**Chapter 47   
Treatment and evaluation of specific toxins**

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**Introduction**

This chapter discusses several chemicals often inhaled, but ingestion and dermal exposures are encountered for a few. EMS physicians and personnel must have appropriate training, personal protective equipment (PPE), and medical protocols to deal with a variety of potential toxic exposures. The offending agent is often unidentified or misidentified during early phases of the response (see Volume 2, [Chapter 46](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/Vol2/c46.xhtml#c46)); extreme caution should be exercised until the situation has been fully defined.

The toxic effects of most chemicals can be classified into a general range of syndromes, and appropriate triage, decontamination, treatment, and transport often will be based on signs and symptoms. Responders may use patterns of vital signs, mental status, pupil size, mucous membrane irritation, lung examination, and skin examination (for burns or discoloration) to identify suspected toxidromes. Irritant gas exposure, such as chlorine or ammonia, results in irritation of upper airways and mucous membranes. Acetylcholinesterase inhibitors such as organophosphate and carbamate pesticides and nerve agents result in cholinergic symptoms including wheezing, salivation, lacrimation, vomiting, sweating, diarrhea, and sometimes seizures or coma. Solvent exposure may cause lightheadedness, nausea, confusion, and loss of consciousness. On contact with skin or mucous membranes, most solvents cause skin irritation or injury. Metabolic poisons such as cyanide (CN), carbon monoxide (CO), or hydrogen sulfide (H2S) can result in rapid loss of consciousness and cardiorespiratory collapse. Finally, fear of potential exposure may cause persons to present with symptoms such as chest pain, palpitations, shortness of breath, and syncope, attributable to generalized autonomic arousal.

Recognition of potential clinical syndromes will guide prehospital care and notification of authorities and receiving facilities. Poison centers are a resource that should be considered for additional clinical information regarding antidotal therapy, local trends or uncommon clinical presentations; this resource is available to any health care provider.

Some of the agents discussed in this chapter injure the skin and mucous membranes on contact by chemical reaction. Decontamination must be approached in a knowledgeable and focused manner. It is impractical and dangerous to conduct unnecessary decontamination when there is no need; precious minutes will be lost donning excessive protective gear and establishing decontamination stations when not necessary – minutes that may result in greater casualties. Overall, victims exposed to gas or vapors only, without skin or eye irritation and with no grossly apparent deposition of toxins on their person, have very low risk of secondary contamination and may be evacuated immediately; eye irritation alone may be addressed with gentle irrigation during transport.

**Organophosphates and nerve agents**

Organophosphates have widespread civilian use as agricultural pesticides and have been used in military campaigns and terrorist attacks as highly lethal nerve agents. Although organophosphate pesticides are less potent than the military versions, both have the capability to cause significant morbidity or death. In Japan, the Aum Shinrikyo cult used sarin (a nerve agent) in two terrorist events resulting in 19 deaths, 1,000 hospitalizations, and 5,000 people seeking medical attention [1].

**Pathophysiology and clinical presentation**

Toxicity from organophosphate compounds can occur via almost any route of exposure, including dermal, ocular, inhalation, ingestion, or injection. The onset, severity, and duration of effects depend on the potency of the agent; the route, concentration, and duration of exposure; and the use of antidotal therapy. Patients with vapor exposure experience a rapid onset of effects, whereas dermal exposure will often have a delayed onset of toxicity.

Organophosphates bind to the enzyme responsible for acetylcholine hydrolysis, acetylcholinesterase, resulting in an elevated synaptic concentration of acetylcholine at both nicotinic and muscarinic receptors. Initially the binding is reversible; water may enter the enzyme active site and hydrolyze the organophosphate moiety off. However, after a time, depending upon the organophosphate, the moiety bound to the enzyme undergoes a chemical change and is no longer able to undergo hydrolysis. This is called aging and results in permanent inhibition of the acetylcholinesterase enzyme. The carbamate pesticides are very similar clinically and pharmacologically to the organophosphosphate compounds, the main difference being that they will not age and pralidoxime is not necessary for therapy.

