

## Arsenical Pesticides

Many arsenic compounds have been discontinued in the United States as a result of government regulations. However, they are still widely available in some countries, and many homes and farms have leftover supplies that continue to present risk. Arsenic trioxide is still used in some ant bait stations, which have been a source for childhood exposure via ingestion in recent years.<sup>1</sup> Another arsenic compound, arsine gas, is not a pesticide but is released as a byproduct in pesticide manufacturing and metal refining operations and is the most toxic of all forms of arsenic. It is discussed separately in this chapter.

### Toxicology

**Arsenic** is a natural element having both metal and nonmetal physical/chemical properties. In one respect or another, it resembles nitrogen, phosphorus, antimony and bismuth in its chemical behavior. In nature it exists in elemental, trivalent (-3 or +3) and pentavalent (+5) states. It binds covalently with most nonmetals (notably oxygen and sulfur) and with metals (*e.g.*, calcium and lead). It forms stable trivalent and pentavalent organic compounds. In biochemical behavior, it resembles phosphorus, competing with phosphorus analogs for chemical binding sites. Toxicity of the various arsenic compounds in mammals extends over a wide range, determined, in part, by the unique biochemical actions of each compound, but also by absorbability and efficiency of biotransformation and disposition. After arsine gas, arsenites (inorganic trivalent compounds) represent the next most toxic hazard of arsenic compounds. Doses of 78-180 mg of arsenic trioxide (~1-2.5 mg/kg in a child) are considered high enough to be lethal.<sup>2</sup> Inorganic pentavalent compounds (arsenates) are somewhat less toxic than arsenites, while the organic (methylated) pentavalent compounds (arsonates) incur the least hazard of the arsenicals that are used as pesticides.<sup>3</sup>

The pentavalent arsenicals are relatively water soluble and absorbable across mucous membranes, while trivalent arsenicals, having greater lipid solubility, are more readily absorbed across the skin.<sup>4</sup> However, acute, systemic poisonings that arise following dermal absorption of either form have been extremely rare. There are numerous dermal manifestations of arsenic poisoning, which will be discussed later in the chapter. Ingestion has been the usual basis of poisoning; gut absorption efficiency depends on the physical form of the compound, its solubility characteristics, the gastric pH, gastrointestinal motility and gut microbial transformation. Inhalation is the major route of arsine exposure; toxic effects may also occur with other arsenicals through inhalation of aerosols.

Once absorbed, many arsenicals cause toxic injury to cells of the nervous system, blood vessels, liver, kidney and other tissues. Two biochemical mechanisms of toxicity are recognized: (1) reversible combination with thiol groups contained in tissue proteins and enzymes and (2) substitution of arsenic anions for phosphate in many reactions, including those critical to oxidative phosphorylation.<sup>5,6</sup> Arsenic is readily metabolized in the liver to a methylated form, which is much less toxic and easily excreted. However, it is prudent to manage cases of arsenical pesticide ingestion as though all are highly toxic.

### Arsenic Compounds HIGHLIGHTS

Life-threatening effects on CNS, blood vessels, kidney, liver

### SIGNS & SYMPTOMS

Acute cases

Garlic odor of the breath and feces

Metallic taste in mouth

Adverse GI symptoms

Also CNS, renal & cardiovascular symptoms

Jaundice

Chronic cases

Muscle weakness

Fatigue

Weight loss

Hyperpigmentation

Hyperkeratosis

Mees lines

### TREATMENT

Skin, eye, GI decontamination

IV hydration

Chelation therapy with BAL, DMSA, or d-penicillamine

Consider hemodialysis

## Inorganic Trivalent

### **Arsenic trioxide**

“White arsenic.” Arsenous oxide. Has been discontinued but still stocks may still be on hand from prior registrations.

### **Sodium arsenite**

Sodanit, Prodalumnol  
Double. Used as a fungicide in vineyards.

### **Calcium arsenite**

Mono-calcium arsenite.  
Flowable powder for insecticidal use on fruit.

### **Copper arsenite**

**(Acid copper arsenite)**  
Wettable powder, for use as insecticide, wood preservative

### **Copper acetoarsenite**

Insecticide. Paris Green, Schweinfurt green, emerald green, French green, mitis green. No longer used in the United States; still used outside the United States.

### **Arsine**

Not a pesticide.

Occasionally generated during manufacture of arsenicals.

See separate discussion in subsection on p. 140.

## Signs and Symptoms of Poisoning

Manifestations of **acute poisoning** (large amount absorbed over a short time) are distinguishable from those of chronic poisoning (lesser doses absorbed over a longer time interval).

