Oya-Ohta et al, 1996).
- G. Micronuclei and trisomies were increased in lymphocytes from native Argentine women and children exposed to arsenic in the drinking water, compared with an ethnically similar group not exposed. Sister chromatid exchanges, translocations and cell cycle progression were not affected (Dulout et al, 1996).

3.23 OTHER

3.23.1 ACUTE EFFECTS

- A. CLINICAL FINDING
1. ARSENIC-CONTAINING DEPILATORY - Effects of ingestion are a combination of the effects of calcium hydroxide and arsenic. This depilatory formulation is not commercially available in the US.

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B. OCCUPATIONAL INJURY

1. The usual effects on workers are local, on skin and mucous membranes, etc. A hoarse voice is characteristic of an arsenic worker, and a perforated nasal septum and upper respiratory tract diseases are common results of prolonged inhalation of white arsenic dust or fume. A few documented cases of cirrhosis of the liver due to occupational exposure to arsenic have been recorded (ACGIH, 1996a).

C. AT RISK - FINDING

1. Populations at special risk to exposure to arsenic include individuals with diseases of skin, blood, liver, kidneys, and/or the central nervous system; children; persons with existing diabetes or cardiovascular diseases (HSDB, 1999).
2. ENDEMIC ARSENISM AND FLUOROSIS - A population in China chronically exposed to elevated levels of arsenic and fluorine via well water developed a syndrome characterized by arthralgia, dizziness, paroxysmal paresthesias, fatigue, cold extremities, and itching (Huang et al, 1992). Physical findings included Raynaud's phenomenon, peripheral neuritis, keratosis, abnormal skin pigmentation, basal cell carcinomas and dental fluorosis.
 - a. Groundwater arsenic contamination and endemic poisoning have been reported in multiple Asian countries (i.e., Vietnam, Cambodia, Lao People's Democratic Republic, Pakistan, Myanmar, and Nepal) (Rahman et al, 2001).
3. Major outbreaks have also occurred in Bangladesh and West Bengal, India. It is considered the most severely affected area for arsenic exposure, with approximately 12,195 patients having arsenical skin lesions. Symptoms were found to develop insidiously after 6 months to 2 years and related to the amount of arsenic ingested, the concentration of arsenic in the water and nutritional status. Melanosis (darkening of the skin) of the body or just the palms or spotted pigmentation (spotted melanosis) were common early symptoms (Rahman et al, 2001).
4. ENVIRONMENTAL RISK- Arsenic contamination has been found in soils in residential and public areas at levels greatly exceeding limits expected at waste sites. These elevated arsenic levels at an industrial or hazardous waste site would normally result in regulatory clean-up actions. Pesticides, chromated copper arsenic (CCA)-treated woods, waste recycling and air emissions are sources of this contamination. Belluck et al questioned if this soil contamination is posing a significant health risk to the general population and if there is an emerging regulatory health crisis.
 - a. A literature review and survey of government health and environmental protection departments was performed, looking for cases of morbidity and mortality from elevated arsenic levels in soils. No verifiable cases of human morbidity and mortality were found. The authors suggest that this is a significant emerging health crisis that is undefined, largely due to inadequate government and private party attention (Belluck et al, 2003).

4.0 MEDICAL SURVEILLANCE/LABORATORY

4.1 MONITORING PARAMETERS/LEVELS

4.1.1 SUMMARY

- A. Monitor CBC, serum electrolytes, urinalysis, spot urine arsenic, a 24 hour urinary arsenic collection, liver and renal function tests, and a blood arsenic level in symptomatic patients. A 24 hour urinary arsenic collection exceeding 100 mcg is usually abnormal, even after chelation.

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- B. Obtain an ECG and institute continuous cardiac monitoring in symptomatic patients.
- C. An abdominal x-ray should be obtained in all patients who are suspected of having ingested arsenic because it is radiopaque. Obtain a chest radiograph in patients with severe poisoning or pulmonary effects.
- D. Initial and periodic biological monitoring and medical surveillance are required for employees exposed to arsenic.

4.1.2 SERUM/BLOOD

A. ACUTE TOXICITY

1. A blood level of arsenic less than 7 mcg/100 mL (70 mcg/L) is considered in the normal range. Blood levels are highly variable and may be useful only after acute exposure to confirm diagnosis (Fesmire et al, 1988).
2. HEMODIALYSIS PATIENTS - were found to have highly elevated arsenic levels in serum and packed cells compared with age-matched historical controls: mean levels were 11.5 ng As/mL versus 0.38 ng/ml for serum and 9.5 ng As/g versus 3.17 ng/g for packed cells (DeKimpe et al, 1993).

B. HEMATOLOGY

1. CHRONIC TOXICITY - The following findings were reported following chronic arsenic exposure: leucocytosis followed by leucopenia with depressed neutrophils; thrombocytopenia; rapidly decreasing hemoglobin indicating hemolytic anemia or GI bleed; aplastic anemia; basophilic stippling of erythrocytes; macrocytosis. Also, a reduction in hemoglobin concentration, reduction in total cell counts, and a rise of mean corpuscular volume (MCV) and hemoglobin mass (MCH), indicating an alteration of heme biosynthetic pathways were present (Rahman et al, 2001).

C. BIOCHEMISTRY

1. CHRONIC TOXICITY - Monitor hepatic and renal function. Elevated serum creatinine transaminases and bilirubin, and depressed haptoglobin levels have been reported following chronic arsenic exposure. Liver histology has shown cirrhosis and noncirrhotic portal fibrosis (Rahman et al, 2001).

D. OTHER

1. CHRONIC TOXICITY - Obtain a skin biopsy as indicated. Carcinomatous changes or Bowen's disease have been described following chronic arsenic exposure (Rahman et al, 2001).

4.1.3 URINE

A. URINARY LEVELS

1. 24-Hour Levels - Even with chelation an unexposed individual should not have more than 100 mcg per 24-hour total urine output.
 - a. Concentrations of arsenic in 24-hour urine in a male agricultural worker exposed to arsenic from the immersion of his foot in a storage container of concentrated arsenic acid ranged from a high of 2,500 mcg to a low of 160 mcg (McWilliams, 1989).
2. SEAFOOD - Urinary arsenic may be elevated up to 0.2 to 1.7 mg/L within 4 hours after eating some seafoods containing organoarsenical compounds (Baselt, 1997).

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- a. Mussels gave significant elevations of urinary monomethyl- and dimethylarsonic acid, while ray, cod, and plaice did not (Buchet et al, 1994).
3. VARIATION - In Michigan from 1985 to 1991, 7% of arsenic poisoned patients had some visible signs of arsenic poisoning. Sampled urine arsenic levels ranged from below detection to 198,000 mcg/L, with 36% having greater than 200 mcg/L (Kuslikis et al, 1991).
4. PORPHYRIN EXCRETION - Garcia-Vargas et al (1991) reported that no increase in urinary porphyrin excretion was found in a chronically arsenic exposed human population; however, the coproporphyrin/uroporphyrin ratio was observed to be reversed in most exposed individuals due to both an increase in uroporphyrin excretion and a decrease in coproporphyrin excretion.
 - a. In a study of patients exposed to arsenic in drinking water (0.4 milligrams/liter), reduced coproporphyrin III excretion and increased uroporphyrin excretion were found as compared with subjects whose drinking water contained 0.020 milligrams/liter of arsenic (Garcia-Vargas et al, 1994).
5. A study by the Nofer Institute of Occupational Medicine in Lodz, Poland assessed the relationship between inhalation exposure and urinary excretion of total inorganic arsenic in copper smelting workers. According to the findings, daily exposure to arsenic concentrations of 10 mcg/m³ and 50 mcg/m³ led to concentrations of inorganic arsenic metabolites of about 30 mcg/L and 70 mcg/L, respectively (International Archives of Occupational and Environmental Health, 1998).
6. CHRONIC TOXICITY - proteinuria, hematuria and pyuria have been reported following chronic arsenic exposure (Rahman et al, 2001).

