

An editorial supplement from Jems Communications  
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# SMOKE INHALATION & HYDROGEN CYANIDE POISONING

A silhouette of a firefighter wearing a helmet and breathing apparatus, looking out from a doorway into a bright, hazy area. The firefighter is holding a hose. The background is a dark, textured wall, possibly brick or concrete, with a doorway leading to a bright, hazy area.

**THE DANGER POSED TO FIREFIGHTERS  
& VICTIMS IN STRUCTURE FIRES**

Acute cyanide poisoning: signs & symptoms 

Intervention & treatment

Also: Cyanide as an agent of terror

# SMOKE INHALATION & HYDROGEN CYANIDE POISONING

The Danger Posed to Firefighters & Victims in Structure Fires



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#### SMOKE INHALATION & HYDROGEN CYANIDE POISONING

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# HYDROGEN CYANIDE

## Fire Smoke's Silent Killer

### TREATMENT FOR SMOKE INHALATION

in the United States has not changed much during the past several years: We remove the victim from the source, provide high-flow 100% oxygen and assist with ventilation, if needed. Responding EMS personnel and firefighters are primarily concerned with carbon monoxide poisoning and hypoxia in smoke-inhalation patients. However, hydrogen cyanide poisoning is an increasingly common byproduct of fire smoke in structure fires, threatening both fire victims and firefighters. Unfortunately, it is rarely treated in the United States, and when it is, the current U.S. drug therapy for cyanide poisoning carries a risk of actually doing more harm than good.

At the International Association of Fire Chiefs EMS Section's Fire-Rescue Med Conference in April, I served as the moderator for a panel of experts who addressed the topic of cyanide poisoning in smoke inhalation and chemical terrorism. The presentations, compiled in this special issue, are designed to educate emergency response professionals on the risks of cyanide poisoning, as well as the treatment options.

In the first article, Richard Alcorta, MD, medical director at the Maryland Institute for Emergency Medical Services System, notes that smoke inhalation causes 5,000–10,000 deaths and more than 23,000 injuries—including 5,000 firefighters—in the United States annually. Dr. Alcorta presents data from several studies revealing elevated cyanide concentrations in smoke-inhalation victims, highlighting the direct relationship between cyanide blood concentrations and probability of death, and indicating that cyanide and carbon monoxide enhance the toxic effects of one another. He also reviews the current treatment for smoke inhalation, which some authorities do not rec-

ommend using, and discusses how important rapid treatment is to improving chances for survival.

In the second presentation, Jean-Luc Fortin, MD, chief of medicine for the Third Division of the Paris (France) Fire Brigade, provides data on an alternative cyanide antidote that is currently available in Europe. Hydroxocobalamin is routinely used in France to treat smoke-inhalation victims at the scene of fires. Dr. Fortin reviews data from a retrospective study of 81 smoke-inhalation victims treated with hydroxocobalamin by the Paris Fire Brigade. The results are promising, with a 62.1% survival rate following hydroxocobalamin administration as part of treatment for cyanide poisoning and carbon monoxide exposure.

The final presenter, Marc Eckstein, MD, medical director for the Los Angeles Fire Department and an associate professor of emergency medicine at the University of Southern California School of Medicine, discusses the intentional use of cyanide as an agent of war and terror. He notes that cyanide is plentiful, readily available and does not require special expertise to use. Dr. Eckstein also indicates that if hydroxocobalamin becomes available in the United States, cyanide poisoning may be successfully treated in a prehospital setting.

Collectively, the presentations provide a broad overview of cyanide poisoning and its treatment, both in conjunction with smoke-inhalation exposure and as an agent of chemical terrorism. I believe you will find the articles extremely informative and timely. Armed with this knowledge, I am optimistic that we can eventually reduce the significant number of smoke-inhalation deaths experienced each year in this country, as well as enhance our level of emergency preparedness for the potential use of cyanide in chemical terrorism. 🔥



**Deputy Chief Ken Riddle**

has more than 30 years' experience with emergency services in both the private and public sectors. A

member of the Las Vegas Department of Fire & Rescue for 25 years, Riddle currently serves as the city's fire marshal. As a chief officer for the past 10 years, he has been responsible for the operations, administration and medical services divisions. While serving in those positions, he designed and developed several major programs, including an ambulance transport program for the department. Riddle was certified as a paramedic for several years and also served as a flight medic. An author and frequent speaker on fire-based EMS issues, he is the immediate-past chair of the International Association of Fire Chiefs EMS Section and the past president of the Southern Nevada Fire Chiefs Association. Riddle continues to serve as the conference manager for the EMS Section's Fire-Rescue Med Conference, held annually in Las Vegas.

# SMOKE INHALATION & ACUTE CYANIDE POISONING

## Hydrogen cyanide poisoning proves increasingly common in smoke-inhalation victims

BY RICHARD ALCORTA, MD, FACEP

### **The family had gone to bed only two hours before the fire started.**

*A space heater in the living room ignited a sofa cushion, which smoldered for a period of time, emitting toxic gases even before the flames appeared. Within minutes after flames appeared, the fire spread upward from the burning sofa cushions and ignited first the draperies, then the ceiling. As the fire gained force, toxic smoke filled the room and entered the hallway. The smoke detector located down the hall finally activated and awakened the family. Meanwhile, a neighbor saw the flames while he was walking his dog and called 9-1-1.*

*The fire's heat and its dense black smoke prevented the family from exiting via the stairs. When firefighters arrived within four minutes of the 9-1-1 call, they had to rescue the three victims through a second-story window. All were found huddled close to the window, disoriented or unconscious, with soot in their noses and mouths. The mother and four-year-old boy were given oxygen and transported to a hospital where they survived. The father, who had rushed into the hall and into his son's room in an attempt to rescue him, went into full respiratory arrest. He had only 10% burns on his face and hands, but his condition, which initially appeared to stabilize, rapidly deteriorated en route to the hospital, despite 100% oxygen and supportive care. He died without regaining consciousness.*



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**EMERGENCY** medical and fire-rescue professionals tend to equate cyanide poisoning with accidental or intentional ingestion. However, cyanide toxicity from smoke inhalation in a structural or an enclosed-space fire is the most likely cause of cyanide

toxicity that EMS and fire professionals will encounter.

Smoke inhalation is an important but often overlooked cause of cyanide poisoning. A substantial body of evidence reveals that cyanide can be as great a threat as carbon monoxide in fire smoke.



Photo: Glen E. Ellman

## Objectives

- List reasons for the increased incidence of smoke inhalation-associated cyanide poisoning.
- Determine the role of cyanide in smoke inhalation-associated morbidity and mortality.
- Describe the management of smoke inhalation-associated cyanide poisonings.

This article will discuss:

- Why cyanide poisoning is a growing concern in the fire and EMS communities;
- The role of cyanide in smoke inhalation-associated morbidity and mortality as evidenced by two prospective studies—a 2002 meta-analysis of fire victim studies and animal research on cyanide-related incapacitation; and
- The factors involved in the management of smoke inhalation-associated cyanide poisoning—its mechanism, manifestations, recognition and treatment.

### SMOKE TOXICITY

Smoke inhalation is a more common source of fire-related mortality than burns. It causes 5,000–10,000 deaths annually in the United States and more than 23,000 injuries, including approximately 5,000 firefighter injuries. In fact, the United States has one of the highest fire-death rates among industrialized countries.<sup>1</sup>

Smoke toxicity is an increasing concern, particularly in the fire service, because the industrial products used today are changing. Over the past two decades, we've seen a shift away from woods and natural materials toward lighter construction materials, synthetics and petrochemical-based materials. These materials ignite and burn two to three times hotter and faster than conventional materials and, when heated, emit a gas or smoke that will also ignite two to three times faster and burn two to three times hotter than gas or smoke emitted from conventional materials.

