CYANIDE POISONING

History and Epidemiology
Cyanide exposure is associated with smoke inhalation, laboratory mishaps, industrial incidents, suicide attempts, and criminal activity. Cyanide is a chemical group that consists of one atom of carbon bound to one atom of nitrogen by three molecular bonds (C≡N). Inorganic cyanides (also known as cyanide salts) contain cyanide in the anion form (CN⁻) and are used in numerous industries, such as metallurgy, photographic developing, plastic manufacturing, fumigation, and mining. Common cyanide salts include sodium cyanide (NaCN) and potassium cyanide (KCN). Sodium salts react readily with water to form hydrogen cyanide. Organic compounds that have a cyano group bonded to an alkyl residue are called nitriles. For example, methyl cyanide is also known as acetonitrile (CH₃CN). Hydrogen cyanide (HCN) is a colorless gas at standard temperature and pressure with a reported bitter odor. Cyanogen gas, a dimer of cyanide, reacts with water and breaks down into the cyanide anion. Cyanogen chloride (CNCl) is a colorless gas that is easily condensed; it is a listed agent by the Chemical Weapons Convention.

Many plants, such as the Manihot spp, Linum spp, Lotus spp, Prunus spp, Sorghum spp, and Phaseolus spp contain cyanogenic glycosides. The Prunus species consisting of apricots, bitter almond, cherry, and peaches have pitted fruits containing the glucoside amygdalin. When ingested, amygdalin is biotransformed by intestinal β-d-glucosidase to glucose, aldehyde, and cyanide (Fig. 126–1). Laetrile, which contains amygdalin, was inappropriately suggested to have antineoplastic properties despite a lack of evidence to support such claims. When laetrile was administered by intravenous infusion, amygdalin bypassed the necessary enzymes in the gastrointestinal tract to liberate cyanide and did not cause toxicity. However, ingested laetrile can cause cyanide poisoning. Despite data demonstrating its lack of utility in the treatment of cancer, it still is available via the Internet.

FIGURE 126–1.
Biotransformation of cyanogens (A) acetonitrile and (B) amygdalin to cyanide.
Cassava (*Manihot esculenta*) root is a major source of food for millions of people in the tropics. It is a hardy plant that can remain in the ground for up to 2 years and needs relatively little water to survive. Because the shelf life of a cassava root is short once it is removed from the stem, cassava root must be processed and sent to market as soon as it is harvested. However, proper processing must occur to assure the food’s safety. Processed cassava is called *Gari*. Linamarin (2-hydroxyisobutyryl-β-D-glycoside) is the major cyanogenic glycoside in cassava roots. It is hydrolyzed to hydrogen cyanide and acetone in two steps during the processing of cassava roots. Soaking peeled cassava in water for a single day releases approximately 45% of the cyanogens, whereas soaking for 5 days causes 90% loss. If processing is inefficient, linamarin and cyanohydrin, the immediate product of hydrolysis of linamarin, remain in the food. Consumed linamarin is hydrolyzed to cyanohydrin by β-glucosidases of the microorganisms in the intestines. Cyanohydrin present in the food and formed from linamarin then dissociates spontaneously to cyanide in the alkaline pH of the small intestines.

Iatrogenic cyanide poisoning may occur during use of nitroprusside for the management of hypertension. Each nitroprusside molecule contains five cyanide molecules, which are slowly released in vivo. If endogenous sulfate stores are depleted, as in the malnourished or postoperative patient, cyanide may accumulate even with therapeutic nitroprusside infusion rates (2–10 μg/kg/min).

In 1782, the Swedish chemist Carl Wilhelm Scheele first isolated hydrogen cyanide. He reportedly died from the adverse health effects of cyanide poisoning in 1786. Napoleon III was the first to employ hydrogen cyanide in chemical warfare, and it was subsequently used on World War I battlefields. During World War II, hydrocyanic acid pellets (brand name Zyklon B) caused more than one million deaths in Nazi gas chambers at Auschwitz, Buchenwald, and Majdanek. In 1978, KCN was used in a mass suicide led by Jim Jones of the People’s Temple in Guyana, resulting in 913 deaths. Other notorious suicide cases include Wallace Carothers, Herman Goring, Heinrich Himmler, and Ramon Sampedro. In 1982, seven deaths resulted from consumption of cyanide-tainted acetaminophen in Chicago that subsequently lead to the requirement of tamper-resistant pharmaceutical packaging. Numerous copycat murders subsequently have occurred using cyanide-tainted capsules, with the last high-profile case occurring in 2010 involving an Ohio emergency medicine physician who murdered his wife with a cyanide-laden calcium capsule. Cyanide has also been used for illicit euthanasia. Cyanide poisoning accounted for 1148 exposures reported to the American Association of Poison Control Centers from 2007 to 2011 (Chap. 136). One study of poison center data found
that 8.3% of intentional overdose cases died and another 9% developed cardiac arrest but survived; 74% did not receive an antidote, most likely due to the failure of the initial treatment team to recognize the poisoning.\textsuperscript{13} The majority of reported cyanide exposures are unintentional. These events frequently involve chemists or technicians working in laboratories where cyanide salts are common reagents.\textsuperscript{13} The potential for cyanide poisoning also exists following smoke inhalation, especially following the combustion of materials such as wool, silk, synthetic rubber, and polyurethane.\textsuperscript{8,30,108} Ingestion of cyanogenic chemicals (ie, acetonitrile, acrylonitrile, and propionitrile) is another source of cyanide poisoning.\textsuperscript{115} Acetonitrile (C\textsubscript{2}H\textsubscript{3}N) and acrylonitrile (C\textsubscript{3}H\textsubscript{3}N) are themselves nontoxic, but biotransformation via cytochrome P450 liberates cyanide (Fig. 126–1).\textsuperscript{126}

**Pharmacology**

The dose of cyanide required to produce toxicity is dependent on the form of cyanide, the duration of exposure, and the route of exposure. However, cyanide is an extremely potent toxin with even small exposures leading to life-threatening symptoms. For example, an adult oral lethal dose of KCN is approximately 200 mg. An airborne concentration of 270 ppm (μg/mL) of hydrogen cyanide (HCN) may be immediately fatal, and exposures >110 ppm for more than 30 minutes are generally considered lifethreatening. The current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for both hydrogen cyanide and cyanogen is 10 ppm as an 8-hour time-weighted average (TWA) concentration. The Immediately Dangerous to Life or Health (IDLH) value for hydrogen cyanide is 50 ppm.