4.1.4 BIOLOGICAL MONITORING

A. ACGIH BEI Values for CAS7440-38-2 (ACGIH, 2003):

Chemical Name	Status	Determinant	Sampling Time	BEI	Notation (s)	Notes
Arsenic, elemental and soluble inorganic compounds	Adopted Value	Inorganic arsenic plus methylated metabolites in urine	End of workweek	35 mcg As/L	B	Not Listed

1. Editor's Note: The listed values are recommendations or guidelines developed by ACGIH (R) to assist in the control of health hazards. They should only be used, interpreted and applied by individuals trained in industrial hygiene. Before applying these values, it is imperative to read the introduction to each section in the current TLVs(R) and BEI(R) Book and become familiar with the constraints and limitations to their use. Always consult the Documentation of the TLVs(R) and BEIs(R) before applying these recommendations and guidelines.
2. Notation:
 - a. B: Background. This determinant may be present in biological specimens collected from subjects who have not been occupationally exposed, at a concentration which could affect interpretation of the result. Such background concentrations are incorporated in the BEI value.

4.1.5 OTHER

A. OTHER

1. HAIR

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- a. HAIR/NAIL - Arsenic has been demonstrated in hair and nails within hours after exposure (Lander et al, 1965).
 - b. Normal concentration of arsenic in hair and nails is less than 1 mg/kg (Baselt, 1997).
 - c. Many commercial laboratories performing hair analyses for consumers have not been shown to yield consistent and reliable results (Barrett, 1985).
 - d. If hair is sent for arsenic quantitation, pubic hair instead of scalp hair should be sent because of the possibility of scalp hair being contaminated with arsenic from the environment (Jenkins, 1966).
 - e. A comparison of the mean air arsenic concentrations of each occupational exposure group with corresponding arsenic levels in fingernails was highly correlated (Agahian et al, 1990).
 - f. In a Finnish population, hair arsenic content correlated well with chronic or past exposure to arsenic in drinking water. Hair arsenic concentration increased 0.1 mg/kg for each increase of 10 mcg/L of arsenic in drinking water or 10 to 20 mcg/day of arsenic intake (Kurtio et al. 1998).
2. EXFOLIATED BLADDER CELLS
- a. Persons exposed to high levels of arsenic in drinking water had a significantly increased presence of micronuclei in exfoliated bladder cells, even when exposures were near the USA Maximum Contaminant Level (MCL) of 50 mcg of arsenic per liter of water (or 100 mcg in a 24-hour urine) (Moore et al, 1997)(Rahman et al, 2001).
3. OTHER
- a. CHRONIC TOXICITY - Other diagnostic studies which may be beneficial (based on a patient's clinical presentation) include: ultrasonography of the abdomen, upper gastrointestinal endoscopy, lung function tests, nerve conduction studies (Rahman et al, 2001).

4.2 RADIOGRAPHIC STUDIES

A. ABDOMINAL RADIOGRAPH

1. Arsenic is radiopaque and an abdominal film should be obtained whenever arsenic ingestion is suspected (Hilfer & Mendel, 1962)(Gousios & Adelson, 1959)(Lee et al, 1995).

4.3 METHODS

A. OTHER

1. Quantitative 24-hour urine collections are the most reliable laboratory measure of arsenic poisoning.
2. Blood arsenic or spot urine arsenic levels have not correlated with chronic occupational exposure to cacodylic acid (dimethylarsenic acid) among forestry workers (Wagner & Weswig, 1974).
3. A method for a quick spot test of the urine (Reinsch test) has been described (Grande et al, 1987) but its clinical utility is uncertain.
4. Farmer & Johnson (1990) report a method of analyzing inorganic arsenic based on urinary concentration and speciation of arsenic. This technique can distinguish between occupational exposure to inorganic arsenic and dietary exposure to inert organoarsenicals in seafood.
5. Arsenic can be measured in human urine by an inductively coupled plasma mass spectrometry (ICP-MS) method (Amarasiriwardena et al, 1998).
6. A short-column liquid chromatography with hydride generation atomic fluorescence detection method can measure and speciate nanogram/mL quantities of arsenite, arsenate,

monomethylarsonic acid, and dimethylarsinic acid within 3 minutes (Le & Ma, 1998).

7. Arsenic can be speciated into inorganic arsenic, monomethylarsonate, and dimethylarsenate in human urine with an hydride cold-trapping technique (Ng et al, 1998).

5.0 CASE REPORTS

A. ROUTE OF EXPOSURE

1. **INGESTION** - Marcus (1987) reported the case of a 16-year-old patient who ingested 2 ounces of technical grade arsenic trioxide in a suicide attempt that demonstrates that early chelation may not always prevent development of peripheral neuropathy.
 - a. Vomiting, diarrhea, and abdominal pain occurred about 6 hours after ingestion and prompted emergency department evaluation where ipecac and activated charcoal were given. Tachycardia and hypotension developed which responded to fluid administration.
 - b. Chelation with BAL at 4 milligrams per kilogram every 4 hours was started immediately and continued until gastrointestinal symptoms were subsiding. The patient then received oral D-penicillamine at 30 milligrams per kilogram per day.
 - c. Although blood arsenic levels rapidly decreased, urine arsenic levels only gradually fell from 50,000 micrograms per day to 20 micrograms per day over a 31 day period. Elevated liver enzyme levels were found beginning on the third day after exposure. Hypoesthesias of the legs and bilateral foot drop developed with an onset two weeks after hospitalization, and significant residual muscular weakness in both lower extremities persisted one year later.
2. **INGESTION** - A 30-year-old male survived an ingestion of 6 ounces of a rodenticide containing 1.5 percent arsenous oxide (equivalent to 2,150 mg metallic arsenic) with aggressive fluid resuscitation, chelation therapy, and hemodialysis (instituted prior to evidence of renal insufficiency) (Fesmire et al, 1988).
3. **INGESTION** - A 22-year-old woman in the 20th week of pregnancy ingested 340 mg of arsenic in a suicide attempt. She presented to the emergency room 2 hours post-ingestion and had vomited once. Treatment included ipecac, activated charcoal, cathartic, and chelation therapy with dimercaprol (BAL; 150 mg). Chelation therapy continued and was reduced slowly as the 24-hour urinary arsenic level fell from an initial 3030 mcg/L to less than 200 mcg/L. No clinical signs of neurological, gastrointestinal, or renal toxicity were observed and the remainder of the pregnancy was normal. The patient, with a 24-hour arsenic level of less than 50 mcg/L, delivered a normal baby (Daya et al, 1989).
4. **INGESTION** - A 2-year-old female ingested 1 oz of 2.27 percent sodium arsenate with almost immediate onset of diarrhea and vomiting. The patient was lavaged. She was pale and lethargic and continued to have GI symptoms. Sinus tachycardia was noted with heart rate up to 200. She received 2 mg/kg BAL. In 12 hours she was asymptomatic and was started on oral d-penicillamine. She was discharged on day 6 and continued d-penicillamine as an outpatient. Baseline urine arsenic level was 4880 mcg/L on day one.
 - a. Patient was re-admitted on day 9 with a urine arsenic level of 650 mcg/L and a rash. D-penicillamine was discontinued and DMSA therapy was initiated. After 4 more days her urine arsenic level had dropped to 96 mcg/L. Excretion half-life was 2.5 days. DMSA may be preferred therapy over d-penicillamine due to its efficacy and lower adverse events profile (Wolf et al, 1993).
5. **INGESTION** - A 30-year-old male and 39-year-old female who was 28 weeks pregnant ingested chocolate contaminated with arsenic trioxide. Both patients presented to the emergency room with severe abdominal cramps, nausea and vomiting, diarrhea, hypotension, and increased pulse rate. Both patients were diagnosed with staphylococcal food poisoning, treated with hydration and released the following day asymptomatic.