These materials result in more fires reaching **flashover** and a shorter time per fire between ignition and flashover. Consequently, firefighters have less time to gain control of a fire. Smoke-inhalation victims have less time to escape and are more likely to be incapacitated from the toxic smoke, thereby increasing the risk of other injuries, such as thermal injuries. More effective prehospital treatment will save lives.

Studies completed by the National Institute of Standards and Technology in conjunction with the Fire Protection Research Foundation document a significant increase in toxic gases in smoke immediately before flashover occurs, as well as after flashover.<sup>2</sup> Conditions of high temperature and low oxygen promote degradation of synthetics, which release hydrogen cyanide and other toxic gases.

### FIRE SMOKE

Smoke is composed of particulate matter; heated gases, including irritants, such as hydrochloric acid, sulfur dioxide and ammonia; **asphyxiates**, such as carbon dioxide; and **toxins**, such as hydrogen sulfide and hydrogen cyanide.

The constituents of smoke vary from fire to fire and from one location to another in a given fire, depending on such factors as the composition of the burning material, the rate of burning, the absolute temperature and the ambient oxygen level. However, carbon monoxide and hydrogen cyanide are very likely to be two of the most prevalent gases.<sup>3</sup>

## Sources of Cyanide in Fire Smoke

### Natural substances

- Wool
- Silk
- Cotton
- Paper

### Synthetic substances

- Plastics
- Other polymers

Hydrogen cyanide, the gaseous form of cyanide, is generated by the combustion of nitrogen- and carbon-containing substances, including wool, silk, cotton and paper, as well as synthetic substances, such as plastics and other polymers. Because of our extensive reliance on the polymer industry's nitrogen- and carbon-containing products, these hydrogen cyanide substrates are ubiquitous in occupied structures. Hydrogen cyanide is likely to be produced under burning conditions

Cyanide toxicity from **smoke inhalation** in a structural or enclosed-space fire **is the most likely cause of cyanide toxicity** that EMS & fire professionals will encounter.

of high temperature and low oxygen, both of which are characteristic of closed-space fires. An enclosed space serves as a container for the toxic gases in smoke, such as hydrogen cyanide.<sup>4,5</sup>

Our two greatest threats in fire smoke are carbon monoxide poisoning, of which most of us are aware, and cyanide poisoning, of which many are not aware. Both carbon monoxide and hydrogen cyanide are silent killers. Both agents are colorless and odorless, dulling their victim's cognitive function and impairing the fight-or-flight response while their victim is completely unaware of their presence.

#### KEY CYANIDE STUDIES

Two prospective studies performed in Paris, France, and Dallas County, Texas, elucidate cyanide's contribution to smoke inhalation-associated mortality.<sup>6,7</sup> These studies were designed to assess cyanide's role in fire-related morbidity and mortality. The researchers overcame many other studies' limitations by collecting blood samples close to the time of smoke exposure and measuring cyanide in survivors rather than only in fatalities.

In the Paris study, the first medical squads to arrive on scene at residential fires in Paris collected blood in dry heparin over the span of a year (1988–1989). The blood cyanide data compared 109 fire victims (66 survivors and 43 fatalities) with 114 control individuals (40 with drug intoxication, 29 with carbon monoxide poisoning [none fire-related] and 45 with major trauma).

The results show that mean blood cyanide concentrations in both fire victims who survived (21.6 mol/L, or 0.58 mg/L) and in those who died (116.4 mol/L, or 3.14 mg/L) were significantly ( $p < 0.001$ ) higher than those in control subjects (5.0 mol/L, or 0.01 mg/L), and levels in victims who died were significantly higher than those in victims who survived. Clearly, all those who died had a very high or lethal level of cyanide, perhaps due to the fact that cyanide affects the heart and brain and caus-

## PARIS FIRE Study Conclusions

- Cyanide and carbon monoxide were both important determinants of smoke inhalation-associated morbidity and mortality;
- Cyanide concentrations were directly related to the probability of death;
- Cyanide poisoning may have predominated over carbon monoxide poisoning as a cause of death in some fire victims; and
- Cyanide and carbon monoxide may have potentiated the toxic effects of one another.

es altered mental status and confusion, possibly preventing the victims from escaping.

Several deaths occurred in victims whose blood cyanide and carbon monoxide levels were both in the nontoxic range.<sup>6</sup> These deaths could possibly be attributed to causes other than the two toxins. However, the deaths among individuals having nontoxic cyanide and carbon monoxide levels may also be explained by the potentiation of either or both compounds' toxic effects. This possibility is consistent with previous reports of fire victims having sublethal concentrations of carbon monoxide and no other apparent cause of death.<sup>8,9</sup> It is also consistent with animal studies showing the syn-

**Treatment for hydrogen cyanide poisoning must be administered as quickly as possible after exposure. Therefore, presumptive diagnosis and empiric treatment prove necessary to save lives.**



Photo: Glen E. Ellman

## DALLAS FIRE Study Conclusions

- Elevated cyanide concentrations were pervasive among smoke-inhalation victims;
- Cyanide concentrations were directly related to the probability of death; and
- Cyanide poisoning may have predominated over carbon monoxide poisoning as a cause of death in some fire victims.

ergistic lethality of cyanide and carbon monoxide in the absence of changes in blood concentrations.<sup>10</sup>

The Dallas County study assessed two groups of smoke-inhalation victims over the same two-year period. One group comprised 144 smoke-inhalation patients who were alive at the time of initial evaluation in the University of Texas Health Science Center emergency department (ED). The second group comprised 43 individuals who were dead on arrival at the Dallas County medical examiner's office.

The results show that mean blood

cyanide concentrations in the 144 smoke-inhalation victims who arrived alive at the ED were lower than concentrations in the 43 victims who were dead on arrival (0.65 mg/L versus 2.15 mg/L). Of the 144 patients who were alive when they arrived at the ED, 12 had blood cyanide concentrations exceeding 1 mg/L, the lower limit of the range defined as potentially lethal in this study. Of these 12 patients, eight died. None of them had blood **carboxyhemoglobin (HbCO)** concentrations suggesting carbon monoxide as the cause of death (e.g.,  $\geq 50\%$ ). Although some of the patients who died had extensive burns that may have contributed to death, three of them had  $\leq 4\%$  total body surface area burn.<sup>6</sup>

These data are consistent with the results of the Paris study in showing pervasive elevated cyanide concentrations and a direct relationship between blood cyanide concentration and probability of death and in suggesting that cyanide poisoning may predominate over carbon monoxide poisoning as a cause of death in some fire victims. It is clear that every victim metabolizes cyanide differently—some better than others. For those who do not metabolize it well, it remained in their system and was apparently compounded by carbon monoxide, leading to their deaths. A limited amount of cyanide is converted to byproducts through the sulfur transferase/rhodanese enzymes and the availability of sulfur donor compounds. Patients with existing liver disease or inherent limitation of these enzymes will have reduced clearance and increased toxicity.