Acetylcholinesterase inhibition results in prolongation and potentiation of acetylcholine action at cholinergic synapses. In the central nervous system, this causes confusion, agitation, and seizures. In the autonomic nervous system, increased cholinergic transmission results in diaphoresis, bradycardia (tachycardia is seen for other reasons), miosis (not always present), lacrimation, salivation, vomiting, defecation, and urination due to overstimulation of muscarinic receptors. The latter constellation of symptoms is represented by the cholinergic toxidrome mnemonic DUMBBELS (diarrhea, urination, miosis, bronchorrhea/bronchospasm/bradycardia, emesis, lacrimation, and salivation). Increased cholinergic activity at neuromuscular junctions results in muscle fasciculations and motor weakness.

Late effects of organophosphate poisoning include “intermediate syndrome,” a return of weakness and neuromuscular symptoms 1–4 days after initial clinical improvement. Patients may require additional supportive therapy or reintubation. Late neurological sequelae include peripheral neuropathies, persistent miosis, and neuropsychiatric sequelae (nightmares, headache, anxiety); this effect is likely to compound the psychological effect of a nerve agent attack.

**Decontamination and personal protective equipment**

The risk of provider poisoning by an organophosphate depends upon the class of the agent. With the highly lethal war nerve agents (GA, GB, VX, etc.), most are volatile (except VX) and very small doses will potentially be lethal. For protection, a level A fully encapsulated garment is required. Personnel responding to war nerve agent attacks are at significant risk of becoming secondarily exposed and suffering from adverse effects from insufficiently decontaminated victims. In the Tokyo sarin attack, first responders and nurses suffered adverse effects from the vapors of insufficiently decontaminated patients in poorly ventilated areas, but injuries were mild with improvement once they ventilated the vehicles during transport [2].

Exposures to organophosphate pesticides are more common and less lethal to humans. These agents have much lower volatility than the war agents; the smell reported is partially due to the solvent hydrocarbon. Unless the patient is completely drenched in concentrated organophosphate pesticide, standard universal precautions with double nitrile gloves should be sufficient to prevent any significant exposure. The vomitus from patients ingesting concentrated organophosphate pesticide should be handled with caution. Although there is a report about secondary ED staff contamination by “pesticide vapors,” there are uncertainties about the exact etiology of this event [3].

Decontamination includes removal of all clothing and jewelry, physical removal of visible residue, and irrigation with water or soap and water; for the organophosphate pesticides, significant scrubbing with soap and water will be required. Items of leather and cloth are difficult to clean and should not be returned to the patient. There is no consensus regarding gastric decontamination of pesticide organophosphates. In many cases, the patient will already have vomited and so the utility of lavage is questionable. Activated charcoal could be of benefit, but this should only be considered when the airway is secure (i.e. intubation) to prevent possible aspiration.

### Detection and diagnosis

First responders should be vigilant for potential organophosphate exposures in instances in which there are multiple casualties presenting with similar symptoms. In the 1995 sarin attacks in Tokyo, the most common physical sign was miosis, with presenting symptoms ranging from eye pain, headache, and bronchorrhea to apnea and death [1]. The miosis was a very useful sign to separate those suffering from toxicity from those who were “worried well.” Note that miosis is not useful in organophosphate toxicity with other routes of exposure (such as ingestion). Rapid development of the cholinergic toxidrome in a number of casualties should prompt immediate consideration of an organophosphate. Activity of red blood cell cholinesterase and plasma cholinesterase may assist diagnosis in hospital.

### Treatment and disposition

After decontamination, supportive care includes airway maintenance and support of ventilation, as respiratory failure is the primary reason for death with organophosphates. Aggressive suctioning may be required because of copious airway secretions and vomiting; aspiration is not uncommon with organophosphate pesticide ingestion. If intubation is required, succinylcholine should be avoided because it may lead to prolonged neuromuscular blockade due to the organophosphate inhibition of butyrylcholinesterase. The mainstay of treatment in nerve agent and organophosphate poisoning consists of antidotal therapy with atropine, pralidoxime, and diazepam.