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- a. On day 3 both patients were readmitted with abdominal pain, hypersalivation, heartburn, and hematemesis. On day 5 both patients exhibited signs of early peripheral neuropathy, a paralytic ileus, and generalized edema. A chest roentgenogram revealed bilateral pleural effusions. Muscle weakness increased by day 6, as well as confusion and hallucinations. On day 5 fetal death was confirmed. On day 7 sinus tachycardia and a diffuse maculopapular rash was noted. On day 8 arsenic poisoning was confirmed through toxicological examination of the chocolate and BAL, 3 mg/kg/4 hr, was begun. Also on day 8 both patients became tachypneic with development of ARDS. The patients were intubated. Other laboratory results revealed liver involvement with abnormal liver function tests, renal involvement, and bone marrow suppression.
 - b. Three weeks following hospital admission, the liver, renal, and hematological functions returned to normal. All toxic effects disappeared by the end of week 3 except the severe polyneuropathy which improved over the next 2 years (Bolliger et al, 1992).
6. INHALATION/INGESTION - A Swedish worker at a copper smeltry was buried in arsenic trioxide. The filter mask he was wearing became clogged so he removed it. He was promptly rescued by a coworker. In the rescue process he had inhaled and swallowed arsenic dust. He arrived at a local hospital within 40 minutes of the incident and was vomiting, coughing, and dyspneic. Decontamination of the GI tract included lavage and administration of activated charcoal. Intravenous betamethasone was given to prevent airway obstruction. Within 3 hours of admission he also received promethazine 50 mg IM, doxycycline 200 mg IV, BAL 300 mg IM, and 2,3-dimercapto-1-propanol. He deteriorated quickly despite symptomatic and supportive care. He died 6 hours after the incident (Gerhardsson et al, 1988). The authors did not report how the worker was decontaminated at the incident site.
 7. ROUTE OTHER (PERCUTANEOUS ABSORPTION) - McWilliams (1989) reported the case of acute arsenic poisoning in a 23-year-old male agricultural worker whose foot was accidentally immersed in concentrated arsenic acid. He continued to be in direct contact with the saturated clothing for 8 hours. The patient incurred 2nd to 3rd degree burns. Dense white lines in the subcutaneous tissue, thought to be metallic arsenic, were observed through x-ray. 24-hour urine levels ranged from 2500 mg to 160 mg over the 8 weeks following exposure. Acute encephalopathy was present at 5 days, and at 21 days after exposure a painful motor neuropathy developed. Dimercaprol (BAL) was administered once followed by penicillamine treatment for 2 months. Recovery was hampered by drug abuse.

6.0 TREATMENT

6.1 LIFE SUPPORT

- A. Support respiratory and cardiovascular function.

6.4 MONITORING

- A. Monitor CBC, serum electrolytes, urinalysis, spot urine arsenic, a 24 hour urinary arsenic collection, liver and renal function tests, and a blood arsenic level in symptomatic patients. A 24 hour urinary arsenic collection exceeding 100 mcg is usually abnormal, even after chelation.
- B. Obtain an ECG and institute continuous cardiac monitoring in symptomatic patients.

- C. An abdominal x-ray should be obtained in all patients who are suspected of having ingested arsenic because it is radiopaque. Obtain a chest radiograph in patients with severe poisoning or pulmonary effects.
- D. Initial and periodic biological monitoring and medical surveillance are required for employees exposed to arsenic.

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6.8 ORAL/PARENTERAL EXPOSURE

6.8.1 PREVENTION OF ABSORPTION/PREHOSPITAL

A. EMESIS

1. INDICATIONS/CAUTIONS

- The decision to induce or not to induce emesis is often controversial, is not automatic, and must be carefully considered. Ipecac administration has never been shown to alter clinical outcome after overdose. Several studies (involving volunteers and patients) have shown that ipecac administration soon after ingestion reduces serum drug levels (Bond et al, 1993)(McNamara et al, 1989)(Danel et al, 1988)(Tenenbein et al, 1987)(Neuvonen & Olkkola, 1984)(Neuvonen et al, 1983). More data is needed to support or exclude ipecac use. If used, ipecac is most appropriate in the prehospital setting. It is generally NOT recommended for use in the emergency department (Krenzelok et al, 1997).
- CONTRAINDICATIONS to ipecac-induced emesis include: ingestion of toxicant that might compromise airway protective reflexes or require advanced life support within 60 minutes; coma; seizures; signs of oral, pharyngeal, or esophageal irritation; central nervous system excitation or depression; ingestion of a corrosive substance; ingestion of a substance with a high aspiration potential (particularly hydrocarbons); debilitated elderly patients or those with medical conditions that might be adversely affected by induced emesis (Krenzelok et al, 1997).
- Emesis is most effective if initiated within 30 minutes of ingestion.

2. DOSE OF IPECAC SYRUP

- ADULT: Dose: 15 to 30 milliliters (USP DI, 2002)
- ADOLESCENT: Dose: 15 to 30 milliliters (USP DI, 2002)
- CHILD 1 TO 12 YEARS: Dose: 15 milliliters
- CHILD 6 TO 12 MONTHS: Dose: 5 to 10 milliliters. Position child in left lateral decubitus position to reduce risk of aspiration.
- CHILD UNDER 6 MONTHS OF AGE: NOT recommended for prehospital use.
- FLUIDS
 - Prior to or after the dose is given, encourage clear fluids, 8 ounces (240 milliliters) in adults and adolescents and 4 to 8 ounces (120 to 240 milliliters) in a child.

g. ADVERSE EFFECTS

- Common complications may include diarrhea, lethargy/drowsiness, and prolonged vomiting.
- Refer to the IPECAC/TREATMENT management in for further information on administration and adverse reactions.

B. ACTIVATED CHARCOAL

1. PREHOSPITAL ACTIVATED CHARCOAL ADMINISTRATION

- Consider prehospital administration of activated charcoal as an aqueous slurry in patients with a potentially toxic ingestion who are awake and able to protect their

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airway. Activated charcoal is most effective when administered within one hour of ingestion. Administration in the prehospital setting has the potential to significantly decrease the time from toxin ingestion to activated charcoal administration, although it has not been shown to affect outcome (Thakore & Murphy, 2002) Spiller & Rodgers, 2001).

1. In patients who are at risk for the abrupt onset of seizures or mental status depression, activated charcoal should be administered by medical or paramedical personnel capable of airway management to prevent aspiration in the event of spontaneous emesis.
2. The addition of flavoring agents (cola drinks, chocolate milk, cherry syrup) to activated charcoal improves the palatability for children and may facilitate successful administration in the home (Guenther Skokan et al, 2001)(Dagnone et al, 2002).

2. CHARCOAL DOSE

- a. Use a minimum of 240 milliliters of water per 30 grams charcoal (FDA, 1985). Optimum dose not established; usual dose is 25 to 100 grams in adults and adolescents; 25 to 50 grams in children aged 1 to 12 years (or 0.5 to 1 gram/kilogram body weight) ; and 1 gram/kilogram in infants up to 1 year old (USP DI, 2002) (Chyka & Seger, 1997).
 1. Routine use of a cathartic with activated charcoal is NOT recommended as there is no evidence that cathartics reduce drug absorption and cathartics are known to cause adverse effects such as nausea, vomiting, abdominal cramps, electrolyte imbalances and occasionally hypotension (Barceloux et al, 1997).
- b. ADVERSE EFFECTS/CONTRAINDICATIONS
 1. Complications: emesis, aspiration (Chyka & Seger, 1997). Aspiration may be complicated by acute respiratory failure, ARDS or bronchiolitis obliterans (Pollack et al, 1981; Harris & Filandrinos, 1993; (Elliot et al, 1989) Harsh, 1986; (Rau et al, 1988)(Golej et al, 2001)(Graff et al, 2002). Refer to the ACTIVATED CHARCOAL/TREATMENT management for further information.
 2. Contraindications: unprotected airway, gastrointestinal tract not anatomically intact, therapy may increase the risk or severity of aspiration; ingestion of most hydrocarbons (Chyka & Seger, 1997).

