

Chapter 2

CYANIDE

Summary

NATO Codes: AC, CK

Signs and Symptoms: Few; seizures, respiratory and cardiac arrest after exposure to high concentrations.

Field Detection: The Joint Chemical Agent Detector (JCAD), M256A1 Chemical Agent Detector Kit, M18A2 Chemical Agent Detector Kit, and M90 Chemical Warfare Agent Detector detect hydrogen cyanide (AC) as vapor or gas in the air, and the M272 Chemical Agent Water Testing Kit detects AC in water.

Decontamination: Skin decontamination is usually not necessary because the agents are highly volatile. Wet, contaminated clothing should be removed and the underlying skin decontaminated with water or other standard decontaminants to prevent off-gassing as a hazard.

Management: *Antidote:* intravenous (IV) sodium nitrite, inhalational amyl nitrite, and sodium thiosulfate. *Supportive:* oxygen, correct acidosis.

Overview

Cyanide is a rapidly acting, lethal agent that is limited in its military usefulness by its high median lethal concentration (LC₅₀) and high volatility. Death occurs about 8 minutes after inhalation of a high concentration. Amyl nitrite, sodium nitrite, and sodium thiosulfate are effective antidotes. An alternative antidote, hydroxocobalamin, is also effective. With any antidote, 100% oxygen has been empirically shown to be beneficial.

History and Military Relevance

The French used cyanide in World War I without notable military success, possibly because of the insufficient amounts delivered and the nature of the chemical. In Germany, Nazis used cyanide in the extermination of death camp prisoners. Zyklon B, a cyanide-based pesticide, was used in enclosed chambers. Nazi leaders used cyanide to commit suicide. The United States maintained a small number of cyanide munitions during World War II. Japan allegedly used cyanide against China before and during World War II, and Iraq may have used cyanide against the Kurds in the 1980s. In 1978 the Jim Jones cult staged a mass suicide in Guyana, where over 900 followers drank a cyanide-laced beverage. In 1982 cyanide contamination of Tylenol (McNEIL-PPC, Inc; Fort Washington, PA) led to the production of tamper-proof bottle caps and caplets. In 1995, the Aum Shinrikyo cult used cyanide in train station restrooms with poor success.

Nomenclature

The term *cyanide* refers to the anion CN⁻, or to its acidic form, hydrocyanic acid (HCN). Cyanogen (C₂N₂) is formed by the oxidation of cyanide ions; however, the term *cyanogen* has also come to refer to a substance that forms cyanide upon metabolism and produces the biological effects of free cyanide. Simple *cyanide* (HCN, NaCN) is a compound that dissociates to the cyanide anion (CN⁻) and a cation (H, Na⁺). A *nitrile* is an organic compound that contains cyanide. A cyanogen usually refers to a nitrile that

liberates the cyanide anion during metabolism and produces the biological effects of the cyanide anion. Cyanogens may be simple (cyanogen chloride) or complex (sodium nitroprusside).

Cyanides are also called “blood agents,” an antiquated term still used by many in the military. At the time of the introduction of cyanide in World War I, other chemical agents in use caused mainly local effects. In contrast, inhaled cyanide produces systemic effects and was thought to be carried in the blood, hence the term. The widespread distribution of absorbed nerve agents and vesicants via the blood invalidates this term as a specific designator for cyanide. Also, blood agent carries the connotation that the main site of action of cyanide is in the blood, whereas cyanide actually acts primarily outside the bloodstream.

Materials of interest as chemical agents are the cyanide *hydrogen cyanide* (HCN, AC) and the simple cyanogen *cyanogen chloride* (CK). Cyanogen bromide was used briefly in World War I but is of no present interest.

Sources Other Than Military

The cyanide ion is ubiquitous in nearly all living organisms that tolerate and even require the ion in low concentrations. The fruits and seeds (especially pits) of many plants of the Rosaceae family, such as cherries and peaches, as well as almonds and lima beans contain cyanogens capable of releasing free cyanide following enzymatic degradation. The edible portion (the roots) of the cassava plant (widely used as a food staple in many parts of the world) contains the cyanogenic glucoside linamarin. The combustion of any material containing carbon and nitrogen has the potential to form cyanide; some plastics (particularly acrylonitriles) predictably release clinically significant amounts when burned. Industrial concerns in the United States manufacture over 300,000 tons of hydrogen cyanide annually. Cyanides find widespread use in chemical syntheses, electroplating, mineral extraction, dyeing, printing, photography, agriculture, and in the manufacture of paper, textiles, and plastics.