Atropine competitively antagonizes excess acetylcholine effects at central and peripheral muscarinic receptors but has no effect at nicotinic receptors. Atropine can effectively reverse bronchorrhea, bradycardia, and gastrointestinal symptoms and treat seizures, but has no effect on nicotinic symptoms such as fasciculations, weakness, or paralysis [4]. Side-effects may include delirium, tachycardia, and agitation. The initial dose of atropine is 2 mg in adults (0.05 mg/kg in children, minimum 0.1 mg) administered intravenously or intramuscularly. Although it can be administered via the endotracheal route, this has disadvantages because of the excessive secretions and ventilation difficulties. The dose is titrated to effect and may be repeated every 1–5 minutes; although tachycardia may develop, atropine is given until the patient is well ventilated as demonstrated by reduced secretions and resolution of bronchoconstriction and/or is no longer bradycardic. Atropine will also potentially decrease vomiting, diarrhea, and bradydysrhythmia. The required dose of atropine can be very large for oral pesticide poisoning, with some patients requiring hundreds of milligrams of atropine; much less is required to treat war nerve agent poisoning. Unless symptoms resolve with a single dose of atropine, patients who require administration of atropine following organophosphate exposure should also receive pralidoxime.

Pralidoxime chloride is an oxime that reactivates acetylcholinesterase by reacting with the phosphorus moiety, resulting in an oxime-phosphate compound that leaves the regenerated enzyme. Oxime therapy must be administered before the aging of that bond is complete, a process that can begin within minutes of exposure and depends upon the organophosphate. The initial dose is 1–2 g for adults (25–50 mg/kg for children), and repeated dosing may be required; continuous infusions of 8–10 mg/kg/hour have been recommended. Slow administration over 15–30 minutes has been advocated to minimize side-effects which include hypertension, headache, blurred vision, weakness, epigastric discomfort, nausea, and vomiting. Rapid administration can result in laryngospasm, muscle rigidity, and transient impairment of respiration.

Benzodiazepines are used for the treatment and prevention of seizures. Diazepam 5–10 mg intravenously may be used, but repeated dosing may potentiate organophosphate-induced respiratory depression.

All three of these agents are available as autoinjectors; the commercially available MARK I autoinjector contains both 2 mg of atropine and 600 mg of pralidoxime and requires two injections. A new autoinjector, the Antidote Treatment Nerve Agent Auto-Injector (ATNAA or DuoDote®), allows for both atropine (2.1 mg) and pralidoxime (600 mg) to be injected simultaneously; one disadvantage to this device is the inability to give more atropine without also giving more pralidoxime [5].

## Gases (irritants and hydrocarbons)

Irritant gases include a number of chemicals found or produced throughout our modern society; this section will be limited to chlorine, phosgene, anhydrous ammonia, and hydrofluoric acid (HF). Irritant gases, such as chlorine and phosgene, have had extensive military use as chemical warfare agents. In addition to military use, these agents, as well as anhydrous ammonia, are used in industrial processes and are sometimes transported in massive quantities. Phosgene is rarely transported in bulk; however, it can be formed in small quantities by the heating of chlorinated hydrocarbons. Compounds like hydrogen fluoride and hydrogen chloride are commonly used as aqueous solutions as hydrofluoric acid and hydrochloric acid, although there are some industrial processes that use the gas form. See Volume 1, [Chapter 46](https://jigsaw.vitalsource.com/books/9781118990827/epub/OPS/c46.xhtml#c46) for discussions on caustic exposures, noting that HF also has systemic toxicity from large and/or concentrated exposures.

The solubility of a gas in water allows prediction of its warning properties and clinical presentation. Chlorine (good water solubility), HF (excellent water solubility), and ammonia (excellent water solubility) have pungent odors and cause rapid onset of irritant symptoms, a warning property that may prompt victims to escape and limit their exposure. These gases dissolve rapidly on contact with the water in the eyes and upper airway mucosa, where they cause eye irritation, lacrimation, corneal burns, rhinorrhea, and sneezing. With longer duration or higher concentrations of exposure, lower respiratory effects also manifest with alveolar damage and pulmonary edema. However, phosgene (low water solubility) has a subtle odor reported to be similar to newly mown hay that may not be perceptible to all individuals. Phosgene has poor warning properties; it does not cause immediate symptoms and it results in a lower respiratory injury as the lack of water solubility allows for penetration deep into the distal airways, potentially resulting in a more severe exposure.