### 2002 META-ANALYSIS OF FIRE DEATHS

Results of a 2002 meta-analysis of fire casualty databases suggest that cyanide poisoning is a significant and independent contributor to smoke-inhalation deaths.<sup>11</sup> In the meta-analysis, data from seven published studies in which blood cyanide concentrations were reanalyzed in a uniform manner to facilitate compar-

## Glossary

- **Asphyxiate:** A gas that is non-toxic but will displace oxygen from the atmosphere, thus causing a life-threatening environment due to a lack of oxygen.
- **Carboxyhemoglobin (HbCO):** The laboratory measurable component of blood that is the bound percent of hemoglobin with carbon monoxide. Carbon monoxide once attached to hemoglobin prevents oxygen from binding to those sites on the hemoglobin.
- **Flashover:** In a compartment fire there can come a stage in which the total thermal radiation from the fire plume, hot gases and hot compartment boundaries causes the generation of flammable products of pyrolysis from all exposed combustible surfaces within the compartment. Given a source of ignition, this will result in the sudden and sustained transition of a growing fire to a fully developed fire. The rapid transition to a state of total surface involvement in a fire of combustible materials within a compartment.
- **Histo-toxin:** A cellular poison or a substance that has a direct poisonous effect at the cellular (histo) level. The substance can inhibit cellular respiration/metabolism.
- **Pyrolysis:** A form of incineration that chemically decomposes organic materials by heat in the absence of oxygen or is the decomposition/transformation of a chemical compound caused by heat.
- **Toxin:** A poisonous substance that can be produced during metabolism or growth of an organism, or produced by the combination/combustion of materials.

isons between studies. In most of the studies measuring blood cyanide, HbCO (carboxyhemoglobin), which is formed by the union of carbon monoxide with hemoglobin and is a marker of carbon monoxide poisoning, was also measured.

The results of the meta-analysis should be interpreted in the context of its limitations, including the retrospective data collection and analysis of many of the studies included in the meta-analysis, inconsistencies between studies in blood sampling methods, and timing and significant delays in some studies in analyzing blood samples. (Data from studies in which only carbon monoxide was measured were also reported in the meta-analysis but are not described here. In addition, data from a 1966 report that included blood cyanide measurements are not included here because no details about the study sample were described.)

The results show that, across studies, significant proportions (33–87%) of fire victims had blood cyanide levels of at least 1 mg/L, values above which are potentially lethal. Blood cyanide levels  $\geq 3$  mg/L were found in 5–46% of victims across studies. The percentage of victims with potentially lethal levels of carbon monoxide ranged from 5–98% across studies.

Cyanide perhaps played a greater role in mortality than carbon monoxide in two particular fires considered in the meta-analysis: the Manchester aircraft fire at Manchester International Airport in 1985 and the Dupont Plaza Hotel fire in San Juan, Puerto Rico, in 1986. Victims of the Manchester fire were not severely burned and were determined to have died of smoke inhalation. The majority (87%) of the 54 individuals who died had potentially lethal blood cyanide levels of  $\geq 1$  mg/L (median=2.3 mg/L), whereas only 21% of victims had HbCO levels exceeding 50% (median HbCO=39%).

Similarly, in the Dupont Plaza Hotel fire, approximately half (48%) of the 53 victims had potentially lethal blood cyanide levels of  $\geq 1$  mg/L



Photo: Glen E. Eilman

**Although poor tissue utilization of oxygen in cyanide poisoning should theoretically render supplemental oxygen useless, supportive care with administration of oxygen has proven effective in a number of poisonings.**

## 2002 META-ANALYSIS Conclusions

- Exposure to potentially lethal cyanide concentrations was frequent;
- Coexposure to carbon monoxide and cyanide was frequent; and
- In some fire incidents, cyanide may have played a more important role in causing death than carbon monoxide.

(median=1 mg/L), whereas only 5% of victims had HbCO levels exceeding 50% (median HbCO=33%). In this fire, unlike the Manchester aircraft fire, many of the victims were severely burned, and the relative contributions of smoke inhalation and burns to their deaths are difficult to determine. This caveat notwithstanding, the results considered in aggregate are consistent with the possibility that cyanide can sometimes be a more important determinant of smoke inhalation-associated mortality than carbon monoxide, which is usually regarded as the primary toxic threat in fire smoke.

The results of the 2002 meta-analysis show frequent exposure to potentially lethal concentrations of cyanide, as well as coexposure to car-

**Hydrogen cyanide is generated by the combustion of nitrogen- & carbon-containing substances, including wool, silk, cotton & paper, as well as synthetic substances, such as plastics & other polymers.**

**Cyanide poisoning** should be suspected in any fire victim & may be particularly likely in individuals exposed to closed-space fires & in those with soot in the mouth or nose, altered mental status or hypotension.

Firefighters who respond to enclosed-space fires are increasingly exposed to hydrogen cyanide, a byproduct of fire smoke from nitrogen- and carbon-containing materials used in construction and furniture today.



Photo: Glen E. Ellman

bon monoxide and cyanide in smoke-inhalation victims. Consistent with the prospective Paris and Dallas County studies, the meta-analysis results suggest that, in some fire incidents, cyanide may have played a greater role in causing death than carbon monoxide.

#### SUBLETHAL CYANIDE CONCENTRATIONS

Most assessments of cyanide poisoning in smoke-inhalation victims have attempted to define the role of cyanide exposure in fire-related deaths. The role of sublethal concentrations of cyanide in smoke inhalation-associated morbidity and mortality has not been systematically assessed in humans.

Data from research in which monkeys were exposed to fumes from the **pyrolysis** of polyacrylonitrile—a high-nitrogen polymer used in fiber form for fabrics, upholstery covers, infill padding and clothing—suggest that sublethal levels of cyanide can cause rapid incapacitation that prevents efforts to escape toxic fumes. Under thermal decomposition, approximately half of the mass of polyacrylonitrile becomes available as

hydrogen cyanide.

Cyanide-exposed monkeys hyper-ventilated and then rapidly lost consciousness at a rate dependent on the concentration of exposure. A concentration of 200 parts per million (ppm) was associated with rapid incapacitation but not with elevated blood cyanide concentrations measured hours after exposure. The authors suggest on the basis of these findings that cyanide in smoke can lead to death indirectly via incapacitation, which immobilizes the smoke-inhalation victim and permits more prolonged exposure to potentially fatal concentrations of other toxins and asphyxiates identified as the primary cause of death.<sup>12</sup>

Considered in aggregate, the blood cyanide findings in fire victims support an important role of this **toxin** in smoke inhalation-associated morbidity and mortality. Cyanide poisoning should be suspected in any fire victim and may be particularly likely in individuals exposed to closed-space fires and in those with soot in the mouth or nose, altered mental status or hypotension.<sup>11,13</sup>

#### SIGNS & SYMPTOMS

Smoke inhalation-associated cyanide poisoning manifestations vary. In victims with low inhaled-cyanide concentrations or very recent exposure to moderate or high concentrations, manifestations may include:

- Faintness;
- Flushing;
- Anxiety;
- Excitement;
- Perspiration;
- Vertigo;
- Headache;
- Drowsiness;
- Tachypnea;
- Dyspnea; and
- Tachycardia.

In victims with moderate or high concentrations, manifestations may include:

- Prostration;
- Tremors;
- Cardiac arrhythmia;
- Convulsions;

- Stupor;
- Paralysis;
- Coma;
- Respiratory depression;
- Respiratory arrest; and
- Cardiovascular collapse.

Cyanide is a **histo-toxin**. It causes toxicity by deactivating the mechanism by which cells use oxygen. The heart and brain—organs that rely on a substantial, continuous supply of oxygen—are markedly affected by cyanide poisoning. Accordingly, most signs and symptoms of acute cyanide poisoning reflect the nonspecific effects of oxygen deprivation on the heart and brain. Exposure to smaller concentrations can initially cause respiratory activation (manifested by hyperpnea and tachycardia) in an attempt to compensate for lack of oxygen followed by respiratory and myocardial depression.