Physiochemical Characteristics

The cyanides exist as liquids in munitions but rapidly vaporize upon detonation. The major threat is from vapor. The liquid's toxicity is approximately that of mustard. The low efficiency of cyanide on the battlefield has led to its disuse in combat operations.

Detection and Protection

The immediately dangerous to life and health (IDLH) concentration of AC is 50.0 parts per million (ppm); that for CK is 0.6 mg/m³. The military detectors are capable of detecting AC and CK at the threshold limits given in Table 2-1.

Because the odor of cyanide may be faint or lost after accommodation, olfactory detection of the odor of bitter almonds is not a reliable indicator of cyanide exposure, even for those who possess the gene required to smell cyanide. The activated charcoal in the canister of the chemical protective mask adsorbs cyanide, and the mask affords full protection from this gas in an open field environment.

Table 2-1. Concentration Thresholds for Cyanide Detection

Detector	Concentration Threshold for AC (Hydrocyanic Acid)	Concentration Threshold for CK (Cyanogen Chloride)
JCAD	22.0 mg/m ³	20.0 mg/m ³
M256A1	7.0 mg/m ³	N/A

JCAD: Joint Chemical Agent Detector

Mechanism of Toxicity

Cyanide salts in solid form or in solution are readily absorbed from the gastrointestinal tract when ingested. Moreover, the lower the pH in the stomach, the more hydrogen cyanide is released as gas from ingested salts. Liquid cyanide and cyanide in solution can be absorbed even through intact skin, but this route of entry is usually not clinically significant. Parenteral absorption of liquid cyanide can also occur from wounds. Cyanide is readily absorbed through the eyes, but the most important route of entry in a battlefield or terrorist scenario is likely by inhalation. Following absorption, cyanide is quickly and widely distributed to all organs and tissues of the body. Ingestion leads to particularly high levels in the liver when compared with inhalation exposure, but both routes lead to high concentrations in plasma and erythrocytes and in the heart, lungs, and brain.

An example of the ability of cyanide to react with metals in the body is its reaction with the cobalt in hydroxycobalamin (vitamin B_{12a}) to form cyanocobalamin (vitamin B₁₂). The reactions of cyanide with metals are reversible and exhibit concentration-dependent equilibria, but the reactions of cyanide with sulfur-containing compounds are catalyzed by the enzyme rhodanese and are essentially one-way and irreversible. The rate-limiting factor in the rhodanese-mediated reactions is usually the availability of sulfur donors in the body. These reactions can be accelerated therapeutically by providing a sulfane such as sodium thiosulfate. The reaction products, thiocyanates and sulfites, are significantly less toxic than cyanide itself and are eliminated in the urine. Cyanide also reacts with carbonyl and sulfhydryl groups (directly or via 3-mercaptopyruvate sulfurtransferase and other enzymes). However, the two most important kinds of reactions to understand are the reactions with metals and the enzyme-catalyzed reactions with sulfur-containing compounds. Cyanide is eliminated unchanged from the body in breath, sweat, and urine. It is excreted as sodium thiocyanate in the urine and as iminothiocarboxylic acid from reaction with sulfhydryl groups at the cellular level. High concentrations of cyanide in the body also lead to measurable increases in urinary elimination of cyanocobalamin.

Toxicity

The LCt_{50} of AC by inhalation has been estimated to be half the LCt_{50} for CK. The median lethal dose (LD_{50}) for IV administration of hydrogen cyanide can be compared to a value of 1. Skin exposure is estimated to require a dose 100 times greater than IV for the same reaction. Oral exposure is estimated at 100 to 200 times greater than IV.

Cyanide is unique among military chemical agents because it is detoxified at a rate that is of practical importance, about $17 \mu\text{g}/\text{kg}\cdot\text{min}$. As a result, the LCt_{50} is greater for a long exposure (eg, 60 minutes) than for a short exposure (eg, 2 minutes).