Injury is caused through production of reactive chemical species in the aqueous environment (i.e. pulmonary tract, mucous membranes). Chlorine reacts with water to release hydrochloric acid, hypochlorous acid, and free radicals. Anhydrous ammonia combines with water to form the caustic ammonium hydroxide. Phosgene combines with water to release hydrochloric acid; it also reacts directly with cellular macromolecules. The alveolar damage from phosgene causes delayed-onset non-cardiogenic pulmonary edema and sometimes hypovolemic shock. HF gas is a “weak” acid, meaning it does not completely dissociate in an aqueous environment (but weak ≠ benign). Being undissociated, the fluoride ion is readily absorbed systemically where it binds with calcium to form insoluble calcium fluoride. Fatal hypocalcemia and hyperkalemia occur with significant fluoride exposures.

Because these agents are gases at ambient temperatures and pressure, there is little need for decontamination with the gaseous form of these compounds once patients are evacuated to a safe environment. Removal of clothing and gentle eye irrigation for those with ocular irritation are all that is usually required; note that patients with eye exposure to anhydrous ammonia gas may suffer significant corneal injury. There are no specific antidotes for respiratory irritants, although the use of nebulized sodium bicarbonate has been reported to potentially neutralize the acidic compounds formed by chlorine exposure.

More severe upper airway exposures can result in development of upper airway edema and laryngospasm. Respiratory distress or stridor mandates intubation to prevent airway compromise. Other supportive measures include supplemental oxygen, suctioning, beta-agonists, anticholinergic agents for bronchospasm, and fluid resuscitation for hypovolemic shock. Steroids (inhaled, oral) have been used following exposure to irritant gas exposure; they may be beneficial but there is not strong clinical evidence to routinely recommend their use. Patients with mild exposures to water soluble agents who remain asymptomatic 6 hours after exposure are unlikely to worsen, whereas delayed pulmonary edema is common with exposure to poor water solubility compounds such as phosgene thus requiring prolonged observation.

For hydrogen fluoride exposures, field administration of IV calcium gluconate to individuals with significant inhalation exposure should be considered prophylactically as the onset of fatal arrhythmias often occurs without warning and the calcium may be normal when first checked; large amounts of IV calcium may be required.

Hydrocarbon gases such as methane and propane have minimal physiological effect. At high levels, some can be narcotizing but the primary mechanism for causing human illness is oxygen displacement and resulting hypoxia. Individuals exposed to high levels of volatile hydrocarbons should be removed from the source and provided with 100% oxygen. The initial responder should consider the flammable and explosive nature of the hydrocarbon gas in their initial management; also, care should be taken not to enter a potentially hypoxic environment resulting when hydrocarbon gas levels are extremely high.

Hydrocarbon abuse where the individual deliberately inhales the hydrocarbon for euphoric reasons is called huffing (from a rag), sniffing (from a container), or bagging (from a bag). The greatest initial concerns are the cardiac sensitization that occurs with many of the chlorinated or fluorinated hydrocarbons. This is manifested by “sudden cardiac death” when a surge of epinephrine triggers a fatal ventricular arrhythmia. For the first responder, awareness of this phenomenon and restraint from using epinephrine are important. The bio-accumulation of the desired hydrocarbon, its metabolite, or other hydrocarbons in the product may also have consequences. Individuals who huff methanol-containing products may develop acidosis and visual disturbances. Huffing metallic spray paints for the toluene results in an acidosis and severe hypokalemia, sometimes to the point of paralysis. Solvents containing methylene chloride will be metabolized to carbon monoxide in the body, necessitating treatment as discussed below.

### Carbon monoxide

Carbon monoxide is an odorless, colorless gas responsible for thousands of ED visits annually. Unintentional CO poisonings occur with the use of malfunctioning equipment that utilizes combustion, generators and portable heaters in poorly ventilated areas during power outages or with people riding behind mechanized vehicles such as boats or farm machinery. Carbon monoxide may be produced chemically; this has rarely been used as a suicide method [6]. The manifestations of CO poisoning form a spectrum ranging from mild, non-specific symptoms to severe illness with hemodynamic instability and central nervous system toxicity.