Early neurologic manifestations, reflecting initial effects of brain oxygen deprivation, include headache, giddiness and anxiety. Later manifestations of exposure to smaller concentrations or early manifestations of exposure to large concentrations include cardiac arrhythmias, stupor, coma and seizure that culminate in respiratory depression and death.<sup>4,14,19</sup>

Successful intervention for cyanide poisoning depends primarily on the concentration of exposure and the time between exposure and treatment. Clearly, it is critical that treatment is administered as quickly as possible after exposure. Therefore, presumptive diagnosis of cyanide poisoning and empiric treatment prove necessary.

#### PREHOSPITAL INTERVENTION

Prehospital management of acute cyanide poisoning in the smoke-inhalation victim involves moving the victim from the source of exposure (while maintaining appropriate provider respiratory protection, SCBA), restoring or maintaining airway patency, administering 100% oxygen via non-rebreather mask or bag-valve mask technique, aggres-

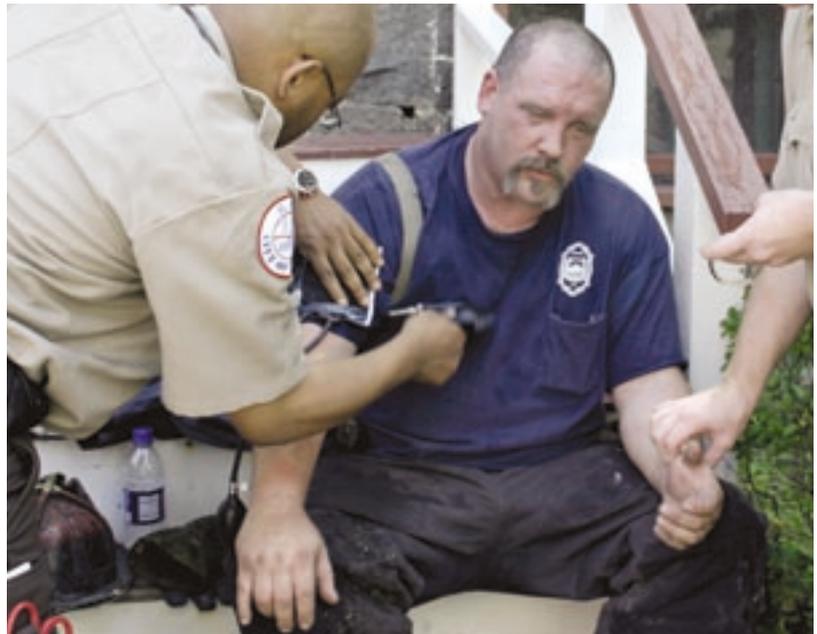


Photo: Jeffrey Mayes

**Firefighters and victims with smoke inhalation-associated cyanide poisoning often experience cognitive dysfunction and drowsiness that can impair the fight-or-flight response.**

## PREHOSPITAL Care

### Aggressive airway management with delivery of 100% oxygen can save lives:

- Intubate if the patient is unconscious or the airway cannot be protected.
- Establish an IV line, and provide cardiac monitoring.
- Administer sodium bicarbonate if the patient is unconscious or hemodynamically unstable.
- Administer cyanide antidotes in prehospital care if diagnosis is relatively certain. Avoid the sodium nitrite portion of the Taylor cyanide antidote kit (also called the Lilly or Pasadena kit) in patients with smoke inhalation. Such treatment generally should involve online medical control. Anticonvulsants may be needed for generalized seizures. Vasopressors (e.g., epinephrine) are indicated for hypotension not responsive to a fluid challenge.
- Although poor tissue utilization of oxygen in cyanide poisoning should theoretically render supplemental oxygen administration useless, supportive care with administration of oxygen alone has proven effective in a number of poisonings.

### Emergency Department Care: Initial ED care is identical to that provided in prehospital phase:

- Consider antidotal therapy if diagnosis is strongly suspected.
- Begin antidotal therapy without waiting for laboratory confirmation.
- Avoid sodium nitrite portion of the Taylor cyanide antidote kit in patients with smoke inhalation unless carboxyhemoglobin concentration is very low (<10%).<sup>1</sup>



**Prehospital management of acute hydrogen cyanide poisoning includes moving the victim away from the source of exposure, restoring or maintaining airway patency, administering 100% oxygen via a non-rebreather mask or bag-valve technique, providing aggressive advanced airway management and cardiopulmonary support, and stabilizing vital signs.**

sive advanced airway management, including early intubation, providing cardiopulmonary support and stabilizing vital signs, including the use of trauma and burn management (Parkland formula). When clinically indicated, anticonvulsants (benzodiazepines) should be given for seizures, epinephrine and antiarrhythmics to stabilize cardiovascular function, and sodium bicarbonate to correct metabolic acidosis if known.<sup>4,5,13,15,19</sup>

Effective cyanide antidotes exist. However, a cyanide antidote appropriate for use in smoke-inhalation victims is not yet available in the United States, where the cyanide antidote kit (also called the Lilly kit, Taylor kit or Pasadena kit) is the only antidote currently available. The kit consists of amyl nitrite, thio-sulfate and sodium nitrite.<sup>15</sup>

The cyanide antidote kit should not be used outside of a hospital in smoke-inhalation victims. The nitrites in the kit reduce the blood's oxygen-carrying capacity by binding with hemoglobin to form methemoglobin, which binds and neutralizes cyanide. Problematically, inducing methemoglobinemia can also significantly reduce the blood's oxygen-carrying capacity. In smoke-

inhalation victims with cyanide poisoning, concurrent carbon monoxide poisoning almost always compromises the blood's oxygen-carrying capacity. Superimposing additional reductions in oxygen-carrying capacity of the blood from antidote-induced methemoglobinemia is potentially dangerous and even fatal. The currently available cyanide antidote may also cause severe hypotension, an effect that counteracts efforts to achieve hemodynamic stability in fire victims.<sup>3,16,17</sup>

Hydroxocobalamin, a precursor of vitamin B12, is being investigated for possible introduction in the United States to meet the need for an antidote that can be used safely on an empiric basis. Hydroxocobalamin has been available for nearly a decade in France, under the name Cyanokit™ (Merck-Santé s.a.s) and is the antidote used by the Paris Fire Brigade.<sup>1</sup> Hydroxocobalamin detoxifies cyanide by binding with it to form cyanocobalamin (vitamin B12), which in excess is excreted in the urine.<sup>17,18</sup> Should it become available in the United States, hydroxocobalamin potentially will enable prehospital antidotal treatment of cyanide poisoning in smoke-inhalation victims. The ability to administer an antidote in the prehospital setting should increase the speed of intervention and, arguably, its effectiveness.

For now, the best course of prehospital intervention is the provision of rapid transport to a hospital ED or burn center where definitive treatment can be delivered.