Acute toxicity occurs through a variety of routes, including inhalation, ingestion, dermal, and parenteral. Hydrogen cyanide readily crosses membranes because it has a low molecular weight (27 Da) and is nonionized. After absorption and dissolution in blood, cyanide exists in equilibrium as the cyanide anion (CN\textsuperscript{-}) and undissociated HCN. Hydrogen cyanide is a weak acid with a pK\textsubscript{a} of 9.21. Therefore, at physiologic pH 7.4 it exists primarily as HCN. Rapid diffusion across alveolar membranes followed by direct distribution to target organs accounts for the rapid lethality associated with HCN inhalation.

**Toxicokinetics**

Cyanide is eliminated from the body by multiple pathways. The major route for detoxification of cyanide is the enzymatic conversion to thiocyanate. Two sulfurtransferase enzymes, rhodanese (thiosulfate-cyanide sulfurtransferase) and β-mercaptopyruvate-cyanide sulfurtransferase, catalyze this reaction. The primary pathway for metabolism is rhodanese, which is widely distributed throughout the body and has the highest concentration in the liver. This enzyme catalyzes the transfer of a sulfane sulfur from a sulfur donor, such as thiosulfate to cyanide to form
thiocyanate. In acute poisoning, the limiting factor in cyanide detoxification by rhodanese is the availability of adequate quantities of sulfur donors. The endogenous stores of sulfur are rapidly depleted, and cyanide metabolism slows. Hence, the efficacy of sodium thiosulfate as an antidote stems from its normalization of the metabolic inactivation of cyanide. The sulfation of cyanide is essentially irreversible, and the sulfation product thiocyanate has relatively little inherent toxicity. Thiocyanate is eliminated in urine. A number of minor pathways of metabolism (<15% of total) account for cyanide elimination, including conversion to 2-aminothiazoline-4-carboxylic acid, incorporation into the 1-carbon metabolic pool, or in combination with hydroxycobalamin to form cyanocobalamin.

Limited human data regarding the cyanide elimination half-life are available. Elimination appears to follow first-order kinetics, although it varies widely in reports (range 1.2–66 hours). Disparity in values may result from the number of samples used to perform calculations and the effects of antidotal treatment. The volume of distribution of the cyanide anion varies according to species and investigator, with 0.075 L/kg reported in humans.

**Pathophysiology**

Cyanide is an inhibitor of multiple enzymes, including succinic acid dehydrogenase, superoxide dismutase, carbonic anhydrase, and cytochrome oxidase. Cytochrome oxidase is an iron containing metalloenzyme essential for oxidative phosphorylation and, hence, aerobic energy production. It functions in the electron transport chain within mitochondria, converting catabolic products of glucose into adenosine triphosphate (ATP). Cyanide induces cellular hypoxia by inhibiting cytochrome oxidase at the cytochrome a₃ portion of the electron transport chain (Fig. 126–2). Hydrogen ions that normally would have combined with oxygen at the terminal end of the chain are no longer incorporated. Thus, despite sufficient oxygen supply, oxygen cannot be utilized, and ATP molecules are no longer formed. Unincorporated hydrogen ions accumulate, contributing to acidemia.

**FIGURE 126–2.**

Pathway of cyanide and hydrogen sulfide toxicity and detoxification.

Hyperlactemia occurs following cyanide poisoning because of failure of aerobic energy metabolism. During aerobic conditions, when the electron transport chain is functional, lactate is converted to pyruvate by mitochondrial lactate dehydrogenase. In this process, lactate donates
hydrogen moieties that reduce nicotinamide adenine dinucleotide (NAD\(^+\)) to NADH. Pyruvate then enters the tricarboxylic acid cycle, with resulting ATP formation. When cytochrome a\(_3\) within the electron transport chain is inhibited by cyanide, there is a relative paucity of NAD\(^+\) and predominance of NADH, favoring the reverse reaction, in which pyruvate is converted to lactate.

Cyanide is also a potent neurotoxin. Cyanide exhibits a particular affinity for regions of the brain with high metabolic activity. Central nervous system (CNS) injury occurs via several mechanisms, including impaired oxygen utilization, oxidant stress, and enhanced release of excitatory neurotransmitters. Cranial imaging of survivors of cyanide poisoning reveals that injury occurs in the most oxygen-sensitive areas of the brains, such as the basal ganglia, cerebellum, and sensorimotor cortex.

Cyanide enhances \(N\)-methyl-d-aspartate (NMDA) receptor activity and directly activates the NMDA receptor, which increases release of glutamate and inhibits voltage-dependent magnesium blockade of the NMDA receptor. This NMDA receptor stimulation results in \(\text{Ca}^{2+}\) entry into the cytosol of neurons. Cyanide also activates voltage-sensitive calcium channels\(^{64}\) and mobilizes \(\text{Ca}^{2+}\) from intracellular stores\(^{81,98}\). As a result, cytosolic \(\text{Ca}^{2+}\) rises and activates a series of biochemical reactions that lead to the generation of reactive oxygen species and nitrous oxide\(^{70,84,106}\). These reactive oxygen species initiate peroxidation of cellular lipids, which, together with cyanide-induced inhibition of the respiratory chain, adversely affect mitochondrial function, initiating cytochrome c release and execution of apoptosis, necrosis, and subsequent neurodegeneration\(^{6,64,97,107}\). Experimental studies demonstrate that NMDA inhibitors such as dextrophan and dizocilpine, antioxidants, and cyclooxygenase inhibitors all protect neurons against cyanide-induced damage\(^{61,77,125}\).

Sulfurtransferase metabolism via rhodanese is crucial for detoxification. However, the aforementioned cyanide-induced metabolic derangement may decrease enzyme detoxification. Decreased ATP and reactive oxygen species and increased cytosolic \(\text{Ca}^{2+}\) stimulate protein kinase C activity, which in turn inactivates rhodanese\(^3\).