6.8.2 PREVENTION OF ABSORPTION

A. GASTRIC EMPTYING

1. Aggressive decontamination with gastric lavage is recommended. If X-ray demonstrates arsenic in the lower GI tract, whole bowel irrigation should be considered. Activated charcoal may not bind significant amounts, but is recommended until definitive quantitative data are available. Fluid repletion should be begun as soon as possible.
2. INDICATIONS: Consider gastric lavage with a large-bore orogastric tube (ADULT: 36 to 40 French or 30 English gauge tube {external diameter 12 to 13.3 mm}; CHILD: 24 to 28 French {diameter 7.8 to 9.3 mm}) after a potentially life threatening ingestion if it can be performed soon after ingestion (generally within 60 minutes).
 - a. Consider lavage more than 60 minutes after ingestion of sustained-release formulations and substances known to form bezoars or concretions.
3. PRECAUTIONS:
 - a. SEIZURE CONTROL: Is mandatory prior to gastric lavage.
 - b. AIRWAY PROTECTION: Alert patients - place in Trendelenburg and left lateral decubitus position, with suction available. Obtunded or unconscious patients - cuffed

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b. ADVERSE EFFECTS/CONTRAINDICATIONS

1. Complications: emesis, aspiration (Chyka & Seger, 1997). Aspiration may be complicated by acute respiratory failure, ARDS or bronchiolitis obliterans (Pollack et al, 1981; Harris & Filandrinos, 1993; (Elliot et al, 1989) Harsh, 1986; (Rau et al, 1988)(Golej et al, 2001)(Graff et al, 2002). Refer to the ACTIVATED CHARCOAL/TREATMENT management for further information.
2. Contraindications: unprotected airway, gastrointestinal tract not anatomically intact, therapy may increase the risk or severity of aspiration; ingestion of most hydrocarbons (Chyka & Seger, 1997).

C. WHOLE BOWEL IRRIGATION (WBI)

1. Whole bowel irrigation with polyethylene glycol electrolyte lavage solution may be a relatively safe and effective means of rapid gastrointestinal decontamination (Lee et al, 1995).
 - a. CONTRAINDICATIONS: This procedure should not be used in patients who are currently or are at risk for rapidly becoming obtunded, comatose, or seizing until the airway is secured by endotracheal intubation. Whole bowel irrigation should not be used in patients with bowel obstruction, bowel perforation, megacolon, or toxic colitis.
 - b. DOSE: Polyethylene glycol solution (e.g. Golytely(R)) is taken orally or infused by nasogastric tube at a rate of 20 milliliters/kilogram/hour in children or 2 liters/hour in adults or adolescents until the rectal effluent is clear and there is no radiographic evidence of toxin remaining in the gastrointestinal tract.
 - c. ADVERSE EFFECTS: Include nausea, vomiting, abdominal cramping and bloating. Fluid and electrolyte status should be monitored, although significant fluid and electrolyte abnormalities have not been reported. Prolonged periods of irrigation may produce a mild metabolic acidosis.

6.8.3 TREATMENT

A. HYPOTENSIVE EPISODE

1. Hypotension from acute arsenic ingestion is likely due to intravascular volume depletion from vomiting, diarrhea, or third spacing of fluids.
2. The initial treatment should consist of adequate volume replacement with crystalloid or blood products.
3. Aggressive monitoring of volume status should be undertaken even in the absence of hypotension initially. Bladder catheterization to monitor hourly urine output, a central venous catheter, or a Swan-Ganz catheter should be used as clinically warranted.
4. Pressors should be used only if volume replacement does not reverse the hypotension.
5. DOPAMINE
 - a. PREPARATION: Add 400 milligrams to 250 milliliters of normal saline or dextrose 5% in water to produce 1600 micrograms per milliliter or add 400 milligrams to 500 milliliters of normal saline or dextrose 5% in water to produce 800 micrograms per milliliter.
 - b. DOSE: Begin at 5 micrograms per kilogram per minute progressing in 5 micrograms per kilogram per minute increments as needed. Norepinephrine should be added if more than 20 micrograms/kilogram/minute of dopamine is needed.
 - c. CAUTION: If VENTRICULAR DYSRHYTHMIAS occur, decrease rate of administration. Extravasation may cause local tissue necrosis, administration through a central venous catheter is preferred.

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- hypotension ensues, or the QRS is widened by 50%, or a total dose of 17 milligrams/kilogram is given (1.2 grams for a 70 kilogram person)
- 2. In urgent situations, up to 50 milligrams/minute intravenous infusion (AHA, 2000).
- 3. Maximum dose: 17 milligrams/kilogram
- b. PROCAINAMIDE/ADULT MAINTENANCE DOSE
 - 1. 1 to 4 milligrams/minute intravenous infusion
- c. PROCAINAMIDE/PEDIATRIC LOADING DOSE
 - 1. 15 milligrams/kilogram intravenously over 30 to 60 minutes; discontinue if hypotension develops or the QRS widens by 50% (AHA, 2000).
- d. PROCAINAMIDE/PEDIATRIC MAINTENANCE DOSE
 - 1. 20 to 80 micrograms/kilogram/minute intravenous infusion (Benitz & Tatro, 1995a).
- e. PROCAINAMIDE/PEDIATRIC MAXIMUM DOSE
 - 1. 100 milligrams/dose or 2 grams/24 hours (Benitz & Tatro, 1995a).
- f. MONITORING PARAMETERS
 - 1. ECG, blood pressure, blood levels

D. TORSADES DE POINTES

1. SUMMARY

- a. Withdraw the causative agent. Hemodynamically unstable patients require electrical cardioversion. Emergent treatment with magnesium, isoproterenol, or arial overdrive pacing is indicated. Detect and correct underlying electrolyte abnormalities (hypomagnesemia, hypokalemia, hypocalcemia) (Smith & Gallagher, 1980)(Keren et al, 1981)(AHA, 2000).

2. MAGNESIUM SULFATE

- a. ADULT DOSE: No clearly established guidelines exist. Administer 1 to 2 grams (8 to 16 mEq) mixed in 50 to 100 milliliters D5W intravenously over 5 minutes, followed if needed by a second 2 gram bolus and an infusion of 0.5 to 1 gram (4 to 8 mEq) per hour in patients not responding to the initial bolus or with recurrence of dysrhythmias (AHA, 2000)(Perticone et al, 1997). Rate of infusion may be increased if dysrhythmias recur.
- b. PEDIATRIC DOSE: 25 to 50 milligrams/kilogram diluted to 10 milligrams/milliliter for intravenous infusion over 5 to 15 minutes.
- c. PRECAUTIONS: Use with caution in patients with renal insufficiency.
- d. MAJOR ADVERSE EFFECTS: High doses may cause respiratory depression, weakness, neuromuscular blockade, and hypotension.
- e. MONITORING PARAMETERS: Heart rate and rhythm, blood pressure, respiratory rate, motor strength, deep tendon reflexes, serum magnesium, phosphorus, and calcium.

3. ISOPROTERENOL

- a. DOSE: 2 to 10 micrograms/minute (children: 0.1 to 1 microgram/kilogram/minute) by continuous monitored intravenous infusion; titrate to heart rate and rhythm response. A 2-microgram/milliliter solution may be prepared by mixing 1 milligram isoproterenol hydrochloride in 500 milliliters of dextrose 5 percent in water.
- b. AVAILABLE FORMS: Isuprel(R) (parenteral solution) 1:100,000; 1:50,000; 1:5000
- c. PRECAUTIONS: Correct hypovolemia before using; do not administer simultaneously with epinephrine; contraindicated in patients with acute cardiac ischemia; may precipitate fatal ventricular fibrillation if the rhythm is not torsades de pointes.
 - 1. Use caution in patients with coronary insufficiency, diabetes, hyperthyroidism,

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- 250 milligrams/dose). Other chelators have been used in similar tests.
3. INTERPRETATION - Either urine collection showing arsenic excretion greater than 100 micrograms/24 hours is diagnostic and should be followed by a 5 day course of D-penicillamine or another chelator. 24-hour urine collections to measure arsenic excretion during chelation are recommended.
 4. SEAFOOD - During the mobilization test the patient should avoid seafood. Ingestion of seafood, particularly shellfish, may transiently increase urinary arsenic levels to .02 - 1.7 mg/L for 4 hours (Baselt, 1997).
 5. SPOT SAMPLES - For diagnostic purposes, a spot urine arsenic, blood arsenic (normal less than 7 micrograms/deciliter), pubic hair arsenic (normal less than 1 microgram/gram), and nail arsenic (normal less than 1.7 micrograms/gram) may be helpful, but results must be carefully interpreted.