Carbon monoxide binds to hemoglobin 240 times more avidly than oxygen and causes a leftward shift in the oxygen hemoglobin dissociation curve that further decreases oxygen delivery to tissues. CO also binds directly to heme-containing cellular proteins, including cytochromes, myoglobin, and guanylate cyclase. Binding to cardiac myoglobin may cause myocardial depression, hypotension, and cardiac arrhythmias. CO may increase nitric oxide levels, creating free radicals and leading to further systemic hypotension and cellular injury.

Acute CO poisoning initially causes non-specific symptoms such as headache, nausea, and dizziness progressing to altered mental status, confusion, syncope, seizures, and coma. Cardiovascular effects include hypotension, cardiac ischemia, infarction, and arrhythmias. Patients with underlying cardiovascular disease are prone to exacerbation of their underlying disease. Other organs may be affected, producing a range of clinical effects including rhabdomyolysis, renal failure, skin bullae, and non-cardiogenic pulmonary edema. Delayed effects of CO poisoning after initial recovery may manifest as long as 40 days after the initial exposure. Memory loss, ataxia, seizures, emotional lability, psychosis, and motor disturbances have been described.

Chronic low-level CO poisoning has caused headaches, lightheadedness, cerebellar dysfunction, and cognitive and mood changes. It is often difficult to identify and quantify as the symptoms may not be recognized as manifestations of CO poisoning. Symptoms are often alleviated by removal of the patient from the environment.

In pregnancy, severe CO toxicity is associated with poor fetal outcomes. Maternal levels do not correlate with fetal exposure, and poor fetal outcomes have been noted with maternal levels that are not extremely elevated. Fetal hypoxia likely contributes to this; the injury is not due to an increased innate fetal hemoglobin affinity for CO over maternial hemoglobin, as was previously believed [7].

Prehospital workers must rely on clinical suspicion and clinical syndromes to recognize CO poisoning. Fire and hazardous material units usually carry CO gas detection equipment, permitting measurement of environmental CO levels. These levels can be useful in making treatment decisions and should be communicated to ED caregivers. The gold standard for diagnosing CO poisoning is CO-oximeter measurement of venous carboxyhemoglobin levels. However, the severity of exposure depends on both the concentration and duration of exposure; therefore blood levels serve to guide, not dictate therapy.

A new commercially available non-invasive CO-oximeter is available for clinical use. The CO-oximeter uses eight wavelengths of light instead of the usual two used by traditional pulse oximeters and has a reported error of ±3% (1 SD) absolute carboxyhemoglobin level. However, one study demonstrated a false-positive rate of 9% and a false-negative rate of 18% so when clinical suspicion is high, formal CO-oximetry should be used to confirm the level [8,9]. The role of prehospital CO-oximetry remains undefined.

Rescuers should initiate field treatment based on clinical symptoms, history, and possibly environmental levels. Prehospital treatment of CO poisoning begins with evacuation of victims from the exposure, initiating high-flow supplemental oxygen by non-rebreather mask, and supporting cardiovascular and respiratory function. The half-life of carboxyhemoglobin decreases from a range of 240–320 minutes in ambient oxygen to a range of 50–100 minutes with inhalation of 100% oxygen at atmospheric pressure [10].

Although the primary treatment for CO poisoning is supplemental oxygen, hyperbaric oxygen therapy (HBO) is likely beneficial for selected patients with severe poisoning and neurological symptoms. HBO rapidly corrects the relative anemia from the carboxyhemoglobin by decreasing the half-life of carboxyhemoglobin to approximately 20 minutes and increasing dissolved oxygen in the blood, augmenting oxygen delivery. HBO also reduces CO binding to other heme-containing cellular proteins. Benefit from HBO may exist even for the patient with a normal carboxyhemoglobin level as HBO may reduce tissue and free radical-mediated cellular injury by reducing endothelial neutrophil adhesion and lipid peroxidation.