Mechanism of Action

Cyanide has a high affinity for certain sulfur and certain metallic complexes, particularly those containing cobalt and the trivalent form of iron (Fe^{3+}). The cyanide ion can rapidly combine with iron in cytochrome a_3 (a component of the cytochrome aa_3 or cytochrome oxidase complex in mitochondria) to inhibit this enzyme, thus preventing intracellular oxygen utilization. The cell then utilizes anaerobic metabolism, creating excess lactic acid and a metabolic acidosis. Cyanide also has a high affinity for the ferric iron in methemoglobin, and one therapeutic stratagem induces the formation of methemoglobin to which cyanide preferentially binds.

The small quantity of cyanide always present in human tissues is metabolized at the approximate rate of $17 \mu\text{g}/\text{kg}\cdot\text{min}$, primarily by the hepatic enzyme rhodanese, which catalyzes the irreversible reaction of cyanide and a sulfane to produce thiocyanate, a relatively nontoxic compound excreted in the urine. (An elevated concentration of thiocyanate in either blood or urine is evidence of cyanide exposure.) The limiting factor under normal conditions is the availability of a sulfane as a substrate for rhodanese, and sulfur is administered therapeutically as sodium thiosulfate to accelerate this reaction. The lethal dose of cyanide is time dependent because of the ability of the body to detoxify small amounts of cyanide via the rhodanese-catalyzed reaction with sulfane. A given amount of cyanide absorbed

slowly may cause no biological effects even though the same amount administered over a very short period of time may be lethal. In contrast, the $LC_{t_{50}}$ of each of the other chemical agents, which are not metabolized to the same extent as is cyanide, is relatively constant over time. A lethal amount causes death whether administered within minutes or over several hours.

Clinical Effects

The organs most susceptible to cyanide are those of the central nervous system (CNS) and the heart. Most clinical effects are of CNS origin and are nonspecific (Table 2-2). Approximately 15 seconds after inhalation of a high concentration of cyanide, there is a transient hyperpnea, followed within 15 to 30 seconds by the onset of convulsions. Respiratory activity stops 2 to 3 minutes later, and cardiac activity ceases several minutes later still, or approximately 6 to 8 minutes after exposure. The onset and progression of signs and symptoms after ingestion of cyanide or

Table 2-2. Effects From Cyanide (AC and CK) Vapor Exposure

Exposure	Signs and Symptoms	Course	Time
Moderate, from low concentration	Transient increase in rate and depth of breathing, dizziness, nausea, vomiting, headache.	These may progress to severe effects if exposure continues.	The time of onset of these effects depends on the concentration but is often within minutes after onset of exposure.
Severe, from high concentration	Transient increase in rate and depth of breathing, in 15 seconds. Convulsions, in 30 seconds. Cessation of respiration, in 2 to 4 minutes. Cessation of heartbeat, in 4 to 8 minutes.	Death if untreated.	Within seconds after onset of exposure.

after inhalation of a lower concentration of vapor are slower. The first effects may not occur until several minutes after exposure, and the time course of these effects depends on the amount absorbed and the rate of absorption.

The initial transient hyperpnea may be followed by feelings of anxiety or apprehension, agitation, vertigo, a feeling of weakness, nausea with or without vomiting, and muscular trembling. Later, consciousness is lost, respiration decreases in rate and depth, and convulsions, apnea, and cardiac dysrhythmias and standstill follow. Because this cascade of events is prolonged, diagnosis and successful treatment are possible.

The effects of cyanogen chloride, the parent complex of HCN, include those described for hydrogen cyanide. Cyanogen chloride is also similar to riot-control agents in causing irritation to the eyes, nose, and airways, as well as marked lacrimation, rhinorrhea, and bronchosecretions.

Physical findings are few and nonspecific. Two are said to be characteristic but in fact are not always observed. These are (1) severe respiratory distress in an acyanotic individual and "cherry-red" skin, and (2) the odor of bitter almonds. The natural complexion of the casualty may mask any cherry-red skin. When seen, cherry-red skin suggests either circulating carboxyhemoglobin from carbon monoxide poisoning or high venous oxygen content from failure of oxygen extraction by tissues poisoned by cyanide or hydrogen sulfide. However, cyanide victims may have normal-appearing skin or may be cyanotic, although cyanosis is not classically associated with cyanide poisoning. In addition, approximately 50% of the population is genetically unable to detect the odor of cyanide.