#### FINAL WORD

Research suggests that cyanide should be expected in fire victims' blood and is often as great a threat as carbon monoxide. Morbidity and mortality from smoke inhalation-associated cyanide poisoning are preventable if cyanide poisoning is suspected or promptly recognized and antidotal therapy initiated shortly after cyanide exposure. Hydroxocobalamin, currently under FDA evaluation, may offer a favorable risk-benefit ratio that allows for

**Successful intervention for cyanide poisoning depends primarily on the concentration of exposure & the time between exposure & treatment.**

its empirical use in the prehospital setting. 🔥

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is the state EMS director for the Maryland Institute for Emergency Medical Services Systems (MIEMSS). He is also the Maryland medical director of the Chemical Stockpile Emergency Preparedness Program and an emergency specialist/physician. A former paramedic liaison at the Suburban Hospital in Bethesda, Md., Alcorta is a fellow of the American College of Emergency Physicians and is board-certified in emergency medicine by the American Board of Emergency Medicine. He is also a certified Maryland state EMT-paramedic instructor, hospital hazardous material instructor and Advanced Trauma Life Support instructor. Alcorta is a member of many professional organizations, including the Alpha Omega Alpha Medical Honor Society, the American Medical Association, the American College of Emergency Physicians, the National Association of EMS Physicians and the National Association of State EMS Directors.

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*Special thanks to Jane Saiers, PhD, who completed the background literature research on cyanide presented in this article*

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This continuing education activity is approved by the Center for Emergency Medicine, an organization accredited by the Continuing Education Board for Emergency Medical Services (CEBEMS), for 1.5 hours credit for First Responder, Basic and Advanced providers.

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(continued on next page)

**1. EMS providers are most likely to encounter acute cyanide poisoning in patients:**

- a. who intentionally overdose on cyanide in a suicide attempt
- b. accidentally poisoned through improper food storage
- c. poisoned through occupational exposures
- d. with smoke inhalation from a closed-space fire

**2. Synthetics used in manufacturing today:**

- a. are heavier than traditional building materials
- b. ignite slowly and burn with low intensity
- c. burn cleanly with little toxic chemical emission
- d. burn hotter than traditional building materials

**3. Two of the most prevalent gases in smoke from most fires are:**

- a. hydrogen cyanide and carbon monoxide
- b. carbon dioxide and hydrogen sulfide
- c. hydrogen sulfide and hydrogen chloride
- d. hydrogen chloride and carbon dioxide

**4. Hydrogen cyanide is likely to be produced:**

- a. in low temperature fire conditions
- b. in fires with high oxygen content
- c. by burning synthetic materials, never natural materials
- d. by the combustion of nitrogen-containing products

**5. Which of the following is true of hydrogen cyanide?**

- a. Hydrogen cyanide has a distinctive smell
- b. Hydrogen cyanide is colorless
- c. Hydrogen cyanide impairs muscular ability but not cognitive function
- d. Hydrogen cyanide plays no role in early fire-related deaths

**6. One of the findings from the Paris cyanide study was that:**

- a. Cyanide may play a more important role than CO as a cause of death
- b. Cyanide levels at the scene were not closely related to cyanide levels measured later
- c. Cyanide played no role in determining the probability of death
- d. Carbon monoxide and cyanide appear to function independently of one another

**7. Cyanide in the body:**

- a. is not metabolized—it must be removed with blood filtration
- b. is metabolized less efficiently by patients with liver disease
- c. remains active until an antidote is delivered
- d. only presents a problem if CO is present

**8. HbCO is a measure of:**

- a. the interaction between cyanide and carbon monoxide
- b. cyanide levels in the blood
- c. carbon monoxide poisoning
- d. cyanide levels in inhaled air

**9. A conclusion from the 2002 meta analysis of fire deaths is that:**

- a. patients rarely were exposed to both cyanide and carbon monoxide
- b. patients frequently had lethal cyanide exposures
- c. carbon monoxide was a better determinant of death than cyanide
- d. carbon monoxide levels were not a determining factor in patient deaths

**10. Sub-lethal concentrations of cyanide can lead to:**

- a. rapid incapacitation
- b. minor changes in alertness
- c. changes in mental status, but are rarely life-threatening
- d. few changes in patient condition unless concentrations increase

**11. Cyanide poisoning is especially likely in those patients who:**

- a. were in open-air fires
- b. have hypertension following exposure to smoke
- c. have a normal level of consciousness following an enclosed space fire
- d. have soot in their nose or mouth

**12. Which of the following is typical of low concentration cyanide poisoning:**

- a. stupor
- b. headache
- c. tremors
- d. respiratory depression

**13. Organs most commonly affected by cyanide poisoning include the:**

- a. lungs and heart
- b. liver and kidneys
- c. heart and brain
- d. stomach and intestines

**14. Cyanide antidote kits available in the United States:**

- a. should be administered as soon as possible to all smoke inhalation victims
- b. should be administered if CO poisoning is suspected in addition to cyanide poisoning
- c. should be administered if the oxygen saturations in the blood are low
- d. should not be administered outside of the hospital

**15. Which of the following is true of cyanide antidotes?**

- a. Currently, no effective antidote exists
- b. Effective antidotes for smoke-inhalation patients are not available in the United States
- c. The current cyanide antidote kit used in the United States is an effective and safe treatment
- d. The antidote kit available in the United States may not be effective, but it will do no harm

**16. Hours after exposure, the cyanide blood level of monkeys exposed to sub-lethal cyanide doses showed:**

- a. no elevation
- b. moderate elevation
- c. marked elevation
- d. extremely high levels

**17. Cyanide causes toxicity by:**

- a. blocking the release of neurotransmitters
- b. deactivating the mechanism by which cells use oxygen
- c. releasing histamine
- d. causing cells to rapidly use all available oxygen

**18. Patients with cyanide poisoning should be:**

- a. intubated only if they are in cardiac arrest
- b. intubated if they cannot maintain their own airway
- c. managed without intubation due to potential damage to the trachea
- d. managed with low-flow oxygen to slowly restore oxygen levels

**19. Known metabolic acidosis due to cyanide poisoning should be treated with:**

- a. vasopressors
- b. anticonvulsants
- c. epinephrine
- d. sodium bicarbonate

**20. Which medication from the cyanide poisoning antidote kit should not be administered in the prehospital setting?**

- a. amyl nitrite
- b. thiosulfate
- c. sodium nitrite
- d. atropine



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## CE Answer Sheet #199

Smoke Inhalation & Acute Cyanide Poisoning

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# HYDROXOCOBALAMIN: Treatment for Smoke Inhalation-Associated Cyanide Poisoning

## Meeting the Needs of Fire Victims

BY J. L. FORTIN, MD, M. RUTTIMAN, MD, L. DOMANSKI, MD, & J. J. KOWALSKI, MD

**The United States lacks a cyanide antidote useful for smoke-inhalation victims when cyanide toxicity is suspected on the basis of physical symptoms but is unconfirmed by laboratory assay—arguably the most common occurrence of acute cyanide poisoning. However, hydroxocobalamin, a cyanide antidote with a favorable history of usage by the Paris (France) Fire Brigade, may offer a treatment option superior to that which is currently available in the United States. The cyanide antidote kit made by Taylor Pharmaceuticals (also known as the Pasadena kit or the Lilly kit for the company that originally made it) is the only currently available cyanide antidote in the United States.**

### THE PROBLEM IS THAT

the Taylor kit has its limitations. The Taylor kit, a multicomponent kit consisting of inhaled amyl nitrite, IV sodium nitrite and IV sodium thiosulfate, may be associated with such effects as severe hypotension, vomiting and methemoglobinemia formation, which results in a reduction of the blood's oxygen-carrying capacity. The latter effect, in particular, precludes the use of the Taylor kit in most smoke-inhalation victims. In addition to being a source of cyanide poisoning, smoke inhalation is almost always associated with concomitant carbon monoxide poisoning, a state characterized by deficient blood oxygenation. Like carbon monoxide, the amyl nitrite and sodium nitrite found in the Taylor kit are methemoglobin formers, which reduce oxygenation of the blood.