G. DIMERCAPROL

1. BAL/DIMERCAPROL INDICATIONS: Used for the treatment of severe heavy metal poisoning (mercury, arsenic, lead) most often when an oral chelating agent can not be tolerated.
2. DOSE: 5% solution (wt/vol) in peanut oil is administered by deep intramuscular injection at a dose of 3 to 5 milligrams/kilogram every 4 to 6 hours. Therapy is generally switched to a less toxic oral chelator as soon as tolerated. MPPARA = ADVERSE EFFECTS: Common effects include pain at the injection site and fever (especially in children). Other effects include nausea, vomiting, headache, burning sensations of the mouth and eyes, lacrimation, salivation, myalgias, tingling of the extremities, diaphoresis, hypertension, tachycardia, chest pain and agitation. Adverse effects are dose related; they develop in 1 percent of patients receiving 2.5 milligrams/kilogram every 4 to 6 hours, 14 percent of patients receiving 4 milligrams/kilogram every 4 to 6 hours and 65 percent of patients receiving 5 milligrams/kilogram every 4 to 6 hours (Eagle & Magnuson, 1946).
3. PRECAUTIONS: Generally contraindicated in patients with liver dysfunction. May cause hemolysis in G6PD deficient patients. Avoid in patients with peanut allergy. BAL metal chelate disassociates in acid environment; urinary alkalization is usually recommended. Do not administer with iron therapy as BAL iron complex may cause vomiting. NOT indicated for methyl mercury poisoning (Howland, 2002).
4. DOSE - The dose used is dependent on the severity of the patient's symptoms and the urinary arsenic levels.
 - a. Limited supplies of dimercaprol following an acute massive epidemic (N=718) of sodium arsenite poisoning prompted health care providers to modify the dosing regimen of dimercaprol (Roses et al, 1991). The study population (N=307) was divided into 3 treatment groups based on urinary arsenic concentrations. All subjects in all treatment groups were free of arsenic related symptomatology at 1 and 2 year follow-up.
 1. Two hundred forty-six subjects with urinary arsenic concentrations up to 75 micrograms/deciliter were given no dimercaprol.
 2. Forty-nine subjects with urinary arsenic concentrations from 76 to 500 micrograms/deciliter received dimercaprol 2 milligrams/kilogram intramuscularly once daily for 10 days.
 3. Twelve subjects with urinary arsenic concentrations greater than 500 micrograms/deciliter were administered dimercaprol 2 milligrams/kilogram intramuscularly every 8 hours on days 1 and 2, every 12 hours on days 3 and 4, and every 24 hours from day 5 to 10. Three subjects in this group also received supportive treatment.

5. EFFICACY

- a. Dimercaprol (BAL) is an effective arsenic chelator but has the disadvantages of requiring painful intramuscular injections and having numerous side effects.
- b. CHILDREN - BAL has been reported to result in clinical improvement and decrease in hospital days in children poisoned with arsenic (Woody & Kometani, 1948). It has also been reported to effect complete recovery in a woman and her 20-week fetus after an acute ingestion of inorganic arsenic by the mother (Daya et al, 1989).
- c. ANIMALS - BAL has been shown to reduce the organ deposition of arsenic in a rabbit model using subcutaneous injections of Lewisite at the LD10 and LD40 and 4 doses of BAL of 35 mg/kg each (Snider et al, 1990).

H. PENICILLAMINE

1. USUAL ADULT DOSE
 - a. 1000 to 1500 milligrams/day divided every 6 to 12 hours, before meals.
2. USUAL PEDIATRIC DOSE
 - a. Initially 10 milligrams/kilogram/day, gradually increase to 30 milligrams/kilogram/day divided in two or three doses as tolerated. Doses up to 100 milligrams/kilogram/day in four divided doses may be used depending on the severity of poisoning and adverse effects. Give before meals; maximum 1 gram/day (Benitz & Tatro, 1995).
3. Avoid in patients with penicillin allergy.
4. Monitor for proteinuria and hematuria; heavy metals may also cause renal toxicity.
5. Monitor CBC with differential, platelet count, and hepatic enzymes.
6. COMMON SIDE EFFECTS/CHRONIC DOSING: fever, CNS depression, anorexia, nausea, vomiting, diarrhea, abdominal pain, proteinuria, and myalgia.
 - a. SERIOUS ADVERSE EFFECTS: Nephrotic syndrome, hypersensitivity reactions, leukopenia, thrombocytopenia, aplastic anemia, agranulocytosis, cholestatic hepatitis, and various autoimmune responses (Prod Info Cuprimine (R), 1999; (Kay, 1986).
7. Use of penicillamine throughout pregnancy has been associated with connective tissue abnormalities, hydrocephalus, cerebral palsy, cardiac and great vessel anomalies, webbing of fingers and toes, and arthrogryposis multiplex (Linares et al, 1979)(Solomon et al, 1977)(Anon, 1981)(Beck et al, 1981)(Rosa, 1986). However, the teratogenic effect when used in low doses or for short periods of time, as in metal chelation, has yet to be determined.
 - a. Penicillamine is considered FDA pregnancy category D (Briggs et al, 1998).
8. EFFICACY
 - a. CHILDREN - D-penicillamine has been successfully used in acute arsenic poisoning in children (Peterson & Rumack, 1977)(Kuruvilla et al, 1975)(Watson et al, 1981).
 - b. ANIMALS - In an experimental animal model, mice and guinea pigs were injected subcutaneously with 8.4 milligrams/kilogram arsenic trioxide and 30 minutes later 0.7 millimole/kilogram (104.5 milligrams/kilogram) of d-penicillamine was administered. D-penicillamine was found to lack effectiveness in this model (Kreppel et al, 1989).

I. SUCCIMER

1. EFFICACY
 - a. SUMMARY - 2,3-Dimercaptosuccinic acid (DMSA, Succimer), is currently approved for the treatment of childhood lead poisoning. It appears to be an effective chelator of arsenic in experimental animals (Graziano et al, 1978)(Hannemann et al, 1995) and man (Lenz et al, 1981)(Kosnett & Becker, 1987)(Fournier et al, 1988). It has been efficacious in pediatric arsenic poisoning (Cullen et al, 1995).
 1. DMSA has been shown to have a safety ratio of 20 times greater than BAL. The total dosage of BAL is limited by its intrinsic toxicity, and the greater

safety ratio of DMSA allows for longer and more prolonged dosing of DMSA (Inns & Rice, 1993).

2. CHRONIC ENVIRONMENTAL ARSENIC POISONING - In a randomized placebo-controlled clinical trial, DMSA was NOT EFFICACIOUS in improving a clinical scoring system, skin lesions, or various biochemical laboratory measurements when administered to patients in India with chronic arsenic poisoning from drinking contaminated groundwater (Guha Mazumder et al, 1998).
 3. CASE REPORT - In a patient treated with DMSA (30 milligrams/kilogram/day for 5 days) for long term ingestion of arsenic, plasma concentrations were unchanged after treatment and renal excretion of arsenic increased 1.5 fold (Fournier et al, 1988).
2. SUCCIMER(DMSA)/DOSE/ADMINISTRATION
- a. CHILDREN: initial dose is 10 milligrams/kilogram or 350 milligrams/square meter orally every 8 hours for 5 days (Prod Info Chemet(R), Succimer, 2001).
 1. The dosing interval is then increased to every 12 hours for the next 14 days. Repeat course may be given if indicated by elevated blood levels. A minimum of 2 weeks between courses is recommended.
 2. DMSA capsule contents may be administered mixed in a small amount of food.
 - b. ADULTS: DMSA is not FDA approved for use in adults, however it has been shown to be safe and effective when used to treat adults with poisoning from a variety of heavy metals (Fournier et al, 1988a). Initial dose is 10 milligrams/kilogram orally every 8 hours for 5 days.
 1. The dosing interval then is increased to every 12 hours for the next 14 days. Repeat course may be given if indicated by elevated blood levels. A minimum of 2 weeks between courses is recommended.
 2. DMSA may be used following EDTA and/or BAL. There is no data available on concurrent use of DMSA and EDTA or BAL, thus the manufacturer does not recommend concurrent use.
3. MONITORING PARAMETERS
- a. The manufacturer recommends monitoring liver function and complete blood count with differential and platelet count weekly during therapy (Prod Info Chemet(R), Succimer, 2001).
 - b. Succimer therapy did not worsen pre-existing borderline abnormal liver function tests in a prospective evaluation of 15 children with lead poisoning (Kuntzelman & Angle, 1992).
4. The following occurred in children and adults during clinical trials (Prod Info Chemet(R), Succimer, 2001).
- a. Transient LFT elevations 4% to 10.4%
 - b. Mucosal vesicular eruption 1 case
 - c. Rash, pruritus 2.6% to 11.2%
 - d. Nausea, vomiting, diarrhea 12% to 20.9%
 - e. Drowsiness, paresthesia 1% to 12.7%
 - f. Sore throat, rhinorrhea 0.7% to 3.7%
 - g. Thrombocytosis, eosinophilia 0.5% to 1.5% mild/moderate neutropenia
5. ODOR: Succimer has a sulfurous odor that may be evident in the patient's breath or urine (Prod Info Chemet(R), Succimer, 2001).
6. CASE STUDY: Of 41 children and 22 adults treated, side effects of succimer were generally benign.
- a. HYPERTHERMIA: One adult developed acute severe hyperthermia associated with hypotension; rechallenge resulted in hyperthermia with shaking chills and