The casualty may be diaphoretic with normal sized or large pupils. A declining blood pressure and tachycardia follow an initial hypertension and compensatory bradycardia. Terminal hypotension is accompanied by bradyrhythmias before asystole.

Time Course of Effects

Effects begin 15 seconds following inhalation of a lethal Ct (concentration time); death ensues in about 6 to 8 minutes. The onset of effects following inhalation of lower Cts may be as

early as minutes after the onset of exposure. After exposure is terminated by evacuation to fresh air or by masking, there is little danger of delayed onset of effects.

The time course for ingested cyanide is longer, with the victim initially complaining of stomach upset, due to the alkaline nature of potassium cyanide. This is followed after a period of approximately 7 minutes by hyperpnea, a feeling of anxiety in the patient, and within 15 minutes the patient feels weakness and experiences a loss of consciousness. Convulsions follow. Within 25 minutes apnea occurs, and soon the heart stops and death occurs. Typically, death occurs within 30 minutes after cyanide ingestion, depending on the dose ingested and the physiological make-up of the victim.

Differential Diagnosis

Inhalation exposure to either cyanide or a nerve agent may precipitate the sudden onset of loss of consciousness, followed by convulsions and apnea. The cyanide casualty has normal sized or dilated pupils, few secretions, and muscular twitching but no fasciculations. In contrast, the nerve agent casualty has miosis (until shortly before death), copious oral and nasal secretions, and muscular fasciculations. In addition, the nerve agent casualty may be cyanotic, whereas the cyanide casualty usually is not.

Laboratory Findings

There are several confirmatory laboratory tests for cyanide poisoning, listed below. However, due to rapid clinical deterioration, antidotal treatment must be provided immediately if signs and symptoms are clearly indicative of cyanide poisoning, rather than waiting for lab results.

- **An elevated blood cyanide concentration.** Mild effects may be apparent at concentrations of 0.5 to 1.0 $\mu\text{g}/\text{mL}$. Concentrations of 2.5 $\mu\text{g}/\text{mL}$ and higher are associated with coma, convulsions, and death and are used primarily for forensic confirmation.
- **Acidosis.** Metabolic acidosis with a high concentration of lactic acid (lactic acidosis) or metabolic acidosis with an

unusually high anion gap (if the means to measure lactic acid are not available) may be present. Because oxygen cannot be utilized, anaerobic metabolism with the production of lactic acid replaces aerobic metabolism. Lactic acidosis, however, may reflect other disease states and is not specific for cyanide poisoning. Test results are fairly rapid and valuable as an early confirmatory lab result.

- **Oxygen content of venous blood greater than normal.** This also is a result of poisoning of the cellular respiratory chain and the resulting failure of cells to extract oxygen from arterial blood. This finding is also not specific for cyanide poisoning. It is helpful in confirming a diagnosis and evaluating methemoglobin levels for later adjustments in the dose levels of methemoglobin-forming antidotes.

Medical Management

Management of cyanide poisoning begins with self-protection, then removal of the casualty to fresh air. Dermal decontamination is unnecessary if exposure has been to vapor only. With liquid exposure, wet clothing should be removed, and if liquid on the skin is a possibility, the underlying skin should be washed either with soap and water or with water alone. A casualty who has ingested cyanide does not require decontamination. In the case of ingestion, gavage and administer activated charcoal. All vomit should be collected so that vapors from it do not sicken the staff.

Attention to the basics of intensive cardiorespiratory supportive care is critical and includes mechanical ventilation as needed, circulatory support with crystalloids and vasopressors, correction of metabolic acidosis with IV sodium bicarbonate, and seizure control with benzodiazepine administration. Administration of 100% oxygen has been found empirically to exert a beneficial effect and should be a part of general supportive care for the cyanide casualty.