**Clinical Manifestations**

**Acute Exposure to Cyanide.**

The amount, duration of exposure, route of exposure, and premorbid condition of the individual influence the time to onset and severity of illness. A critical combination of these factors overwhelms endogenous detoxification pathways, allowing cyanide to diffusely affect cellular function within the body. No reliable pathognomonic symptom or toxic syndrome is associated with acute cyanide poisoning\(^4\). The initial clinical effects of acute cyanide poisoning may be nonspecific, generalized, and nondiagnostic, thereby making the correct diagnosis difficult to
obtain. Clinical manifestations reflect rapid dysfunction of oxygen-sensitive organs, with central nervous and cardiovascular findings predominating. The time to onset of symptoms typically is seconds with inhalation of gaseous HCN or intravenous injection of a water soluble cyanide salt and several minutes following ingestion of an inorganic cyanide salt. The clinical effects of cyanogenic chemicals often are delayed, and the time course varies among individuals (ranging from 3–24 hours), depending on their rate of biotransformation. Clinically apparent cyanide toxicity may occur within hours to days of initiating nitroprusside infusion, although concurrent administration of thiosulfate or hydroxocobalamin may prevent toxicity (Chap. 63).

CNS signs and symptoms are typical of progressive hypoxia and include headache, anxiety, agitation, confusion, lethargy, nonreactive dilated pupils seizures, and coma. A centrally mediated tachypnea occurs initially, followed by bradypnea and apnea. Cardiovascular responses to cyanide are complex. Studies of isolated heart preparations and intact animal models show that the principal cardiac insult is slowing of rate and loss of contractile force. Several reflex mechanisms, including catecholamine release and central vasomotor activity, may modulate myocardial performance and vascular response in patients with cyanide poisoning. In laboratory investigations, a brief period of increased inotropy caused by reflex compensatory mechanisms occurs before myocardial depression. Clinically, an initial period of tachycardia and hypertension may occur, followed by hypotension with reflex tachycardia, but the terminal event is consistently bradycardia and hypotension. Ventricular dysrhythmias do not appear to be an important factor.

Pulmonary edema may be found at necropsy. Inhalation of HCN may be associated with mild corrosive injury to the respiratory tract mucosa.

Gastrointestinal toxicity may occur following ingestion of inorganic cyanide and cyanogens and includes abdominal pain, nausea, and vomiting. These symptoms are caused by hemorrhagic gastritis, which is frequently identified on necropsy, and are thought to be secondary to the corrosive nature of cyanide salts. However, if death occurs rapidly, this gastritis may not be seen at autopsy because development of inflammation occurs over time. Following ingestion, a smell of bitter almonds should not be relied upon to be emitted from the gastrointestinal system as health care providers in nearly all case reports published do not mention this finding.

Cutaneous manifestations may vary. Traditionally, a cherry-red skin color is described as a result of increased venous hemoglobin oxygen saturation, which results from decreased utilization of oxygen at the tissue level. This phenomenon may be more evident on funduscopic examination, where veins and arteries may appear similar in color. Despite the inference in the name, cyanide
does not directly cause cyanosis. The occurrence of cyanosis is commonly reported in published case reports and is likely due to cardiovascular collapse and subsequent poor perfusion.

**Delayed Clinical Manifestations of Acute Exposure.**
Survivors of serious, acute poisoning may develop delayed neurologic sequelae. Parkinsonian symptoms, including dystonia, dysarthria, rigidity, and bradykinesia, are most common. Symptoms typically develop over weeks to months, but subtle findings can be present within a few days. Head computerized tomography and magnetic resonance imaging consistently reveal basal ganglia damage to the globus pallidus, putamen, and hippocampus, with radiologic changes appearing several weeks after onset of symptoms. Whether delayed manifestations result from direct cellular injury or secondary hypoxia is unclear. Extrapyramidal manifestations may progress or resolve. Response to pharmacotherapy with antiparkinsonian agents is generally disappointing.

**Chronic Exposure to Cyanide.**
Chronic exposure to cyanide may result in insidious syndromes, including tobacco amblyopia, tropical ataxic neuropathy, and Leber hereditary optic neuropathy. Tobacco amblyopia is a progressive loss of visual function that occurs almost exclusively in men who smoke cigarettes. Affected smokers have lower serum cyanocobalamin and thiocyanate concentrations than unaffected smoking counterparts, suggesting a reduced ability to detoxify cyanide. Cessation of smoking and administration of hydroxocobalamin often reverses symptoms. Tropical ataxic neuropathy is a demyelinating disease associated with improperly processed cassava consumption. Neurologic manifestations include Parkinson disease, spastic paraparesis, sensory ataxia, optic atrophy, and sensorineural hearing loss. Concomitant dermatitis and glossitis suggest an association of high dietary cassava with low vitamin B₁₂ intake. Elevated thiocyanate concentrations in affected individuals further implicate cyanide as the etiology. Removal of dietary cassava and institution of vitamin B₁₂ therapy alleviates symptoms. Leber hereditary optic atrophy, a condition of subacute visual failure affecting men, is thought to be caused by rhodanese deficiency.

Chronic exposure to cyanide is associated with thyroid disorders. Thiocyanate is a competitive inhibitor of iodide entry into the thyroid, thereby causing the formation of goiters and the development of hypothyroidism. Chronic exposure to cyanide in animals is associated with hydropic degeneration in hepatocytes and epithelial cells of the renal proximal tubules; however, these morphologic lesions are not linked to functional alternations.

**Diagnostic Testing**
Because of nonspecific symptoms and delay in laboratory cyanide confirmation, the clinician must rely on historical circumstances and some initial findings to raise suspicion of cyanide poisoning and institute therapy (Table 126–1).

### Table 126–1. Cyanide Poisoning: Emergency Management Guidelines

Laboratory findings suggestive of cyanide poisoning reflect the known metabolic abnormalities, which include metabolic acidosis, elevated lactate concentration, and increased anion gap. Elevated venous oxygen saturation results from reduced tissue extraction. A venous oxygen saturation >90% from superior vena cava or pulmonary artery blood indicates decreased oxygen utilization. This finding is not specific for cyanide and could represent cellular poisoning from other agents such as carbon monoxide, clenbuterol, hydrogen sulfide, and sodium azide, or medical conditions such as sepsis high-output cardiac syndromes and left to right intracardiac shunts.

Hyperlactatemia is found in numerous critical illnesses and typically is a nonspecific finding. However, a significant association exists between blood cyanide and serum lactate concentrations. ABG analysis of whole blood may provide additional information. Arterial pH correlates inversely with cyanide concentration. The finding of a narrow arterial–venous oxygen difference also may suggest cyanide toxicity.