hypertension (Marcus et al, 1991).

7. AVAILABLE FORMS: Succimer (Chemet (R)), from Sanofi Phamaceuticals Inc., 100 milligram capsules.
8. An intravenous preparation of DMSA was used to treat a 26-year-old man with multi organ system failure after acute trivalent arsenic overdose (Hantson et al, 1995).
 - a. A solution was prepared with 1.6 grams of DMSA diluted in 50 milliliters of sterile water and titrated with 10N NaOH to pH 7.2 to 7.4 and filtered through a 0.22 micron filter. The solution was administered in 500 milliliters of 0.9 percent saline solution as an infusion over 1 hour at a dose of 20 milligram/kilogram/day for 5 days followed by 10 milligram/kilogram/day. The DMSA solution was also given via peritoneal dialysis, 20 milligrams/liter of dialysate with 12 liters exchanged daily for 5 days.

J. UNITHIOL

1. EFFICACY

- a. SUMMARY - 2,3-dimercapto-1-propanesulphonic acid (DMPS) is used in Europe as a chelating agent for heavy metal poisonings (Kruszewaska et al, 1996). It appears to be an effective chelator of arsenic in experimental animals (Inns et al, 1990)(Kreppel et al, 1990)(Aposhian et al, 1984)(Hsu et al, 1983)(Aposhian et al, 1981) and humans (Goebel et al, 1990)(Kew et al, 1993)(Moore et al, 1994)(Zilker et al, 1999).
 - b. CASE SERIES/CHRONIC TOXICITY - In a small (n=10) prospective, randomized, placebo-controlled, single-blind study of untreated patients with chronic arsenicosis following groundwater contamination, DMPS treatment was found to improve some clinical parameters (i.e., weakness, pigmentation and lung disease), and to increase total urinary excretion of arsenic. The treatment dose was 100 mg DMPS (orally) given four times per day for 1 week and repeated in the 3rd, 5th and 7th week of the study (Mazumder et al, 2001).
2. DMPS/INDICATIONS: A derivative of dimercaprol used for heavy metal poisoning, especially in Europe.
 3. DMPS/DOSING

a. ACUTE TOXICITY

1. ADULT ORAL DOSE (Arbeitsgruppe BGVV, 1996):

- a. Initial dose: 1200 to 2400 mg/day in equal divided doses (100 to 200 mg 12 times daily).
- b. Maintenance dose: 100 to 300 mg one to three times daily.

2. ADULT INTRAVENOUS DOSE (Arbeitsgruppe BGVV, 1996):

- a. If oral DMPS therapy is not feasible or in severe toxicity, it may be given intravenously.
- b. ADMINISTRATION: DMPS should be injected immediatery after breaking open the ampule and should not be mixed with other solutions. DMPS should be injected slowly over 3 to 5 minutes. The opened ampules cannot be reused.
- c. First 24 hours: 250 mg intravenously every 3 to 4 hours (1500 to 2000 mg total).
- d. Day two: 250 mg intravenously every 4 to 6 hours (1000 to 1500 mg total).
- e. Day three: 250 mg intravenously every 6 to 8 hours (750 to 1000 mg total).
- f. Day four: 250 mg intravenously every 8 to 12 hours (500 to 750 mg total).
- g. Days five and six: 250 mg intravenously every 8 to 24 hours (250 to 750 mg total).

- h. Depending on the patient's clinical status, therapy may be changed to the oral route after the fifth day: 100 to 300 mg three times daily.
- 3. PEDIATRIC ORAL DOSE (Arbeitsgruppe BGVV, 1996):
 - a. There are insufficient clinical data regarding the pediatric use of DMPS. It should be used only if medically necessary.
 - b. Initial dose: 20 to 30 mg/kg/day in many equal divided doses.
 - c. Maintenance dose: 1.5 to 15 mg/kg/day.
- 4. PEDIATRIC INTRAVENOUS DOSE (Arbeitsgruppe BGVV, 1996):
 - a. There are insufficient clinical data regarding the pediatric use of DMPS. It should be used only if medically necessary.
 - b. If oral DMPS therapy is not feasible or in severe toxicity, it may be given intravenously.
 - c. ADMINISTRATION: DMPS should be injected immediately after breaking open the ampule and should not be mixed with other solutions. DMPS should be injected slowly over 3 to 5 minutes. The opened ampules cannot be reused.
 - d. First 24 hours: 5 mg/kg intravenously every four hours (total 30 mg/kg).
 - e. Day two: 5 mg/kg intravenously every six hours (total 20 mg/kg).
 - f. Days three and four: 5 mg/kg intravenously every 8 to 24 hours (total 5 to 15 mg/kg).
- b. CHRONIC TOXICITY
 - 1. ADULT DOSE (Arbeitsgruppe BGVV, 1996):
 - a. 300 to 400 mg/day orally (in single doses of 100 mg). The dose may be increased in severe toxicity.
 - c. DMPS/ADVERSE REACTIONS
 - 1. Chills, fever, and allergic skin reactions such as itching, exanthema or maculopapular rash are possible (Hla et al, 1992). Cardiovascular effects such as hypotension, nausea, dizziness or weakness may occur with too rapid injection of DMPS.

SOURCES

- d. Pharmaceutical grade DMPS is produced by Heyl Chemical-Pharmaceutical Company in Germany. DMPS is not FDA approved; however both oral and intravenous formulations are available in the US from compounding pharmacies.

K. EXPERIMENTAL THERAPY

- 1. N-ACETYLCYSTEINE - N-acetylcysteine (NAC) has been shown to increase the LD50 of mice poisoned with sodium arsenite (Shum et al, 1981). NAC has the advantage of being both an oral and an intravenous agent, and so may become the only chelator which can be given intravenously for acute arsenic poisoning.
- 2. METHYL GROUP DONORS - Sulfo-adenosyl-L-methionine (Samyr(R), Bio-research, Milan) has been proposed as an agent which may promote methylation and subsequent urinary elimination of arsenic (Mahieu et al, 1987).

L. NEUROPATHY

- 1. Early administration (within 18 hours of acute exposure) of BAL may be effective in preventing arsenical neuropathy (Jenkins, 1966). However, once neuropathy has developed (usually 1 to 3 weeks after acute exposure), chelation with BAL may not be effective in reversing it (Heyman et al, 1956)(Donofrio et al, 1987)(Le Quesne & McLeod, 1977).

M. EXPERIMENTAL THERAPY

- 1. IMMUNOTHERAPY - Use of immunotherapy for the treatment of sodium arsenite toxicity

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is being investigated in animal models. Leikin et al (1991) demonstrated a protective effect of anti-arsenic reactive serum female balb/c mice. Applicability of immunotherapy to treatment of human poisonings has not been determined.