When added to the blood oxygen-depriving effects of carbon monoxide poisoning, antidote-induced reductions in the oxygen-carrying capacity of smoke-inhalation victims' blood can be dangerous and possibly fatal.

Because of this potential toxicity, the Taylor kit is rarely used to treat smoke-inhalation victims and is administered only when cyanide poisoning is confirmed by a laboratory or very strongly suspected via direct evidence of cyanide exposure or ingestion. Further, its use is often restricted to hospital settings because of the demands of managing potentially dangerous antidote-associated side effects. The cyanide antidotes dicobalt-EDTA and 4-dimethylaminophenyl are available in Europe; however, they, like the Taylor kit, are associated with some significant safety concerns.

## HYDROXOCOBALAMIN

The cyanide antidote hydroxocobalamin (Cyanokit™, Merck-Santé s.a.s.) is being studied for possible introduction in the United States to address the unmet need for a safe and effective antidote that may be used empirically for victims of smoke inhalation as well as for other sources of cyanide poisoning. Hydroxocobalamin, a precursor of vitamin B12 (see figure p. 20), neutralizes cyanide by fixing it to form cyanocobalamin (vitamin B12), a nontoxic compound that is eliminated in the urine.

Hydroxocobalamin has been approved for use in France since mid 1996 and appears to be very well tolerated, even at the high doses necessary to treat cyanide poisoning. To date, it has no known major toxicities, and when administered acutely as a cyanide antidote, it has not been associated with any clinically relevant adverse events. However, it should be noted that the FDA has requested an additional safety study in human volunteers.

Because the molecule is red in color, hydroxocobalamin turns mucous membranes, skin and urine red, and it may interfere with some specific colorimetric clinical laboratory values, including aspartate aminotransferase, total bilirubin, creatinine and magnesium. No allergic reactions have been documented to the antidote administration; however, chronic use of small doses of hydroxocobalamin for vitamin B12 deficiency has been associated with rare allergic responses.

Hydroxocobalamin has a history of clinical use for decades in countries other than the United States. Merck-Santé s.a.s. commercially registered hydroxocobalamin as an antidote for acute cyanide poisoning in France in 1996; however, it was prepared and used by multiple hospital pharmacies in France for several years prior to that time. It has also been used and studied as a cyanide antidote in other European countries, such as Spain, where it is considered to be an effective antidote for cyanide toxicity from any

## SYNERGISTIC EFFECTS

### Carbon Monoxide

- Neurological alteration
- Normal respiration

### Hydrogen Cyanide

- Neurological alteration
- Respiratory frequency disturbance or apnea

source or route. Other published therapeutic uses of hydroxocobalamin include its use in treatment of pernicious anemia, hepatic insufficiency, encephalopathy, neuropathy, amblyopia and various neuropsychiatric syndromes.

Hydroxocobalamin is commercially available in Europe as Cyanokit™. According to its labeling, each kit includes two vials of 2.5 g hydroxocobalamin lyophilizate for reconstitution with 100 mL saline per vial before use and two sterile transfer kits. The initial adult dose of hydroxocobalamin is typically 5 g intravenously. Additional doses of up to 15 g can be given according to the clinical status of the patient per the labeling. The dosing instructions for hydroxocobalamin in the United States (should the antidote be approved as anticipated) have yet to be established.

The Taylor kit may be associated with such effects as severe hypotension, vomiting & methemoglobinemia formation, **which result in a reduction of the blood's oxygen-carrying capacity.**

**In addition to expected supportive care, victims of smoke-inhalation from structural fires in the United States may benefit from prehospital treatment with hydroxocobalamin, which is routinely administered in the field to smoke-inhalation victims of structural or enclosed-space fires in France.**



Photo: Glen E. Eilman

## Conclusions Based on Preliminary DATA FROM PARIS FIRE BRIGADE

- Hydroxocobalamin appears to be a safe, effective cyanide antidote suitable for prehospital use for acute cyanide poisoning caused by smoke inhalation.
- An effective dose is 5 g (70 mg/kg) intravenously.

Hydroxocobalamin, a precursor of vitamin B12, **neutralizes cyanide** by fixing it to form cyanocobalamin (vitamin B12), a nontoxic compound that is eliminated in the urine.

### PARIS FIRE BRIGADE USE OF HYDROXOCOBALAMIN

The Paris Fire Brigade comprises 7,020 firefighters divided among 77 fire stations and responds to more than 18,000 fire-related incidents annually. The department serves 759 square kilometers (roughly 450 square miles) with a population of more than 6 million. To meet the population's needs, the Paris Fire Brigade employs 50 doctors who specialize in emergency medicine, 60 nurses and 36 intensive-care ambulance drivers who operate seven intensive-care ambulances. Each intensive-care mobile unit has one doctor, one nurse and one driver on board. Hydroxocobalamin is part of the Paris Fire Brigade's standard treatment protocol for cyanide poisoning victims.

### CIRCUMSTANCES OF ACUTE HYDROGEN CYANIDE POISONING IN FIRES

Hydrogen cyanide is frequently associated and acts synergistically with carbon monoxide in cases of smoke toxicity in structural or enclosed-space fires where degrading synthetic or natural substances release cyanide. The synergistic adverse interaction of hydrogen cyanide with carbon monoxide should not be underestimated. This interaction can result in a reduction of respiratory frequency, even apnea, as well as hypotension

and possibly a state of shock. In addition, hydrogen cyanide poisoning is responsible for a deterioration of the neurological state. An increase in lactate, in particular, is related to hydrogen cyanide poisoning associated with carbon monoxide toxicity, because the body makes a compensatory switch to anaerobic metabolism.

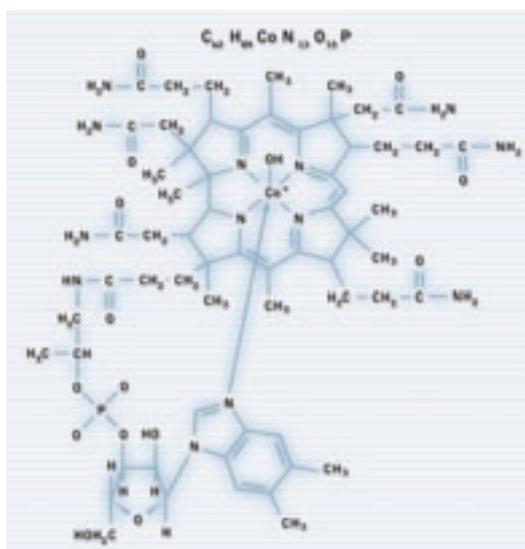
### PARIS FIRE BRIGADE STUDY: PRELIMINARY DATA

Hydroxocobalamin is routinely administered in the field to smoke-inhalation victims of structural or enclosed-space fires in France. The prehospital use of hydroxocobalamin by the Paris Fire Brigade over a five-year period from January 1998 to December 2002 was evaluated in a retrospective study. Some data from this study are available, and data collection and analysis are ongoing.

According to a preliminary review of the data, 70 of the 81 patients (41 males and 40 females) treated with hydroxocobalamin (usually at a dose of 5 g or 70 mg/kg) recovered cardiac and/or respiratory function at the fire scene, and 11 died. In a subset of 29 patients in cardiac arrest before hydroxocobalamin administration, 18 patients spontaneously recovered cardiac activity following hydroxocobalamin and adrenalin administration (plus other supportive care) in an average time of 19.3 minutes. Eleven patients receiving hydroxocobalamin and adrenalin died at the fire scene. No side effects attributed to hydroxocobalamin were reported. This resulted in a 62.1% survival rate following hydroxocobalamin administration in conjunction with the expected supportive care.