Cyanide results in nonspecific electrocardiographic (ECG) findings. Rhythm disturbances such as sinus tachycardia, bradydysrhythmias, atrial fibrillation, ventricular tachycardia, and ventricular fibrillation are all reported, as are elevation or depression of the ST segment, shortened ST segments, and fusion of the T wave into the QRS complex.

Blood cyanide concentration determination can confirm toxicity, but this determination is not available in a sufficiently rapid manner to affect initial treatment. Whole blood or serum can be analyzed, with most reports utilizing whole blood for cyanide detection. In mammals, including primates, whole-blood concentrations are twice serum concentrations as a result of cyanide sequestration in red blood cells. Background whole-blood concentrations in nonsmokers range between 0.02 and 0.5 μg/mL. Higher blood concentrations suggest toxicity. Coma and respiratory depression are associated with whole blood concentrations >2.5 μg/mL and death with concentrations >3 μg/mL. Detecting urinary cyanide is difficult, and urinary thiocyanate is a more readily detectable and useful marker of cyanide exposure. Serum thiocyanate
concentrations are of little value in assessing patients with acute poisoning because of little correlation with symptoms but are useful in confirming exposure.

A semiquantitative assay that uses calorimetric paper test strips may immediately detect cyanide. Cyantesmo test strips currently are used by water treatment facilities to detect cyanide. An investigation of the utility of these strips in clinical practice found that the test strips incrementally increased to a deep blue color over a progressively longer portion of the test strip with increasing concentrations of cyanide in the blood. These strips accurately and rapidly detected, in a semiquantifiable manner, CN concentrations >1 μg/mL.

**Management**

Because cyanide poisoning is rare, it is easy to overlook the diagnosis unless there is an obvious history of exposure. Thus, the most critical step in treatment is considering the diagnosis in high-risk situations (Table 126–1) and initiating empiric therapy with 100% oxygen and either hydroxycobalamin or the cyanide antidote kit. The initial care (Table 126–1) of the cyanide-poisoned patient begins by directing attention to airway patency, ventilatory support, and oxygenation. Acidemia should be treated with adequate ventilation and sodium bicarbonate administration.

Intravenous access should be rapidly obtained and blood samples sent for renal function, glucose, and electrolyte determinations. A whole-blood cyanide concentration can be obtained for later confirmation of exposure. ABG analysis and serum lactate concentration will help assess acid–base status. Initiation of crystalloid and infusion of vasopressor for hypotension are warranted.

First responders should exercise extreme caution when entering potentially hazardous areas such as chemical plants and laboratories where a previously healthy person is “found down.” Exposure to cyanide may occur by multiple routes, including ingestion, inhalation, dermal, and parenteral. For patients with inhalation exposure, removal from the area of exposure is critical. Further decontamination is generally unnecessary. Decontamination of the cyanide-poisoned patient occurs concurrently with initial resuscitation. The health care provider should always be protected from potential dermal contamination by using personal protective devices such as water-impervious gowns, gloves, and eyewear. For patients with cutaneous exposure, remove their clothing, brush any powder off the skin, and flush the skin with water. Particular attention should be given to open wounds because CN⁻ or HCN is readily absorbed through abraded skin.

Instillation of activated charcoal often is considered ineffective because of low binding of cyanide (1 g activated charcoal only adsorbs 35 mg cyanide). However, a potentially lethal oral
dose of cyanide (ie, a few hundred milligrams) is within the adsorptive capacity of a typical 1 g/kg dose of activated charcoal. Prophylactic activated charcoal administration improved survival in animals given an LD_{50} dose of KCN. Based on the potential benefits and minimal risks, activated charcoal may be considered in the patient with an intact protected airway.

Although either hydroxocobalamin or the cyanide antidote kit can be administered as soon as cyanide poisoning is suspected, hydroxocobalamin is preferred. Hydroxocobalamin is a metalloprotein with a central cobalt atom that complexes cyanide, forming cyanocobalamin (vitamin B_{12}). Cyanocobalamin is eliminated in the urine or releases the cyanide moiety at a rate sufficient to allow detoxification by rhodanese. One molecule of hydroxocobalamin binds one molecule of cyanide, yielding a molecular weight binding ratio of 50:1. The US-approved adult starting dose is 5 g administered by intravenous infusion over 15 minutes. Depending upon the severity of the poisoning and the clinical response, a second dose of 5 g may be administered by intravenous infusion for a total dose of 10 g. Hydroxocobalamin has few adverse effects, which include allergic reaction and a transient reddish discoloration of the skin, mucous membranes, and urine. No hemodynamic adverse effects other than a potential mild transient rise of blood pressure are observed (Antidotes in Depth: A41).

The cyanide antidote kit contains amyl nitrite, sodium nitrite, and sodium thiosulfate. Both thiosulfate and nitrite individually have antidotal efficacy when given alone in animal models of cyanide poisoning, but they have even greater benefit when they are given in combination. Thiosulfate donates the sulfur atoms necessary for rhodanese-mediated cyanide biotransformation to thiocyanate. The mechanism of nitrite is less clear. Traditional rationale relies on the ability of nitrite to generate methemoglobin. Because cyanide has a higher affinity for methemoglobin than for cytochrome a, cytochrome oxidase function is restored. However, improved hepatic blood flow and nitric oxide formation are alternate explanations (Antidotes in Depth: A39 and A40). Amyl nitrite is contained within glass pearls that are crushed and intermittently inhaled or intermittently introduced into the ventilator system to initiate methemoglobin formation. The amyl nitrite pearls are reserved for cases where intravenous access is delayed or not possible. Intravenous sodium nitrite is preferred and is supplied as a 10-mL volume of 3% solution (300 mg). Adverse effects of nitrites include excessive methemoglobin formation and, because of potent vasodilation, hypotension and tachycardia. Avoiding rapid infusion, monitoring blood pressure, and adhering to dosing guidelines will limit adverse effects. Because of the potential for excessive methemoglobinemia during nitrite treatment, pediatric dosing guidelines are available (Table 126–2). Sodium thiosulfate is the second component of the cyanide antidote kit. It is supplied as 50 mL of 25% solution (12.5 g). It is a substrate for the
reaction catalyzed by rhodanese that is essentially irreversible, converting a highly toxic entity to a relatively harmless compound. However, thiocyanate does have its own toxicity in the presence of kidney failure, including abdominal pain, vomiting, rash, and CNS dysfunction. Thiosulfate itself is not associated with significant adverse reactions. The pediatric dose of thiosulfate is adjusted for weight.