2. 2,3-DITHIOERYTHRITOL - Is a synthesized derivative of BAL. Preliminary laboratory evidence indicates that it is less toxic than BAL or DMSA (Boyd et al, 1989).

N. CORTICOSTEROID

1. MELARSOPROL ENCEPHALOPATHY - Only 4 percent of those patients given corticosteroids (prednisolone, not more than 40 milligrams daily) developed melarsoprol encephalopathy compared to approximately 33 percent in those patients receiving no steroids in a prospective randomized trial involving 600 patients with parasitology-confirmed *Trypanosoma brucei gambiense* infections (Pepin et al, 1989).

6.10 ENHANCED ELIMINATION

A. HEMODIALYSIS

1. Hemodialysis should be performed in the presence of any degree of renal failure, as the main route of excretion will be inhibited if this occurs. As the serum creatinine falls, urinary arsenic may increase (Giberson et al, 1976).
2. Mathieu et al (1992) report the effect of hemodialysis and dimercaprol on arsenic kinetics following an ingestion of 10 grams of sodium arsenate (40 to 50 percent arsenic). During the 15 days of hospitalization, 235 milligrams of arsenic was eliminated in the urine.
 - a. Instantaneous hemodialysis clearance was 85 +/- 75 milliliters/minute without previous BAL and 87.5 +/- 75 milliliters/minute with a previous 250 milligram BAL injection.
 - b. BAL - 250 milligrams was given one time only at approximately 20 hours postingestion.
 - c. One month after discharge the patient was admitted to another hospital for a sensory and motor polyneuritis involving both upper and lower limbs. Arsenic concentrations in blood and urine were not detectable, however, BAL was administered for 8 days at this institution. All neurologic signs resolved over 3 months.
3. In another study, Zilker et al (1999) reported that hemodialysis and CAVHDF did not significantly alter arsenic kinetics in a 24-year-old male who had accidentally ingested arsenic residue with an initial serum arsenic level of 245.8 micrograms/liter. Dimercaptopropane sulfonate (DMPS) 1.2 grams was also given during the first two days of enhanced elimination therapy. During the first 87 hours following admission, 89.67 mg of arsenic was recovered in the urine, while the first hemodialysis removed 0.168 mg of arsenic and 0.061 mg was found in the CAVHDF dialysate.
 - a. Renal function remained normal throughout the period, and the authors suggested that DMPS was an effective therapy for arsenic poisoning when no kidney failure was present. One limitation of the study, however, was that no urinary levels were obtained prior to DMPS treatment.
4. Dialysis clearance rates of arsenic in two patients was 76 and 87 milliliters/minute (Vaziri et al, 1980).
5. Additional studies are needed to evaluate the safety and efficacy of hemodialysis in the treatment of arsenic poisoning in the absence of renal insufficiency before it can be routinely recommended.
 - a. Hemodialysis was instituted 4 hours postadmission in a 30-year-old male who ingested 6 ounces of a rodenticide containing arsenous oxide 1.5 percent (approximately 2,150 milligrams of metallic arsenic) although the patient exhibited no evidence of renal impairment (Fesmire et al, 1988).

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6. Hemodialysis and continuous arterio-venous hemodiafiltration were found to remove negligible amounts of arsenic in an adult who maintained normal renal function after poisoning with arsenic (Zilker et al, 1999).

6.11 OTHER

A. OTHER

1. When the arsenic exposure has been environmental, removing the patient from the source of exposure is beneficial. Children with elevated urinary arsenic concentrations above normal had a substantial reduction in arsenic concentrations after moving away from an area where the soil had been contaminated by a smelter (MMWR, 1987).

7.0 RANGE OF TOXICITY

7.1 SUMMARY

- A. Trivalent arsenic (arsenite) is more toxic than pentavalent arsenic (arsenate). Acute ingestion of more than 100 mg of inorganic arsenic is likely to cause significant toxicity. Acute ingestion of 200 mg or more of arsenic trioxide may be fatal in an adult.

7.3 MINIMUM LETHAL EXPOSURE

A. GENERAL/SUMMARY

1. Different arsenic compounds may have differing lethal dosages.
2. Arsine gas at a concentration of 25-50 ppm is believed to be lethal within thirty minutes (Baselt, 2000).
3. The smallest recorded lethal dose of arsenic is approximately 130 mg (Bingham et al, 2001) (OHM/TADS , 2001).
4. As little as 20 mg of arsenic may produce life-threatening toxicity (Hutton & Christians, 1983)(Schoolmeester & White, 1980)(Zaloga et al, 1970).
5. A single dose of 0.12 g of arsenic trioxide may be fatal (Harbison, 1998).
6. CHILD - One mg/kg of ingested arsenic may be lethal in a child (Alexander, 1964)(Woody & Kometani, 1948).
7. ADULT - Arsenic trioxide in a solubilized form becomes sodium arsenite, which is more toxic than in an unsolubilized form (ACGIH, 1996a). Acute ingestion of 200 mg of arsenic trioxide may be fatal to an adult. Death can occur within a few hours or after several days (Baselt, 2000).
8. ADULT - A 33-year-old male died from hypovolemia, acute circulatory failure and refractory ventricular dysrhythmias following the ingestion of a wood preservative which contained arsenic pentoxide (45%), chromium trioxide (35%), and cupric oxide (20%). The patient died within several hours of ingestion (Hay et al, 2000).

7.4 MAXIMUM TOLERATED EXPOSURE

A. ACUTE

1. SUMMARY

- a. AVERAGE DAILY HUMAN INTAKE OF ARSENIC - 0.025-0.033 mg/kg (in food and water) (Baselt, 2000).
- b. Estimates of acute oral toxic doses of arsenic compounds range from 1 mg to 10 g.
- c. As little as 10 ppm in water may be an acute health hazard (OHM/TADS , 2001).

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2. CASE REPORTS

a. PEDIATRIC

1. Acute ingestion of 9 to 14 mg of arsenic trioxide by a 16-month-old female produced classic GI signs and symptoms of arsenic poisoning but was not lethal (Watson et al, 1981).

b. ADULT

1. A 30-year-old male survived an ingestion of 6 ounces of "Blue Ball Rat Killer" containing 1.5 percent arsenous oxide (2150 mg metallic arsenic per 6 ounces), ethanol, and intranasal cocaine use with aggressive therapy (fluid resuscitation, chelation therapy, and hemodialysis) (Fesmire et al, 1988).
2. LACK OF EFFECT- A 32-year-old female developed only epigastric discomfort and paresthesias in the lower extremities following ingestion of about 2 grams of sodium arsenate; urine arsenic level was 14 mg/L about 13 hours postingestion (Hernandez et al, 1998).
3. A 23-year old man survived ingestion of 1040 mg of arsenic trioxide (13 mg/kg of trivalent arsenic) (Baselt, 2000)(Kamijo et al, 1998).
4. A 33-year-old female survived ingestion of 1850 mg of arsenic trioxide following treatment with 2,3 propanesulphonate (DMPS) and hemodialysis (Kruszewska et al, 1996).
5. A 45-year-old female survived an ingestion of sodium arsenite between 8 and 16 g (serum arsenic concentration was 300 mcg/L on admission). Residual quadriplegia did occur (Bartolome et al, 1999).

B. SPECIFIC SUBSTANCE

1. PENTAVALENT ARSENIC -

- a. Trivalent arsenic (arsenite) is more toxic in animals than the pentavalent form (arsenates) by several orders of magnitude. However, significant toxicity may occur with large amounts of pentavalent salts in humans. Pentavalent arsenic may be converted in vivo to trivalent arsenic.
- b. Of 149 cases of sodium arsenate-containing ant killer poisoning, 91 percent were exposed via the bait station. Most cases were children 3-years-old or younger. Symptoms of self-limiting episodes of vomiting and diarrhea were seen in 3 children (Kingston et al, 1989).
- c. Despite trivial or no symptoms (transient emesis) in children with a history of sodium arsenate ant killer ingestion, significant elevations in 24-hour urine arsenic levels occurred, in the range of 3500 to 5350 mcg/L (Scalzo et al, 1989).
- d. Decreases in the hemoglobin and hematocrit values were the only sequelae possibly associated with an acute ingestion of approximately 1.2 g of arsenic as sodium arsenate by a 44-year-old female (Chan & Mathews, 1990).