Potential complications of HBO include barotrauma, claustrophobia, and oxygen toxicity and unless it is a multiplace chamber, there is no capacity to access the patient when the chamber is pressurized. The Undersea and Hyperbaric Medical Society maintains a directory of hyperbaric facilities ([www.uhms.org](http://www.uhms.org/)). EMS agencies should have preestablished protocols for medical oversight consultation. Depending upon the region and resources, an EMS system may preferentially take stable CO-poisoned patients to an ED within a system that can also offer HBO. This could potentially decrease the time delay for the patient to receive HBO therapy.

Despite years of study, the exact indication for HBO for CO-poisoned patients is not clear. A clinical policy paper by ACEP [11] determined that there was the lowest level of evidence for recommending HBO therapy for CO-poisoned patients and such therapy cannot be mandated. However, considering extensive animal and reasonable human evidence, it is common practice for many to recommend HBO therapy for CO-poisoned patients with loss of consciousness (transient or persistent) and/or neurological symptoms (especially cerebellar) and also for the pregnant patient with evidence of fetal distress. There are no studies in pregnant patients with HBO for CO toxicity, but there is good clinical evidence that HBO therapy will not be harmful to the fetus. Adult patients who have been resuscitated from cardiac arrest from CO poisoning have nearly universally fatal outcomes; only pediatric patients or those with witnessed cardiac arrest should be considered for HBO [12].

Some physicians use cardiovascular manifestations as an indication to perform HBO; others feel that a telemetry admission and cardiac work-up are more beneficial. Some have proposed absolute carboxyhemoglobin levels as indications for HBO therapy; levels proposed include greater than 25% or greater than 15% in pregnant patients. These levels are not evidenced based; it is known that carboxyhemoglobin levels do not correlate with toxicity, and fetal injury can occur with low maternal levels.

If a patient will receive benefit from HBO therapy, it should be provided as soon as possible (ideally within 6 hours) and no later than 24 hours after the exposure. One well-designed clinical trial randomizing patients with elevated carboxyhemoglobin levels or neurological or cardiac symptoms showed statistically significant improvements in symptoms and in neuropsychiatric sequelae with HBO [13].

### Cyanide

Cyanide (CN-) is widely used in industries such as mining, metallurgy, electroplating, and plastic polymer production. Cyanide is encountered as a salt such as sodium cyanide or as the gas hydrogen cyanide (HCN), but there are naturally trace amounts found in certain foods. HCN gas is produced when a cyanide salt is mixed with acid. Cyanide has been used in warfare without great success; however, CN- is a potential agent for terrorism, as evidenced by interest in the mubtakar, an improvised cyanide delivery device [14]. HCN is commonly generated during pyrolysis of natural and synthetic substances such as paper, silk, wool, and plastics. Although smoke inhalation usually results in CO poisoning, toxicity may also result from concurrent HCN exposure and this represents one of the most the most common source in society today.

The cyanide ion binds to the ferric ion of cytochrome c oxidase, halting mitochondrial electron transport and stopping aerobic generation of adenosine triphosphate, so tissues switch to anaerobic respiration. Cyanide first affects tissues with high levels of oxygen consumption such as cardiac myocytes and central nervous system neurons. Inhibition of cellular enzymes leads to increased susceptibility to oxidative stress and lipid peroxidation, and neuronal damage ensues. Increased brain glutamate levels may result in excitatory neurotoxicity, whereas decreased gamma-aminobutyric acid levels may lead to seizures.

Clinical effects from cyanide exposure depend on the dose, route, and duration of exposure. Low-level exposures to cyanide produce non-specific symptoms such as dyspnea, headache, nausea, anxiety, and altered mental status. Higher levels may result in hyperpnea within seconds, and loss of conscious, apnea, and death within minutes. Cyanide-containing hydrocarbons such as acetonitrile require metabolism to free the cyanide and so symptoms may not develop for several hours after exposure, which is quite different from any other cyanide exposure.

Combined with an appropriate history of exposure, the finding of a lactic acidosis and hemodynamic or respiratory compromise that does not respond to supplemental oxygen should prompt consideration for cyanide. Some experts propose lactate levels greater than 10 mmol/L as suggestive of CN poisoning [15]. Other clinical clues to the nature of the exposure may include a bitter almond odor from hydrogen cyanide gas emitted from the patient’s lungs, as well as a cherry red color to the skin or bright red venous blood resulting from the inability to use oxygen. These signs are unreliable as many people cannot recognize the bitter almond odor and the cherry red skin color may not be present. Victims exposed to only HCN gas will not require any decontamination beyond disrobing; cases of secondary cyanide poisoning have resulted from dermal contamination or ingestions of cyanide salts with vomiting or when the stomach is opened during autopsy.