Symptomatic patients, especially those with severe manifestations, may further benefit from specific antidotal therapy. This is provided in a two-step process. First, a methemoglobin-forming agent such as amyl nitrite (crushable

ampoules for inhalation) or sodium nitrite (for IV use) is administered, because the ferric ion (Fe^{3+}) in methemoglobin has an even higher affinity for cyanide than does cytochrome a_3 . The equilibrium of this reaction causes dissociation of bound cyanide from cytochrome a_3 and frees the enzyme to help produce adenosine triphosphate again. Hypotension, produced by nitrite administration, should be monitored. Further, there should be a prudent concern for overproduction of methemoglobin, which may compromise oxygen-carrying capacity. Thus, nitrite is relatively contraindicated in, for example, smoke-inhalation victims. In the standard cyanide antidote kit, the antidotes are already prepared in premeasured vials (amyl nitrite 1 ampule [0.2 mL] for 30–60 seconds; sodium nitrite 300 mg / 10 mL of 3% solution); sodium thiosulfate 12.5 g [50 mL of 25% solution]). The initial adult dose, equivalent to one of the two sodium nitrite vials in the kit, is 10 mL. Pediatric nitrite dosing is dependent on body weight and hemoglobin concentration. The recommended pediatric dose, assuming a hemoglobin concentration of 12 g/dL, is 0.33 mL/kg of the standard 3% solution given slowly, IV, over 5 to 10 minutes.

The second step for treatment is the infusion of a sulfur donor, typically sodium thiosulfate, which is utilized as a substrate by rhodanese for its conversion of cyanide to thiocyanate. Sodium thiosulfate itself is efficacious, relatively benign, and also synergistic with oxygen administration. It may thus be used without nitrites empirically in situations such as smoke inhalation with high carboxyhemoglobin levels. The initial adult dose, equivalent to one of the two large bottles in the cyanide antidote kit, is 50 mL; the initial thiosulfate dose for pediatric patients is 1.65 mL/kg of the standard 25% solution, IV. Second treatments with each of the two antidotes may be given at up to half the original dose if needed. Directions are located on the inside of the kit lid.

Although the combination of sodium nitrite and sodium thiosulfate may save victims exposed to 10 to 20 lethal doses of cyanide and is effective even after breathing has stopped, many patients will recover even without specific antidotal treatment if vigorous general supportive care is provided. Lack of availability of antidotes is therefore not a reason to consider even apneic

cyanide casualties expectant. It is also important to realize that administration of antidotes, especially if given too fast or in extremely large doses, is also associated with morbidity and even mortality. Antidotes should not be withheld in a patient with suspected cyanide poisoning, but infusion rates should be slow, and the drugs should be titrated to effect. Overdosage should be avoided.

Several alternative therapies and experimental antidotes are used in other NATO countries. Germany uses dimethylaminophenol, a rapid methemoglobin former developed for intramuscular and IV use. However, muscle necrosis at the site of injection may occur, and only the IV route of administration is recommended.

Certain cobalt compounds directly chelate cyanide to reduce its toxicity. Because cobalt compounds do not depend upon the formation of methemoglobin, they may exert their antidotal activity more quickly than do methemoglobin formers. Great Britain and France use cobalt edetate, but clear superiority to the methemoglobin formers has not been demonstrated, and cobalt toxicity is occasionally seen, particularly if the patient has only a mild exposure. The other cobalt compound sometimes used in France is hydroxocobalamin (vitamin B_{12a}), which forms a complex with cyanide on a molar basis. Clinical trials of this compound are underway in the United States. All of these compounds have been found to be most effective when combined with the administration of thiosulfate. Other ongoing research is examining whether slow methemoglobin formers can be used as pretreatment to induce clinically asymptomatic methemoglobinemia in troops at high risk for cyanide exposure.

Triage

Immediate casualties present within minutes of inhalation exposure with convulsions or recent onset of apnea. Circulation is intact. Immediate antidote administration is lifesaving.

Minimal casualties have inhaled less than a lethal amount and have mild effects. Antidotes may reduce symptoms but are not lifesaving.

Delayed casualties are recovering from mild effects or successful

therapy. It may be hours before full recovery. Evacuation is not required.

Expectant casualties are apneic with circulatory failure or with a coexposure to other toxicants or trauma resulting in anoxic encephalopathy. Casualties may triage as expectant because of limited resources.

An inhalation exposure casualty who survives long enough to reach medical care will need little treatment. Respiratory support might be a basis for re-triage to a different category.

Return to Duty

Those with mild to moderate effects can usually return to duty within hours, and those successfully treated after severe effects can return within a day. Monitor for neurological damage caused by significant hypoxia.