Of the subset of 15 hemodynamically unstable patients, 12 had recovery of systolic blood pressure to >90 mmHg in 29 minutes, on average, after the end of hydroxocobalamin infusion. Rapid recovery of systolic blood pressure was observed even in severely hypotensive patients. These data suggest that hydroxocobalamin may improve hemodynamic stability in smoke-inhalation victims. This potential hemodynamic-stabilizing

**FIGURE.** Hydroxocobalamin is the precursor of vitamin B12.



property of hydroxocobalamin differentiates it from the cyanide antidote kit currently available in the United States, which can cause severe hypotension. The hemodynamic-stabilizing property of hydroxocobalamin may be particularly important in the prehospital setting, where rapid attainment of hemodynamic stability is crucial for saving lives and enabling timely transport to the hospital.

#### CONCLUSIONS

Accumulating data from an ongoing study on the prehospital use of hydroxocobalamin for cyanide poisoning suggest that it has a favorable risk-benefit ratio and a reasonable safety profile. Hydroxocobalamin at a dose of 5 g appears to be effective and safe in smoke-inhalation victims, as empiric treatment and as prehospital treatment. With this profile, hydroxocobalamin may be capable of fulfilling the currently unmet need in the United States for a cyanide antidote that can be administered safely in the prehospital setting as empiric therapy for smoke inhalation as well as the range of causes of cyanide poisoning. 🔥

**Hydroxocobalamin has been approved for use in France since mid 1996 and appears to be very well tolerated, even at the high doses necessary to treat cyanide poisoning.**



**Lead researcher Jean-Luc Fortin, MD**, is the chief of medicine, third division, of the Paris Fire Brigade, one of the largest urban fire-and-rescue departments in the world. Fortin is also an auxiliary physician in the intensive-care burn unit at the Army Teaching Hospital of Percy in Clamart, France. Before joining the Brigade in 1999, Fortin was an emergency physician at the University Hospital Center of Timone Emergency Medical Aid Service in Timone, France. He also served as an emergency physician for the French military as Director of Medical Care in the Navy Battalion Fire Brigade of Marseille (ambulance, emergency and intensive care service), and as an intensive-care physician at the Renee Le Bas Army Hospital Center in Cherbourg, France. Fortin received two inter-university diplomas—one in subaquatic and hyperbaric medicine in 1993 and another in higher education in emergency medicine in 1999. He received university diplomas in burn care and treatment, pediatric emergencies and radiological evaluation of medical/surgical emergencies. He is licensed in emergency medical assistance, catastrophic medicine, and aeronautical and space medicine.

*Additional researchers:* M. Ruttiman, MD, L. Domanski, MD, and J.J. Kowalski, MD.

**In a subset of 29 patients in cardiac arrest before hydroxocobalamin administration, 18 patients spontaneously recovered cardiac activity following hydroxocobalamin & adrenalin administration (plus other supportive care) in an average time of 19.3 minutes.**

# CYANIDE AS A CHEMICAL TERRORISM WEAPON

**“Chance favors the prepared mind.”** –*Louis Pasteur*

BY MARC ECKSTEIN, MD, FACEP

**Several recent incidents in which cyanide was intended** for use as a weapon of terror should cause emergency services personnel to pause and carefully consider the potential consequences. For example, many are unaware that cyanide was used during the 1993 World Trade Center bombing. In the aftermath, investigators found traces of cyanide in the vans in the parking garage that caused the explosion. Fortunately, the cyanide burned up in the explosion.<sup>1</sup>

**OTHER RECENT INCIDENTS** in which cyanide was used but received little press attention include the 1995 Tokyo subway attack, where the precursors of cyanide were found in the subway bathrooms;<sup>1</sup> the foiled 2002 al-Qaeda attempt to use cyanide gas to kill commuters in the London Underground;<sup>2</sup> the 2002 arrests of four Moroccans (again with ties to al-Qaeda) who were plotting to use cyanide to poison water supplies around the U.S. embassy in Rome;<sup>3</sup> the December 2002 recovery of a cyanide store in Paris linked to three suspected al-Qaeda operatives;<sup>4</sup> and, most recently, the May 2003 cyanide bomb found in the possession of white supremacists in Texas.<sup>5</sup> Although these events were thwarted, it's not difficult to envision a suc-

cessful attack, particularly when we take into account the various cyanide delivery methods available to terrorists.

Cyanide differs from many other biological or chemical agents for which little or no defense is available in that its individual and public-health effects are largely remediable through appropriate preparedness and response. This article discusses cyanide as a potential chemical terrorism weapon, cyanide sources, the attributes that

**Fire smoke is an often-overlooked source of cyanide exposure in terrorist bombings. Following the first World Trade Center bombing in 1993, investigators found traces of cyanide in the vans where the explosion in the parking garage originated.**



AP/Wide World Photos

## CYANIDE & INDUSTRY

Cyanide is commonly found in industry settings, including:

- Fumigating, electroplating and mining operations; and
- Synthetic fiber, plastic, polymer, dye and pesticide production.

Cyanide is also a common by-product from the combustion of:

- Carbon- and nitrogen-containing synthetic substances; and
- Natural substances, such as wood, silk and cotton.<sup>1,13-14</sup>

make it an attractive terrorism tool and recent history of its use or planned use as a terrorist weapon. In addition, strategies will be discussed for enhancing preparedness for a cyanide disaster. Current management of acute cyanide poisoning is considered in the context of Centers for Disease Control and Prevention (CDC) recommendations for preparedness for chemical attacks.

U.S. governmental agencies, including the CDC and the Department of Homeland Security, consider cyanide among the most likely agents of chemical terrorism.<sup>6,7</sup> Other main categories of chemical weapons include nerve, blister and pulmonary agents. One of the most rapidly acting poisons, cyanide shares several characteristics of other chemical agents, such as sarin and chlorine, that render it a useful and effective tool for terrorists.<sup>8-12</sup>

## Agents of CHEMICAL TERRORISM

### Blood agents

- Hydrogen cyanide
- Cyanogen chloride

### Nerve agents

- Tabun
- Sarin
- Soman

### Blister agents

- Lewisite
- Nitrogen and sulfur mustards

### Pulmonary agents

- Phosgene
- Chlorine<sup>6,10</sup>

Among many in the military, cyanide continues to be known as a *blood agent*. This term, which is outdated and somewhat misleading, originated from the perception that cyanide is carried in the blood and that its primary site of action is the bloodstream. Although cyanide is carried in the blood, so too are other chemical weapons, including absorbed nerve agents. Therefore, the term does not differentiate cyanide from other categories of

chemical weapons. Also, cyanide's primary site of action is not necessarily the bloodstream.

## CYANIDE SOURCES

Cyanide exists in several forms, including the gases hydrogen cyanide and cyanogen chloride, soluble cyanide salts and insoluble cyanide salts.<sup>13,14</sup> Both gaseous and solid forms are used in industry. Cyanide is used in the recovery of gold and silver from mineral ores and of silver from photographic materials; in the production of plastics, pigments and dyes; and as a pesticide.<sup>13,14</sup> Moreover, hydrogen cyanide is released as a combustion product during the combustion of plastics and other polymers, silks, wood, cotton and many other nitrogen-containing substances.