C. CHRONIC

1. Subjects chronically exposed to arsenic in drinking water at levels between 0.1 and 0.39 mg/L showed no difference in health effects as determined by questionnaire from subjects whose drinking water contained 0.001 mg/L of arsenic (Valentine et al, 1992).
2. A 67-year-old woman who was treated for persistent psoriasis with Fowler's solution over a 15 year period (estimated at 25 g of arsenic trioxide in all) developed noncirrhotic hepatic fibrosis as a result of the chronic arsenic poisoning (Piontek et al, 1989).
3. Prolonged ingestion of arsenicals at the rate of 0.04-0.09 mg/kg/day frequently produced mild poisoning (Hayes & Laws, 1991).
4. The mountaineers of Styria were reported to ingest arsenic once or twice a week as a tonic, and consequently became tolerant of daily doses estimated at 400 mg or more (Hays &

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Lawes, 1991).

7.5 TOXIC SERUM/PLASMA/BLOOD CONCENTRATIONS

A. TOXIC CONCENTRATION LEVELS

1. CONCENTRATION LEVEL

- a. Concentrations of arsenic in urine, blood, and gastric fluid after admission in a worker buried in arsenic trioxide for about 10 minutes were 1.9, 3.4, and 550 mg/L, respectively (Gerhardsson et al, 1988).
- b. Tissue concentrations in micrograms/gram wet weight of arsenic at autopsy of a worker who was buried for about 10 minutes in arsenic trioxide were brain (frontal cortex) 0.3, myocardium (left ventricle) 1.2, kidney (cortex) 1.4, lung (peripheral) 2.9, liver 3.8, and blood 2.3 (Gerhardsson et al, 1988).

2. CASE REPORTS

- a. A 3-year-old child had a blood arsenic concentration of 1.8 mg/L at 5.5 hours after accidental ingestion of approximately one mouthful of a 44% solution of sodium arsenite (Saady et al, 1989).
- b. A 25-year-old man who died after ingesting 8 g of di-arsenic-trioxide had a serum arsenic concentration of 0.15 mg/L the day of ingestion (Quatrehomme et al, 1992).
- c. A 45-year-old female had an initial serum arsenic concentration of 300 mcg/L following an ingestion of sodium arsenite between 8 and 16 g. The patient survived with residual neurologic injury (i.e., quadriplegia) (Bartolome et al, 1999).

7.6 TOXICITY INFORMATION

7.6.1 TOXICITY VALUES

A. References: ITI, 1995 OHM/TADS, 2001 RTECS, 2001

1. LD - (ORAL) HUMAN:
 - a. 1-2 mg/kg (OHM/TADS, 2001)
2. LD - (ORAL) RABBIT:
 - a. 4-19 mg/kg (OHM/TADS, 2001)
3. LD - (ORAL) RAT:
 - a. 8 mg/kg (OHM/TADS, 2001)
4. LD50 - (INTRAPERITONEAL) MOUSE:
 - a. 46,200 mcg/kg -- ataxia, gastrointestinal hypermotility, diarrhea
5. LD50 - (ORAL) MOUSE:
 - a. 25-47 mg/kg (OHM/TADS, 2001)
 - b. 145 mg/kg -- ataxia, gastrointestinal hypermotility, diarrhea
6. LD50 - (ORAL) PIG:
 - a. 6.5 mg/kg (OHM/TADS, 2001)
7. LD50 - (INTRAPERITONEAL) RAT:
 - a. 13,390 mcg/kg
8. LD50 - (ORAL) RAT:
 - a. 15 mg/kg (OHM/TADS, 2001)
 - b. 112 mg/kg (OHM/TADS, 2001)
 - c. 763 mg/kg -- ataxia, gastrointestinal hypermotility, diarrhea
9. LDLo - (INTRAPERITONEAL) GUINEA_PIG:
 - a. 10 mg/kg -- fatty liver degeneration, changes to the kidney, bladder and ureter
10. LDLo - (SUBCUTANEOUS) GUINEA_PIG:
 - a. 300 mg/kg

ORIGINAL
(RED)

11. LDLo - (SUBCUTANEOUS) RABBIT:
 - a. 300 mg/kg
12. LDLo - (INTRAMUSCULAR) RAT:
 - a. 25 mg/kg (ITI, 1995)
13. TDLo - (ORAL) HUMAN:
 - a. 76 mg/kg for 12Y-Intermittent -- carcinogenic by RTECS criteria, tumors of the liver, hemorrhage
 - b. 7857 mg/kg for 55Y -- dermatitis, change in structure/function of esophagus, hemorrhage
 - c. Child, 4 mg/kg -- changes in leukocyte count, metabolic acidosis, EKG changes not diagnostic
14. TDLo - (IMPLANT) RABBIT:
 - a. 75 mg/kg -- equivocal tumorigenic agent by RTECS criteria, tumors of the lung, thorax and liver
15. TDLo - (ORAL) RAT:
 - a. Female, 580 mcg/kg for 30W prior to mating and 20D of pregnancy -- developmental abnormalities of the musculoskeletal system
 - b. Female, 605 mcg/kg for 35W prior to mating -- pre- and post-implantation mortality
 - c. 1360 mg/kg for 17D-Intermittent -- gastrointestinal changes, changes in cell counts, chronic inflammation of the kidney

7.8 OTHER

A. OTHER

1. SPECIFIC SUBSTANCE

- a. The following toxicity rating scale can be used to compare various arsenic compounds based primarily on animal data. It should be emphasized that this is only a comparative scale, and all arsenic compounds are toxic and potentially lethal (Gosselin et al, 1984).

KEY - NUMERICAL TOXICITY RATING DEFINITIONS (Gosselin et al, 1984)			
		PROBABLE HUMAN ORAL LETHAL DOSE	
	NUMBER	DOSE	70 kg PERSON
Super Toxic	6	<5 mg/kg	<7 drops (a taste)
Extremely Toxic	5	5-50 mg/kg	7 drops - 5 mL
Very Toxic	4	50-500 mg/kg	5-30 mL
Moderately Toxic	3	0.5-5 g/kg	30-400 mL
Slightly Toxic	2	5-15 g/kg	400-1000 mL
Minimally Toxic	1	>15 g/kg	>1 liter

ARSENIC CONTAINING COMPOUNDS

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COMPOUND	RATING	DATA	COMMENTS
Arsenic	5(?)	N/A	Less toxic than arsenic acids and the salts
Arsanilic Acid	3-4	Acute Oral LD50 Newborn rats: 216 mg/kg; Adult rats: 1000 mg/kg; Dermal LD50 Mice: 400 mg/kg	
Arsenates	5	N/A	Arsenates (Pentavalent) less toxic than arsenites (Trivalent) toxic syndromes identical to arsenic trioxide to which pentavalent arsenic is converted in vivo
Arsenic Acid	5	N/A	52.8% arsenic aqueous solution 75-80% H ₃ AsO ₄
Arsenicals			Trivalent and pentavalent arsenic compounds
Arsenic Trioxide	6	Acute Toxic Dose: 5-50 mg in adult human; fatal oral dose 100-500 mg	
Arsenic Trisulfide	5	N/A	Decomposes to more arsenic trioxide
Arsenites	6		Toxic trivalent salts and arsenic acid
Cacodylic Acid	3-4	Safe PO dose 60 mg; Safe IV dose 300 mg	Major urinary metalloid; ingestion of organic arsenic
Calcium Arsenate	5	N/A	26% arsenic
Calcium Arsenite	5-6	N/A	Twice as toxic as calcium arsenate
Copper Acetoarsenite	5	N/A	59% arsenic trioxide equivalent
Copper Arsenate	5	N/A	41% arsenic
Copper Arsenite	5	N/A	40-45% arsenic trioxide equivalent