Currently, there are three antidotal therapies approved for use in the United States: sodium nitrite, sodium thiosulfate, and hydroxocobalamin. Sodium nitrite and sodium thiosulfate are sold as part of one antidotal kit but are available separately as well. Amyl nitrite is no longer part of the FDA-approved cyanide antidotal kit and has very limited use in the USA.

Sodium nitrite produces methemoglobin by oxidizing the hemoglobin iron from 2+ to 3+ with the standard dose resulting in a methemoglobin level of around 12%. Cyanide has a higher chemical affinity for methemoglobin (Fe3+) than for the cytochrome c oxidase, which results in displacing cyanide from mitochondria and binding to the methemoglobin. The toxicity from sodium nitrite includes hypotension and excessive methemoglobinema. When administered inappropriately, fatalities have occurred. Additionally, oxygen delivery in patients with concomitant carbon monoxide toxicity from smoke inhalation may be reduced due to methemoglobinemia. However, the peak of methemoglobinemia after IV sodium nitrite occurs in about 15 minutes, and the probable decline in carbon monoxide level on 100% oxygen closely matches the increase in methemoglobinemia. The sodium nitrite dose in adults is 300 mg over 2–3 minutes; the pediatric dose is based on weight as well as serum hemoglobin.

Sodium thiosulfate is a sulfur donor which enables the endogenous conversion of cyanide to thiocyanate, a relatively non-toxic compound, which is excreted by the kidneys. Sodium thiosulfate is cheap, is packaged in a liquid form ready for injection, and has an extremely safe profile with minimal side-effects reported. Sodium thiosulfate takes time (≈15 minutes) for an effect to be noted. The dose is 12.5 g in adults and in pediatrics it is 0.42 g/kg up to the adult dose; the dose may be repeated once, at half initial dose, if necessary.

The newest approved antidote for cyanide is hydroxocobalamin, a derivative of vitamin B12. A reddish-colored, light-sensitive powder requiring reconstitution before its use, hydroxocobalamin’s mechanism of action is similar to sodium nitrite but instead of turning the hemoglobin into a cyanide scavenger, the hydroxocobalamin is the scavenger. Cyanide has an extremely high affinity for hydroxocobalamin; it binds to the cobalt metal center and forms vitamin B12 (cyanocobalamin), which is excreted by the kidneys. Hydroxocobalamin has a favorable safety profile and causes only minor adverse effects: self-limited reddish skin, urine and serum discoloration, pustular skin rashes, allergic reactions, and elevations in blood pressure [16]. The latter is potentially advantageous because it may reverse the hypotension from cyanide toxicity. However, the discoloration of serum is known to interfere with colorimetric serum assays and has caused problems when attempting hemodialysis [17,18]. The adult dose of hydroxocobalamin is 5 g, with a pediatric dose of 70 mg/kg up to 5 g; it may be repeated in cases of massive cyanide poisoning. It is recommended to be administered over 15 minutes. It is incompatible in the same IV line with many other medications, including sodium thiosulfate.

When considering which antidotal therapy to use, sodium thiosulfate is cheap, safe, and may be administered immediately when IV access is achieved. Hydroxocobalamin is expensive, has some side-effects, has storage stability issues, requires reconstitution before administration, and has a 15-minute infusion time, a time delay not addressed in most comparative studies. For prehospital care, with a weak clinical suspicion of cyanide toxicity, sodium thiosulfate may be administered empirically, immediately with almost no risk. The combination of thiosulfate and hydroxocobalamin (not given simultaneously through the same IV line) has been proposed as an advantage, as suggested by some animal studies. Sodium nitrite is not as safe and will decrease oxygen-carrying capacity, so if there is a choice, hydroxocobalamin should be administered in smoke inhalation victims.