The symptoms and signs of acute arsenic poisoning usually appear within 1 hour after ingestion, but may be delayed several hours. A garlic odor to the breath and feces may help to identify the responsible toxicant in a severely poisoned patient. There is often a metallic taste in the mouth. Gastrointestinal (GI) adverse effects predominate, with vomiting, abdominal pain and rice-water or bloody diarrhea being the most common.<sup>1,3,7,8</sup> Other GI effects include inflammation, vesicle formation and eventual sloughing of the mucosa in the mouth, pharynx and esophagus.<sup>7</sup> These effects result from the action of an arsenical metabolite on blood vessels generally, but the splanchnic vasculature particularly, causing dilation and increased capillary permeability.

The central nervous system is another system commonly affected during acute poisoning. Symptoms may begin with headache, dizziness, drowsiness and confusion. Symptoms may progress to include muscle weakness and spasms, hypothermia, lethargy, delirium, coma and convulsions.<sup>3</sup> Renal injury is manifest as proteinuria, hematuria, glycosuria, oliguria, casts in the urine and, in severe poisoning, acute tubular necrosis. Cardiovascular manifestations include shock, cyanosis and cardiac arrhythmia,<sup>9,10</sup> which are due to direct toxic action and electrolyte disturbances. Liver damage may manifest as elevated liver enzymes and jaundice. Injury to blood-forming tissues may cause anemia, leukopenia and thrombocytopenia. In lethal exposures death usually occurs 1-3 days following symptom onset and is often the result of circulatory failure, although renal failure may also contribute.<sup>3</sup> If the patient survives, painful paresthesias, tingling and numbness in the hands and feet may be experienced as delayed sequelae of acute exposure. This sensorimotor peripheral neuropathy, which may include muscle weakness and spasms, typically begins 1-3 weeks after exposure.<sup>11</sup> The muscle weakness may be confused with Guillain-Barre syndrome.<sup>12</sup>

Other organ systems are affected with arsenic toxicity. Liver injury reflected in hepatomegaly and jaundice may progress to cirrhosis, portal hypertension and ascites. Arsenic has direct glomerular and tubular toxicity resulting in oliguria, proteinuria and hematuria. Electrocardiographic abnormalities (prolongation of the QTc interval and torsades de pointes) and peripheral vascular disease have been reported. The latter includes acrocyanosis, Raynaud's phenomenon and frank gangrene.<sup>3,13</sup> Hematologic abnormalities include anemia, leukopenia and thrombocytopenia.<sup>3</sup> Late sequelae of protracted high intakes of arsenic include skin cancer and an increased risk of lung cancer.<sup>3,14</sup>

Numerous chronic effects are associated with arsenic. Most uses of arsenic as a pesticide, as previously noted, have been discontinued, and most arsenic exposure today is due to naturally occurring arsenic found in shallow well water. Several review articles summarize the evidence of chronic arsenic toxicity.<sup>6,15,16</sup> Repeated absorption of subacutely toxic amounts of arsenic generally has an insidious onset of clinical effects and may be difficult to diagnose. Neurologic, dermal and nonspecific manifestations are usually more prominent than the gastrointestinal effects that characterize acute poisoning. Muscle weakness and fatigue can occur, as can anorexia and weight loss. Hyperpigmentation is a common sign and tends to be accentuated in areas that are already more pigmented such as the groin and areola. Hyperkeratosis is another common sign, especially on the palms and soles.<sup>14,17</sup> Subcutaneous edema of the face, eyelids and ankles; stomatitis; white striations across the nails (Mees lines) and loss of nails or hair are other signs of chronic, continuous exposure.<sup>3,17</sup> Chronic neurologic effects and carcinogenic risks are discussed in **Chapter 21, Chronic Effects**.

## Confirmation of Poisoning

Measurement of 24-hour urinary excretion of arsenic (micrograms per day) is the most common way to confirm excessive absorption and is the preferred method to follow serial levels and evaluate chronic exposure.<sup>3,18</sup> Spot urine arsenic analysis expressed as a ratio with urinary creatinine is the recommended method to evaluate occupational exposures.<sup>19</sup> Methods to determine blood arsenic concentration are available; however, blood levels tend to poorly correlate with exposure or effect except in the initial acute phase.<sup>18,20</sup> Special metal-free, acid-washed containers should be used for sample collection. Arsenic excretion above 100 µg per day should be considered abnormal. Excretions above 200 µg per day reflect a toxic intake, unless seafood was ingested.<sup>18,20,21,22,22</sup> Diets rich in seafood, primarily shellfish eaten in the previous 48 hours, may generate 24-hour urine excretion levels as high as 200 µg/day and sometimes more.<sup>1,7,22</sup> In some labs and reports, urinary arsenic levels are expressed as µg/l. Normal values are 0-50 µg/l for a 24-hour urine level.<sup>1,23</sup>