TABLE 126–2. Cyanide Management: Pediatric Sodium Nitrite Guidelines

In Europe, 4-dimethylaminophenol (4-DMAP), rather than sodium nitrite, is the methemoglobin-inducer of choice.\textsuperscript{54} It generates methemoglobin more rapidly than sodium nitrite, with peak methemoglobin concentrations at 5 minutes after 4-DMAP rather than 30 minutes after sodium nitrite. The dose of 4-DMAP is 3 mg/kg and is coadministered with thiosulfate. As with sodium nitrite, its major adverse effect is excessive methemoglobin formation and potential for hypotension. Cobalt in the form of dicobalt edetate has been used as a cyanide chelator, but its usefulness is limited by serious adverse effects such as hypotension, cardiac dysrhythmias, decreased cerebral blood flow, and angioedema.\textsuperscript{22,86} The cobalamin precursor cobinamide has been used both prophylactically and therapeutically to treat experimental cyanide toxicity, and when given at high enough doses, it has rescued animals from cyanide-induced apnea and coma.\textsuperscript{23} Cobalamin has been used in France to treat human cyanide exposure, either alone or combined with sodium thiosulfate. Cobinamide is an investigational treatment that has a much greater affinity for cyanide ion than cobalamin.\textsuperscript{29} Hyperbaric oxygen has been considered in the past, but recent evidence suggests no benefit in cyanide poisoning.\textsuperscript{76}

In animal models, the antioxidant vitamins A, C, and E diminish the extent of tissue damage caused by subacute cyanide intoxication.\textsuperscript{89} This is especially important in the tropics, where the majority of dietary staples are cyanophoric crops such as cassava.

Patients who do not survive cyanide poisoning are suitable organ donors. Heart, liver, kidney, pancreas, cornea, skin, and bone have been successfully transplanted following cyanide poisoning.\textsuperscript{41}

**HYDROGEN SULFIDE POISONING**

**History and Epidemiology**
Hydrogen sulfide (H₂S) exposures are often dramatic and can be fatal. The American Association of Poison Control Centers’ National Poison Data System reported 5383 exposures from 2007 through 2011 (Chap. 136). Only 1534 of these exposures required evaluation at a health care facility, 457 reported moderate or major effects, and 36 deaths occurred. Over a 10 year period from 1983 to 1992, 5563 exposures and 29 deaths attributed to hydrogen sulfide were reported in the National Poison Data System. Most often, serious consequences of hydrogen sulfide exposures occur through workplace exposures, but they can also occur in environmental disasters and most recently in suicides.

Bacterial decomposition of proteins generates hydrogen sulfide, and the gas is produced in many industrial activities. Decay of the sulfur-containing products such as fish, sewage, and manure produce hydrogen sulfide. Industrial sources include pulp paper mills, heavy-water production, the leather industry, roofing asphalt tanks, vulcanizing of rubber, viscose rayon production, and coke manufacturing from coal. It is a major industrial hazard in oil and gas production, particularly in sour gas fields (natural gas containing sulfur).

Between 1990 and 1999, hydrogen sulfide poisoning was associated with the deaths of 18% of US construction workers killed by toxic inhalation. Many died while working in confined spaces such as sewers or sewer manholes. Agricultural workers operating near livestock manure storage tanks are at greatest risk of harm from an inhalation exposure. Poisoned workers are “knocked down,” prompting coworkers to attempt a rescue. Numerous case reports describe multiple victims because the would-be rescuers often themselves become victims when they attempt a rescue in an environment having high concentrations of hydrogen sulfide. Studies report that up to 25% of fatalities involve rescuers.

OSHA and a variety of occupational organizations such as the American Industrial Hygiene Association, the National Institute of Occupational Safety and Health, the American Shipbuilding Association, and the US Chemical Safety Board recognize the serious dangers of hydrogen sulfide exposures in the workplace and continue to promote safety alerts and educational programs.

Natural sources of hydrogen sulfide are volcanoes, caves, sulfur springs, and underground deposits of natural gas. Hydrogen sulfide is also implicated in several environmental disasters. In 1950, 22 people died and 320 were hospitalized in Poza Rica, Mexico, when a local natural gas facility inadvertently released hydrogen sulfide into the air. Hydrogen sulfide claimed nine lives when a sour gas well failed, releasing a cloud of the poisonous gas into the Denver City, Texas community in 1975. In 2003, a gas drilling incident in southwest China released natural
gas and a cloud of hydrogen sulfide into a populated area, killing more than 200 people, injuring 9000, and necessitating the evacuation of more than 40,000.129

Recently, a large number of suicides called "chemical suicides" or "detergent suicides" have been attributed to mixing common household chemicals such as pesticides or fungicides and toilet bowl cleaners to create hydrogen sulfide gas.116,119 This practice is of concern because the recipes are easily found on Internet sites, precursor chemicals are readily accessible from the cleaning section of many local stores, first responders are at risk of harmful toxic effects from exposure, and the toxic gas can inadvertently expose groups of people in nearby buildings. In Japan, it is reported that more than 500 people killed themselves in the first half of 2008 by this means.130 Information resources on the Internet are implicated for the widespread practice and prompted police to request purging the suicide recipes from Internet sites.44 In the United States, chemical suicides from hydrogen sulfide are likely underreported but rose from 2 in 2008 to 19 in 2010.100 In as many as 80% of incidents, first responders report exposures following attempted rescue of victims.100 Suicide victims using this method to harm themselves inadvertently cause injuries and evacuations because of the toxic gas permeating buildings. One incident in Japan caused 90 people to become ill from the toxic gas as it permeated an apartment building, and another resulted in 350 people evacuating a building.119

**Pharmacology and Toxicokinetics**

Hydrogen sulfide is a colorless gas, more dense than air, with an irritating odor of "rotten eggs." It is highly lipid soluble, a property that allows easy penetration of biologic membranes. Systemic absorption usually occurs through inhalation, and it is rapidly distributed to tissues.101

The tissues most sensitive to hydrogen sulfide are those with high oxygen demand. The systemic toxicity of hydrogen sulfide results from its potent inhibition of cytochrome oxidase, thereby interrupting oxidative phosphorylation.31 Hydrogen sulfide binds to the ferric (Fe³⁺) moiety of cytochrome a₃ oxidase complex with a higher affinity than does cyanide. The resulting inhibition of oxidative phosphorylation produces cellular hypoxia and anaerobic metabolism.31,131

Cytochrome oxidase inhibition is not the sole mechanism of toxicity. Other enzymes are inhibited by hydrogen sulfide and may contribute to its toxic effects.31 Besides producing cellular hypoxia, hydrogen sulfide alters brain neurotransmitter release and transmission through potassium channel–mediated hyperpolarization of neurons, potentiate NMDA receptors, and other neuronal inhibitory mechanisms.90,132 A proposed mechanism of death is poisoning of the brainstem respiratory center through selective uptake by lipophilic white matter in this region.127 The olfactory nerve is a specific target of great interest. Not only does the toxic gas cause olfactory nerve paralysis, but it is thought to be a portal of entry into the central nervous system because
of its direct contact with the brain. It is also cytotoxic through formation of reactive sulfur and oxygen species. It may also react with iron to fuel the Fenton reaction causing free radical injury (Chaps. 12 and 13).