### Hydrogen sulfide

Hydrogen sulfide is a toxin similar to cyanide in that it causes inhibition of cellular aerobic respiration, but the inhibition of the cytochrome c oxidase is not as profound as with cyanide. It is more irritating than hydrogen cyanide and has a strong odor, but individuals experience odor fatigue and thus may mistakenly believe that the gas has dissipated when the odor disappears. Hydrogen sulfide is produced by decaying organic materials and can collect in enclosed spaces. Most tragedies involving hydrogen sulfide occur when the initial victim enters an area and is overcome, followed by one or more rescuers who are also poisoned. There are only a few substances that can cause rapid loss of consciousness like this (CO, hypoxic environments, and nerve agents, to name the most common). It has also been used in suicide events where an individual mixes calcium polysulfide and acid together, evolving hydrogen sulfide gas. Often this is performed in a closed car; the first responder should be aware of this potential etiology and the danger of this gas. Treatment is supportive, with removal from exposure and 100% oxygen being most important. The standard cyanide antidotal therapies are usually not required as the hydrogen sulfide will spontaneously unbind from the cytochrome c oxidase; for those who are critically ill, there is some limited evidence to support the use of sodium nitrite.

## Vesicants

Sulfur mustard and lewisite are vesicants – potent alkylating agents that interact with cellular macromolecules and DNA to cause cell death via necrosis or apoptosis. Sulfur mustard has been used since WWI and still occasionally resurfaces to cause illness in fishermen when old munitions are brought up in their nets. The nitrogen mustards (HN1, HN2, HN3) are a group that uses nitrogen rather than sulfur; now these have new life as chemotherapeutic agents: cyclophosphamide, chlorambucil, ifosfamide, and melphalan. Sulfur mustard melts at 57.0 °F (14.4 °C), meaning that if the environment is above this temperature, there will be possible vapor injury.

The injury caused by vesicants is proportional to the concentration times the duration of exposure, considering the tissue susceptibility, with delicate tissues (cornea) having high sensitivity to injury. With sulfur mustard, there is a delay of several hours between exposure and development of the initial lesions. Skin and mucous membrane exposure results in desquamation and formation of painful blisters. These blisters are filled with straw-colored liquid on an erythematous base; they become confluent as the injury progresses. Severe corneal damage and eye pain occur with eye exposure; gentle early eye irrigation is recommended along with ophthalmological consultation but permanent blindness from vapor exposure is rare. Inhalation of vesicants results in irritation and necrosis of upper airways and possibly pulmonary edema. Bronchoscopy may be necessary to clean out necrotic upper airway tissue to allow for ventilation. Secondary pulmonary infections often ensue. With significant exposures to sulfur mustard, bone marrow suppression occurs, potentially complicating infections. Sulfur mustard is carcinogenic and theoretically increases risk for neoplasias, although the risk from a single exposure is probably low.

Lewisite (an arsenic-containing vesicant) is very similar to sulfur mustard, except the onset of symptoms is much faster (immediate ocular irritation, faster skin changes) rather than hours with sulfur mustard.

Vesicants pose a significant risk of secondary contamination of rescuers. Sulfur mustard penetrates most materials and it has no warning properties. Typically, level A PPE is required for operations in the hot zone and during initial decontamination; cases of secondary caregiver injury exist where decontamination was not adequate. All visible chemical agent and victims’ clothing, jewelry, and personal items must be removed, followed by copious soap and water. The sulfur mustard reacts rapidly with tissues and after about 15 minutes it has all been internalized or locally reacted; however, sulfur mustard on objects has very long persistence. The bullae fluid does not have any sulfur mustard in it, so universal precautions as protection are sufficient.

## Conclusion

Priorities for treatment of toxic exposures include recognizing a potential chemical source, adopting appropriate PPE if necessary, removing victims from the exposure, and appropriate decontamination of victims if necessary. Therapeutic priorities for toxic exposures include supportive care, including stabilization of airway and cardiorespiratory status. Specific measures such as hyperbaric oxygen and antidotal therapy may be appropriate in selected instances of CO, organophosphate, or CN poisoning. Poison centers remain a resource for the first responder that should be considered for additional clinical information regarding local trends or uncommon clinical presentations.

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