The majority of marine arsenic that is excreted is in the methylated form (arseno-betaine) and not considered acutely toxic. However, some of the arsenic released from mussels may contain higher amounts of arsenic trioxide than previously thought.<sup>22</sup> Urinary arsenic should be speciated into inorganic and organic fractions to help determine the source of the exposure and to help guide treatment.

Concentrations of arsenic in blood, urine or other biologic materials can be measured by either wet or dry ashing, followed by colorimetric or atomic absorption spectrometric analysis. This latter method is preferred. Arsenic can be measured in human urine by an inductively coupled plasma mass spectrometry (ICP-MS) method. Blood concentrations in excess of about 100 µg per liter probably indicate excessive intake or occupational exposure, provided that seafood was not ingested before the sample was taken.<sup>7,18,20,21</sup> Blood samples tend to correlate with urine samples during the early stages of acute ingestion,<sup>18</sup> but because arsenic is rapidly cleared from the blood, the 24-hour urine sample remains the preferred method for detection and for ongoing monitoring.<sup>3,18,20</sup>

Hair has been used for evaluation for chronic exposure. Levels in unexposed people are usually less than 1 mg/kg and levels in individuals with chronic poisoning range between 1 and 5 mg/kg.<sup>21</sup> Hair samples should be viewed with caution because external environmental contamination such as air pollution may artificially elevate arsenic levels. Additionally, commercial laboratories have not been shown to have reliably consistent results.<sup>24</sup> Therefore, hair arsenic may be a reasonable tool for use in research but not in the assessment of an acutely poisoned patient.

Special tests for arsine toxicosis are described in the *Arsine Gas* subsection beginning on p. 140.

## Treatment of Arsenic Compound Toxicosis

The following discussion applies principally to poisonings by arsenicals in solid or dissolved form. Treatment of poisoning by arsine gas requires special measures described in the *Arsine Gas* subsection beginning on p. 140.

1. **Skin decontamination.** Wash arsenical pesticide from skin and hair with copious amounts of soap and water.
2. If a high-concentration solution is in contact with the eyes, wash eyes with a profuse amount of water and examine the corneas carefully. If burns have occurred, appropriate ophthalmologic care should be provided. See **Chapter 3, General Principles.**

## Inorganic Pentavalent

### **Arsenic acid**

Hi-Yield Desiccant H-10, Zotox. Water solutions used as defoliants, herbicides.

### **Sodium arsenate**

Disodium arsenate, Jones Ant Killer, Terro Ant Killer. All discontinued, but may still be encountered from old registration.

### **Calcium arsenate**

Tricalcium arsenate, Spra-cal, Turf-Cal. Flowable powder formulations used against weeds, grubs.

### **Lead arsenate**

Gypsin, Soprabel. Limited use in the United States; wettable powder used as insecticide outside the United States.

### **Zinc arsenate**

Powder once used in the United States as insecticide on potatoes and tomatoes.

**Organic (Pentavalent)****Cacodylic acid****(sodium cacodylate)**

Non-selective herbicide, defoliant, silvicide.

Bolate, Bolls-Eye, Bophy, Dillie, Kack, Phytar 560, Rad-E-Cate 25, Salvo.

**Methane arsonic acid**

MAA. Non-selective herbicide.

**Monosodium methane arsonate**

MSMA. Non-selective herbicide, defoliant, silvicide.

Ansar 170, Arsonate Liquid, Bueno 6, Daconate 6, Dal-E-Rad, Drexar 530, Herbi-All, Merge 823, Mesamate, Target MSMA, Trans-Vert, Weed-E-Rad, Weed-Hoe.

**Disodium methane arsonate**

DSMA. Selective post-emergence herbicide, silvicide.

Ansar 8100, Arrhenal, Arsinyl, Crab-E-Rad, Di-Tac, DMA, Methar 30, Sodar, Weed-E-Rad 360.

**Monoammonium methane arsonate**

MAMA. Selective post-emergence herbicide.

**Calcium acid methane arsonate**

CAMA. Selective post-emergence herbicide.

Calar, Super Crab-E-Rad-Calar, Super Dal-E-Rad.