In addition to systemic effects, hydrogen sulfide reacts with the moisture on the surface of mucous membranes to produce intense irritation and corrosive injury. The eyes and nasal and respiratory mucous membranes are the tissues most susceptible to direct injury. Despite skin irritation, it has little dermal absorption.

Along with nitric oxide and carbon monoxide, researchers recently recognized hydrogen sulfide as a signaling molecule of the cardiovascular, inflammatory, and nervous systems, and therefore, they proposed to add hydrogen sulfide as the “third endogenous gaseous transmitter.” In 2005, a report in Science demonstrated mice inhaling a low dose of hydrogen sulfide, which decreased their metabolic demands and caused them to enter a “suspended animationlike state.” This report propelled researchers into studies probing the biosynthesis, metabolism, and physiological responses of hydrogen sulfide in hopes of developing future beneficial therapies to combat the adverse consequences of ischemia/reperfusion injury. The research results reveal fascinating and sometimes puzzling and contradictory results. Administering hydrogen sulfide to rodents appears to switch off metabolic demands and protect some species from ischemic insults. On the contrary, large animal models have yet to show global protection but support local, organ-specific protective effects. In total, these studies reveal hydrogen sulfide to have complex interactions that are variable among organ systems and species while clearly demonstrating a dose-dependent effect with higher exposures producing the well-known toxic effects. Besides its ability to attenuate metabolic demands during ischemia, hydrogen sulfide influences many signaling pathways and has vasodilating, neuromodulating, anti-inflammatory, anti-apoptotic, and antioxidant effects. Using hydrogen sulfide as a therapy requires additional investigation, but several hydrogen sulfide donating drugs are already in clinical trials. Researchers’ enthusiastic pursuit of a better understanding of hydrogen sulfide with an intent to create innovative therapies will likely also benefit our understanding of its mechanisms of toxicity and potentially lead to new treatments for toxic exposures.

Inhaled hydrogen sulfide enters the systemic circulation where it dissociates into hydrosulfide ions (HS⁻), sulfide (S⁻), and sulfate (SO₄²⁻). Once dissociated, hydrosulfide ions interact with metalloproteins, disulfide containing enzymes, and thio dimethyl S transferase. Hydrogen sulfide and dissociation products are then rapidly metabolized by oxidation, methylation, and binding to metalloproteins. The major pathway of detoxification is enzymatic and nonenzymatic oxidation of sulfides and sulfur to thiosulfate and polysulfides. Other pathways, such as methylation to
dimethyl sulfide and conversion to sulfite or sulfate by oxidized glutathione, also may play a role in detoxification and elimination. Sulfhemoglobin is not found in significant concentrations in the blood of animals or fatally poisoned humans.

**Clinical Manifestations**

**Acute Manifestations.**

Hydrogen sulfide poisoning should be suspected whenever a person is found unconscious in an enclosed space, especially if the odor of rotten eggs is noted. The primary target organs of hydrogen sulfide poisoning are those of the CNS and respiratory system. The clinical findings reported in two large series are listed in **Table 126–3**.

<table>
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<th>Hydrogen Sulfide Poisoning</th>
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| Hydrogen sulfide poisoning has a distinct dose response, and the intensity of exposure likely accounts for the diverse clinical findings in the reports. The odor threshold is between 0.01 and 0.3 ppm, and a strong intense odor is noted at 20 to 30 ppm. Mild mucous membrane irritation occurs at 20 to 100 ppm. Olfactory nerve paralysis occurs at 100 to 150 ppm rapidly extinguishing the ability to perceive the gas odor at higher concentrations. Prolonged exposure can occur when the extinction of odor recognition is misinterpreted as dissipation of the gas. Strong irritation of the upper respiratory tract and eyes and ARDS occur at 150 to 300 ppm. At >500 ppm, hydrogen sulfide produces systemic effects. Rapid unconsciousness and cardiopulmonary arrest occur at concentrations >700 ppm. At 1000 ppm, breathing may cease after one to two breaths.

Hydrogen sulfide reacts with the moisture on the surface of mucous membranes to produce intense irritation and corrosive injury. Mucous membrane irritation of the eye produces keratoconjunctivitis. If exposure persists, damage to the epithelial cells produces reversible corneal ulcerations (“gas eye”) and, rarely, irreversible corneal scarring. The irritant effects on the respiratory tract include rhinitis, bronchitis, and ARDS.

Neurologic manifestations are common and may be severe. Hydrogen sulfide’s rapid and deadly onset of clinical effects have been termed the “slaughterhouse sledgehammer” effect. In one case series, 75% of 221 patients with acute hydrogen sulfide exposure lost consciousness at the time of exposure. If the patient is rapidly removed from the exposure, recovery may be prompt and complete. Hypoxia from respiratory compromise can cause secondary neurologic
Neurologic outcome can be quite variable, ranging from no neurologic impairment to permanent sequelae. Delayed neuropsychiatric sequelae may occur after acute exposures. Most evidence suggests that the early rapid CNS effects are direct neurotoxic effects of hydrogen sulfide, whereas the permanent neurologic sequelae result from hypoxia secondary to respiratory insufficiency. Reported neuropsychiatric changes include memory failure (amnestic syndrome), lack of insight, disorientation, delirium, and dementia. Neurosensory abnormalities include transient hearing impairment, vision loss, and anosmia. Motor symptoms are likely caused by injury to the basal ganglia and result in ataxia, position/intention tremor, and muscle rigidity. Common neuropathologic findings observed on neuroimaging and at autopsy are subcortical white matter demyelination and globus pallidus degeneration.

Acute exposures also affect other organ systems. Myocardial hypoxia or direct toxic effects of hydrogen sulfide on cardiac tissue may cause cardiac dysrhythmias, myocardial ischemia, or myocardial infarction. Because unresponsiveness is rapid, trauma from falls should not be overlooked. In a report, 7% of patients experiencing a “knockdown” had associated traumatic injuries.

**Chronic Manifestations.**

Most data about chronic low-level exposures to hydrogen sulfide come from oil and gas industry workers. Mucous membrane irritation seems to be the most prominent problem in patients with low-concentration exposures. Workers report nasal, pharyngeal, and eye irritation, fatigue, headache, dizziness, and poor memory with low-concentration, chronic exposures. The chronic irritating effects of hydrogen sulfide were thought to be the cause of reduced lung volumes observed in sewer workers. Volunteer studies have not demonstrated significant cardiovascular effects after long term exposure to concentrations less than 10 ppm. The liver, kidneys, and endocrine system are unaffected. No studies demonstrate increased incidences of cancer with low-level exposures.

Rapid loss of consciousness from hydrogen sulfide exposure was a well-known and, amazingly, accepted part of the workplace in the gas and oil industry for many years. Some workers experienced repeated “knockdowns,” and these workers reported an increased incidence of respiratory diseases and cognitive deficits. Single or repeated high-concentration exposures resulting in unconsciousness can cause serious cognitive dysfunction. The acute effects of rapid loss of consciousness are most likely due to hydrogen sulfide neurotoxicity. Although a clear association exists between knock-down and chronic neurologic sequelae, many of the case reports are complicated by associated apnea or hypoxemia from respiratory failure, asphyxia or exposure to other xenobiotics in a confined space, head injury from a fall, or near drowning in
liquid manure or sludge. The association of neurotoxic sequelae are less clear with protracted low-concentration exposures. Case series suggest that low-concentration exposures can cause subtle changes that can be measured by only the most sensitive neuropsychiatric tests.

Epidemiologic data regarding the effects of low-concentration environmental exposures to hydrogen sulfide are clouded in populations exposed to complex mixtures of pollutants. Other malodorous sulfur compounds (eg, methyl mercaptan and methyl sulfide) are generated as byproducts of pulp mills. Study populations exposed to this complex mixture of pollutants demonstrate a dose-related increase in nasal symptoms, cough, nausea, and vomiting.

These changes are nonspecific, and the many of the cases have a poorly documented exposure assessment. Currently, the association of protracted and low-concentration hydrogen sulfide exposure with chronic neurological sequelae remains controversial and needs further study.

The strong odor of low concentrations of hydrogen sulfide can magnify irritant effects by triggering a strong psychological response. The odor of hydrogen sulfide at low levels has been the alleged source of mass psychogenic illness cases. Clinical, epidemiologic, and toxicologic analyses suggested that 943 cases of illness in Jerusalem were caused by the odor of low concentrations of hydrogen sulfide gas. The most frequent associated symptoms are headaches; faintness; dizziness; nausea; chest tightness; dyspnea and tachypnea; eye, nose, and throat irritation; weakness; and extremity numbness. Low concentration exposure to hydrogen sulfide may produce nonspecific signs and symptoms that could closely mimic psychogenic illness. Attempting to identify true toxicity from a powerful emotional reaction can be extremely difficult. Therefore, symptomatic patients must be assessed for toxicity even when mass psychogenic illness is suspected.

**Diagnostic Testing**

In hydrogen sulfide poisoning, diagnostic testing is of limited value for clinical decision making following acute exposures, confirmation of acute exposures, occupational monitoring, and forensic analysis following fatal accidents.

Clinicians must base management decisions on history, clinical presentation, and diagnostic tests that infer the presence of hydrogen sulfide because no method is available to rapidly and directly measure the gas or its metabolites. Circumstances surrounding the patient’s illness often provide the best evidence for hydrogen sulfide poisoning. At the bedside, the smell of rotten eggs on clothing or emanating from the blood, exhaled air, or gastric secretions suggests hydrogen sulfide exposure. In addition, darkening of silver jewelry is a clue to exposure.
Paper impregnated with lead acetate changes color when exposed to hydrogen sulfide and is used to detect its presence in the patient’s exhaled air but is not rapidly available. Specific tests for confirming hydrogen sulfide exposure are not readily available in clinical laboratories. Therefore, directly measuring the gas in atmospheric air samples by monitoring devices provides stronger evidence of hydrogen sulfide as the causative agent. Epidemiologic data show hydrogen sulfide as one of the most common causes of death and injury from toxic inhalation in confined spaces, especially manholes and sewers. Recognizing confined spaces as extremely hazardous environments, OSHA published the Confined Space Entry Standard to protect workers. It mandates training, rescue procedures, and atmospheric testing before entry, including measuring for the presence of hydrogen sulfide. Because of OSHA’s regulations, most emergency response teams are equipped to investigate toxic environments from hazardous materials incidents using a “four-gas detection unit” that measures hydrogen sulfide by electrochemical sensors along with measurements for atmospheric oxygen concentration and the presence of explosive gases and carbon monoxide. In general, the clinician must interpret environmental detection results with caution. Toxic gases may dissipate prior to atmospheric air sample collection, leading to negative results, or interfering gases can trigger false positive readings on detection devices. A positive reading on a field device does not equate to confirmation of that specific gas. Clinical decision making should consider correlation with other circumstantial and clinical data and not rely solely on detection results.

In acute poisoning, readily available diagnostic tests that are biomarkers of hydrogen sulfide poisoning may be useful but are nonspecific. ABG analysis demonstrating metabolic acidosis with an associated elevated serum lactate concentration is expected, and oxygen saturation should be normal unless ARDS is present. Hydrogen sulfide, like cyanide, decreases oxygen consumption and is reflected as an elevated mixed venous oxygen measurement. Because sulfhemoglobin typically is not generated in patients with hydrogen sulfide poisoning, an oxygen saturation gap is not expected.