- Gastrointestinal decontamination.** If an arsenical pesticide has been ingested within an hour of treatment, consider GI decontamination, as outlined in **Chapter 3**. Because poisoning by ingested arsenic often results in profuse diarrhea, it is generally not appropriate to administer a cathartic. Although it is not clear how well arsenic is absorbed by charcoal, charcoal and whole bowel irrigation were used in recent case reports.<sup>1,8,25</sup> Gastric lavage is also recommended, especially if there are visible opacities on abdominal X-rays.<sup>8,26</sup>
- Intravenous fluids.** Administer intravenous fluids to restore adequate hydration, support urine flow and correct electrolyte imbalances. Aggressive rehydration is needed to correct the significant amount of fluid lost from the GI tract. Serum electrolytes including magnesium and calcium should be monitored. Monitor intake/output continuously to guard against fluid overload. If acute renal failure occurs, monitor blood electrolytes regularly.
- Hypovolemic shock.** As above, use isotonic fluids (normal saline or lactated ringers) to treat hypovolemia and hypotension associated with shock. Dopamine and/or norepinephrine may be needed.
- Cardiac monitoring.** Obtain an electrocardiogram (ECG) to detect ventricular arrhythmias, including prolonged Q-T interval and ventricular tachycardia and toxic cardiomyopathy (T wave inversion, long S-T interval).
- Chelation therapy.** Use chelation for severe poisoning, including symptomatic poisoning or someone with a recent significant exposure. While there is not a definitive cut-off value at which an asymptomatic patient should be chelated, a urine arsenic level of 200 µg/liter has been suggested.<sup>1,27</sup> Administration of dimercaprol (BAL) has long been the chelator of choice in symptomatic arsenic poisonings.<sup>8,28</sup> However, it is given as painful and frequent intramuscular injections. Oral agents, such as dimercaptosuccinic acid (DMSA, also known as succimer) or d-penicillamine, have also been used more frequently in individual cases;<sup>1,25,29,30,31,32</sup> however, neither has been approved by the FDA for arsenic toxicity. (DMSA is FDA-approved for lead toxicity.) DMSA and d-penicillamine are discussed in greater detail below. The following dosage schedules have proven to be effective in accelerating arsenic excretion.

**Dosage of Dimercaprol (BAL)**

- **Adults:** BAL is provided as a 100 mg/mL solution in peanut oil. The dosage is 3-5 mg/kg q 4-12 hours.
- **Children:** Dosages are similar, but may start with 2.5-3.0 mg/kg.<sup>7,8,28</sup>

**CAUTION:** Disagreeable side effects often accompany the use of BAL: nausea, headache, burning and tingling sensations, sweating, pain in the back and abdomen, tremor, restlessness, tachycardia and hypertension. Acute symptoms usually subside in 30-90 minutes. Antihistamine drugs may provide relief, especially if given prior to BAL. BAL may potentially have other adverse effects. In rabbits, treatment of arsenite exposure with BAL increased brain arsenic levels.<sup>33</sup> Because of these side effects, consider an oral chelation agent if tolerated.

After the gastrointestinal tract is reasonably free of arsenic or if the patient can tolerate oral chelation from the outset, consider an oral chelating agent. D-penicillamine has been suggested; however, its effectiveness for arsenic exposure has been questioned in experimental models, though it has been used with some success in earlier human case reports.<sup>25,30,31,32,34</sup>

### Dosage of D-penicillamine

- **Adults and children over 12 years: 0.5 gm every 6 hours, given 30-60 minutes before meals and at bedtime for about 5 days.**
- **Children under 12 years: 0.1 gm/kg body weight, not exceeding 1.0 gm per day, every 6 hours, 30-60 minutes before meals and at bedtime for about 5 days.**

**CAUTION:** *Adverse reactions to short-term therapy are rare; however, persons allergic to penicillin may suffer allergic reactions to d-penicillamine; they should not receive d-penicillamine.*

DMSA (succimer) has also been shown to be an effective chelator of arsenic, though it is not labeled for this indication.<sup>29</sup> In light of the lack of effectiveness of d-penicillamine, coupled with the low toxicity and high therapeutic index of DMSA, it appears that the latter agent may be the preferred method for chronic toxicity or when oral chelation is acceptable.<sup>1,25,29,34</sup>

### Dosage of DMSA (Succimer)

- **Adults and Children: 10 mg/kg every 8 hours for 5 days, followed by 10 mg/kg every 12 hours for an additional 14 days. (Maximum 500 mg per dose). It should be given with food.**

8. **Extracorporeal hemodialysis.** Consider whether to use extracorporeal hemodialysis. When used in combination with BAL therapy, hemodialysis has limited effectiveness in removing arsenic from the blood. Hemodialysis may be indicated early in the course of poisoning to enhance arsenic elimination and maintain extracellular fluid composition if severe acute renal failure occurs.<sup>35</sup> A recent case with acute renal failure resolved without the need for dialysis.<sup>8</sup>
9. **Urinary arsenic excretion.** Monitor urinary arsenic excretion while any chelating agent is being administered. Once arsenic levels fall into the normal reference range of 0-50 µg/l or less than 50 µg/day, it is reasonable to discontinue chelation therapy.<sup>1</sup>

**Arsine Gas****HIGHLIGHTS**

Powerful hemolysin

**SIGNS & SYMPTOMS**

Fatigue, headaches, malaise, dizziness, nausea, abdominal pain

Hemoglobinuria, jaundice, very dark plasma

**TREATMENT**

Fresh air

IV fluids

Consider red blood cell or plasma exchange transfusion

**ARSINE GAS**

Arsine is not used as a pesticide. However, some poisonings by arsine have occurred in pesticide manufacturing plants and metal-refining operations when arsenicals came into contact with mineral acids or strong reducing agents.<sup>36,37</sup> Arsine may also be released following poisoning by arsenic trioxide.<sup>38</sup>

**Toxicology and Signs and Symptoms of Arsine Poisoning**

**Arsine** is a powerful hemolysin, a toxic action not exhibited by other arsenicals. Arsine exposure occurs through inhalation with very little exposure required to cause a serious hemolytic reaction. Death is due to hemolysis and secondary renal failure. Exposure times of 30 minutes at 25-50 parts per million are considered lethal.<sup>39</sup>

Symptoms of poisoning usually appear 30-60 minutes after exposure but may be delayed for up to 24 hours. Patients may exhibit a garlic odor to their breath. Signs and symptoms are the result of sometimes profound hemolysis leading to hemolytic anemia and include fatigue, headache, malaise, weakness, dizziness, dyspnea, nausea, abdominal pain and vomiting. Red staining of the conjunctiva may be present. Free hemoglobin may be present in plasma. Basophilic stippling of red cells, red cell fragments, and ghosts are seen in the peripheral blood smear. Plasma will appear very dark, almost black, resulting from elevated level of unconjugated bilirubin.<sup>36</sup> Hyperkalemia secondary to hemolysis is possible.

Elevated concentrations of arsenic are found in the urine, but these are not nearly as high as are found in poisonings by solid arsenicals. Dark red urine (hemoglobinuria) is often passed 4-6 hours after exposure. Usually 1-2 days after hemoglobinuria appears, jaundice and bronzing of the skin may be evident. Abdominal tenderness, hepatomegaly, and elevated hepatic enzymes all may occur.<sup>36,40</sup>

Renal failure due to direct toxic action of arsine and to products of hemolysis represents the chief threat to life in arsine poisoning.<sup>41</sup>

Polyneuropathy and a mild psycho-organic syndrome are reported to have followed arsine intoxication after a latency of 1-6 months.

**Treatment of Arsine Toxicosis**

1. Remove the victim to fresh air.
2. Administer intravenous fluids to keep the urine as dilute as possible and to support excretion of arsenic and products of hemolysis. In the past urinary alkalization to pH 7.5 has been recommended, but this therapy is not proven.

**CAUTION:** *Monitor fluid balance carefully to avoid fluid overload if renal failure supervenes. Monitor plasma electrolytes, BUN and creatinine to detect disturbances (particularly hyperkalemia) as early as possible.*

3. Monitor urinary arsenic excretion to assess severity of poisoning. The amount of arsine that must be absorbed to cause poisoning is small, and therefore high levels of urinary arsenic excretion may not always occur, even in the face of significant poisoning.<sup>41,42</sup>
4. If poisoning is severe, consider red blood cell exchange transfusion. It was successful in rescuing one adult victim of arsine poisoning.<sup>36</sup>

5. Consider plasma exchange, which has also been used to treat acute arsine poisoning. A retrospective review study in China reported successful treatment of 12 patients.<sup>40</sup> Another case was treated with a combination of plasma exchange and red blood cell exchange transfusion.<sup>36</sup>
6. Use extracorporeal hemodialysis to maintain normal extracellular fluid composition and to enhance arsenic elimination if renal failure occurs, but it is not very effective in removing arsine carried in the blood.

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