After serious injury from hydrogen sulfide, diagnostic testing for neurologic structure and function may show abnormalities for weeks or months. Brain MRI and head CT studies demonstrate structural changes, such as globus pallidus degeneration and subcortical white matter demyelination. Neuropsychological testing after serious hydrogen sulfide poisoning demonstrates specific abnormalities in cortical functions, such as concentration, attention, verbal abstraction, and short-term retention. Single-photon emission computed tomography (SPECT)/PET brain scans define neurotoxin-induced lesions that correlate well with clinical neuropsychological testing.
No clinically available biological markers or direct measurements of hydrogen sulfide and its metabolites exist, therefore, confirming poisoning is challenging for clinicians, researchers, and forensic specialists. Whole blood sulfide concentrations >0.05 mg/L are considered abnormal. Reliable measurements are ensured only if the concentration is obtained within 2 hours after the exposure and analyzed immediately.

In acute exposures, blood and urine thiosulfate concentrations may be reflective of exposure. Urinary thiosulfate excretion may be useful to monitor chronic low-concentration exposure in the workplace. However, one study could not demonstrate a correlation between the degree of exposure and change in urine thiosulfate from baseline measurements. Another study analyzed the value of blood and urine thiosulfate from data collected in case series of fatal and nonfatal hydrogen sulfide victims. Because thiosulfate was detected in the urine but sulfide and thiosulfate were not detected in the blood of nonfatal exposures, this report concluded that thiosulfate in urine is the only indicator to prove hydrogen sulfide poisoning in nonfatal cases.

Sulfide concentrations obtained in postmortem investigations may be useful, but their use requires rapid sample collection because sulfide concentrations rise with tissue decomposition. In addition to blood sulfide concentrations, sulfide and thiosulfate concentrations are at their highest in lung and brain. If death is rapid, urinary thiosulfate concentrations may be nondetectable despite blood sulfide and thiosulfate concentrations 10-fold or greater than normal concentrations. At autopsy, a greenish discoloration of the gray matter, viscera, and bronchial secretions may be noted.

Management
The initial treatment (Table 126–4) is immediate removal of the victim from the contaminated area into a fresh air environment. High-flow oxygen should be administered as soon as possible. Optimal supportive care has the greatest influence on the patient’s outcome. Because death from inhalation of hydrogen sulfide is rapid, limited human cases reaching the hospital for treatment are reported in the literature. Most patients experience significant delays before receiving treatment. Therefore, specific treatments and antidotal therapies do not show definitive improvement in patient outcome.


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The proposed toxic mechanisms, animal studies, and human case reports suggest that oxygen therapy is beneficial for hydrogen sulfide poisoning. Proposed mechanisms for the beneficial effects of oxygen are competitive reactivation of oxidative phosphorylation by inhibiting hydrogen sulfide–cytochrome binding, enhanced detoxification by catalyzing oxidation of sulfides and sulfur, and improved oxygenation in the presence of ARDS. Recent studies demonstrate hydrogen sulfide’s binding to cytochrome oxidase is readily reversible in the presence of oxygen. Other studies show an inverse relationship between tissue concentrations of hydrogen sulfide and oxygen. Increased oxygen concentrations enhance the consumption of hydrogen sulfide through metabolic pathways, while oxygen deprivation results in the accumulation of hydrogen sulfide in tissue. All patients suspected of hydrogen sulfide poisoning should receive supplemental oxygen. In case reports, poisoned patients receiving HBO had favorable clinical outcomes. However, no clinical data is available to suggest HBO is superior to normobaric oxygen for acute poisoning or preventing delayed neurological sequelae.

The similarities in the toxic mechanism between hydrogen sulfide and cyanide created an interest in the use of nitrite-induced methemoglobin as an antidote. Methemoglobin protects animals from toxicity of hydrogen sulfide poisoning in both pretreatment and postexposure treatment models. Nitrite-generated methemoglobin acts as a scavenger of sulfide. The affinity of hydrogen sulfide for methemoglobin is greater than that for cytochrome oxidase. When hydrogen sulfide binds to methemoglobin, it forms sulfmethemoglobin. Because hydrogen sulfide poisoning is rare, no studies have evaluated the clinical outcomes of patients treated with sodium nitrite. Animal studies suggest that nitrite must be given within minutes of exposure to ensure effectiveness. However, several human case reports showed rapid return of normal sensorium when nitrites were administered soon after exposure. Patients with suspected hydrogen sulfide poisoning who have altered mental status, coma, hypotension, or dysrhythmias should receive sodium nitrite by slow infusion at the same dose given for cyanide poisoning. Sodium thiosulfate is of no benefit in the treatment of hydrogen sulfide. In addition, only a single in vivo mouse model and a single case report with a fatal outcome is published to suggest a beneficial effect of hydroxocobalamin as an antidote for hydrogen sulfide poisoning. Additional research is warranted to determine its usefulness for hydrogen sulfide poisoning.

Treatment of patients with hydrogen sulfide poisoning requires optimal supportive care. Treatments and antidotes beyond supportive care are not of proven clinical benefit. Because hydrogen sulfide toxicity is severe and research studies suggest potential benefits of nitrite
therapy, it should be considered for seriously ill patients exposed to hydrogen sulfide. This therapy should be initiated after optimum supportive care has been ensured.

Only a few inhalation risks are similar to hydrogen sulfide in their ability to rapidly “knock-down” victims. Some examples include low-oxygen environments in an enclosed space, hydrogen cyanide, volatile nerve agents, and carbon monoxide. The etiology may be unclear early in the patient’s emergency care and require clinicians to make treatment decisions without confirmatory evidence of poisoning. Clinicians faced with victims of “knock-down” syndrome should search for clues, such as victims’ activities (eg, working at a manure pit), reports of chemicals detected at the scene by first responders, or suggestive clinical signs. The critical decision is whether to administer specific antidotes empirically. Vapor exposure to volatile nerve agents would likely result in miosis and require antidotes such as atropine, pralidoxime, and benzodiazapines. Which cyanide antidotes to administer in a “knock-down” situation, if any, is most difficult. The basic aims are to gather as many facts and suggestive clues as possible, weigh the risk benefits for treatment or not, and treat early in the course. All this while meticulous attention to optimal supportive care is required.

SUMMARY

- Both cyanide and hydrogen sulfide are high risk xenobiotics.
- There are particular metabolic risks and concerns with regard to exposure to both xenobiotics because they bind specifically to the ferric moiety of the cytochrome a$_3$ oxidase complex.
- Odor recognition is unreliable and is not a definitive approach to diagnosis.
- The laboratory evaluation usually is not timely for diagnostic purposes.
- Decontamination, removal from the site of exposure, and oxygen are essential.

Acknowledgment
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