Most literature on cyanide as a terrorist weapon focuses on the possibility of the intentional release of hydrogen cyanide gas into enclosed spaces, such as office buildings or stadiums.<sup>10-12</sup> Exposure to hydrogen cyanide via inhalation of fire smoke, the most common source of cyanide poisoning in the United States, could also occur during a terrorist attack. Cyanide salts introduced into pharmaceuticals, the food supply and the water supply also pose a terrorist threat.

Fire smoke is often overlooked as a source of cyanide exposure in a terrorist attack. Insofar as a terrorist attack involves explosions and/or fire, cyanide is likely to be involved. In fact, given the frequency with which terrorist attacks involve fire, fire smoke is arguably the most likely source of cyanide in a terrorist attack. Release of hydrogen cyanide as a combustion product in closed-space fires should be considered among the probable outcomes of any terrorist attack involving fire in an enclosed structure or vehicle.

## THE IDEAL WEAPON

What makes cyanide an attractive terrorist weapon? To be most useful to a terrorist, a chemical agent should be plentiful and readily available and should not require

**Cyanide is easily obtainable by virtue of its widespread use in industry & research laboratories.**

special knowledge to use. With these attributes, the terrorist does not need to spend significant time or resources in procuring or preparing to use the weapon and can procure the weapon while arousing minimal notice or suspicion. In addition, a chemical agent should be capable of accomplishing terrorists' primary goals of causing mass incapacitation and casualties as well as causing mass confusion, panic and social disruption. Finally, the ideal terror weapon would require large quantities of specific resources to combat its effects—a feature associated with the reduced likelihood of adequate defense preparations.<sup>6,10</sup>

Cyanide possesses all of these attributes. First, it is plentiful and readily available. Each year, the United States produces approximately three-quarters of a million tons of cyanide. Cyanide is easily obtainable by virtue of its widespread use in industry and research laboratories. It is transported by truck and rail, both of which are susceptible to theft, hijacking attempts and other terrorist acts that could culminate in use of cyanide as a weapon.

Second, cyanide does not require special knowledge to use. Unlike some biological or chemical weapons that require specific technological or scientific proficiency for effective use, cyanide incidents can be planned and implemented successfully by individuals without specific expertise or training.

Third, cyanide is capable of causing mass incapacitation and casualties.

Fourth, cyanide is capable of causing mass confusion, panic and social disruption.

Symptoms of cyanide poisoning are often dramatic and include stupor, seizures and coma. In a terrorist attack, these dramatic effects of cyanide poisoning may occur in the absence of an immediately localizable source of cyanide. The dramatic presentation of cyanide poisoning, its lethality and the difficulty in localizing its source during an emergent terrorist incident contribute to

the potential use of cyanide to create panic, confusion and social disruption during a cyanide-related terrorism event.

Finally, cyanide poisoning requires large quantities of specific resources to combat its effects. Moderate to high concentrations of cyanide can be expected to cause death in the majority of victims unless a cyanide antidote is quickly administered. Public health readiness for a large-scale cyanide disaster would entail stockpiling sufficient quantities of cyanide antidote. Correspondingly, effective use of cyanide as a terrorist weapon is predicated on the lack of availability of large quantities of antidote that can be rapidly disseminated and administered to affected individuals.

#### HISTORICAL USES

The recent history of cyanide's actual and intended use in intentional poisoning illustrates its utility as a weapon. Cyanide has been used as a murder weapon, as a poison in individual and mass suicides and attempted genocide, as a weapon of war and in recent attempted terrorist incidents (described at the opening of this article). The range of settings in which cyanide has been used and its various modes of delivery illustrate its versatility as a weapon. The terrorist plots involving cyanide also suggest that it's an important component of modern terrorists' armamentarium.<sup>2-5,9,15-17</sup>

Cyanide was used as a murder weapon several times in the past two decades in the United States. In the most notorious of these events,

Given the frequency with which terrorist attacks involve fire, **fire smoke is arguably the most likely source of cyanide** in a terrorist attack.

### Attributes of an IDEAL TERRORIST WEAPON

- Plentiful;
- Readily available;
- Does not require a lot of special knowledge to use;
- Capable of causing mass incapacitation and casualties;
- Capable of causing mass confusion, panic and social disruption;
- Requires large quantities of specific resources to combat its effects.

*Cyanide possesses every one of these characteristics.*<sup>6,10</sup>

## SOURCES OF CYANIDE EXPOSURE in a Terrorist Attack

- Hydrogen cyanide gas released into an enclosed space (e.g., a stadium or an office building);
- Fire smoke;
- Cyanide salts in the water supply;
- Cyanide salts in food; and/or
- Cyanide salts in pharmaceuticals.<sup>10-12</sup>

seven Chicagoans were killed in 1982 when they took cyanide-tainted Extra Strength Tylenol® capsules. Other incidents of cyanide's use as a murder weapon involved beverages (Vanilla Coke®) and food (Lipton Cup-A-Soup®).

Cyanide was also used to commit mass suicide in Jonestown, Guyana, where 913 followers of the Reverend Jim Jones died after drinking cyanide-spiked Kool-Aid®. As an agent of genocide, cyanide (as Zyklon B) was used to kill gas chamber victims in concentration camps during World War II.

Cyanide has also been used as a weapon of war, although its military usefulness is limited by its high volatility, which results in rapid evaporation and dispersion, and its relatively high lethal dose compared with that of such agents as sarin. Cyanide was used as a war weapon during WWI and, allegedly, WWII. The Iraqis also allegedly used cyanide against the Kurds in the 1980s.<sup>9</sup>

Cyanide poisons cells by preventing them from using oxygen, an effect that causes them to rely on anaerobic metabolism (i.e., oxygen-independent metabolism, as opposed to the usual oxygen-dependent metabolism), which causes accumulation of toxic byproducts. Accordingly, organs most susceptible to cyanide toxicity include the heart and brain, which normally rely on a substantial and uninterrupted oxygen supply.

Clinical manifestations of cyanide

poisoning primarily reflect the effects of oxygen deprivation on the heart and brain and are dependent on the route of exposure and severity of exposure. The onset of signs and symptoms typically occurs seconds to minutes after exposure, and death can occur within minutes after moderate to high levels of exposure.<sup>13,20</sup>

### MANAGEMENT OF ACUTE CYANIDE POISONING

Prehospital management of acute cyanide poisoning involves moving the victim from the source of exposure and providing supportive care, including administering 100% oxygen, providing cardiopulmonary support and stabilizing vital signs. When clinically indicated, anticonvulsants are given for seizures, epinephrine and antiarrhythmics to stabilize cardiovascular function, and sodium bicarbonate to correct metabolic acidosis.

Supportive care is necessary but usually insufficient to save the lives of cyanide poisoning victims; an antidote must also be given to counter the cellular effects of the toxin. Like supportive care, the antidote must be administered within minutes of exposure to moderate to high concentrations of cyanide in order to be effective.<sup>1,21-22</sup>

### PREPARING FOR A CYANIDE ATTACK

By disabling the blood's mechanism for carrying oxygen, cyanide can kill quickly. At moderate to high concentrations of exposure, victims are

## Recent History:

### *Cyanide as a Murder Weapon*

**1982:** Seven Chicagoans killed

**1986:** One person killed

**1991:** Two people killed

**1992:** One person killed

**2003:** One Maryland teenager killed

### *Cyanide as an Agent of Mass Suicide*

**1978:** Jonestown, Guyana, 913 followers of the Reverend Jim Jones committed suicide with cyanide-spiked Kool-Aid®.

### *Cyanide as an Agent of Genocide*

**World War II:** Cyanide (as Zyklon B) was used in the gas chambers in concentration camps.

### *Cyanide as a Weapon of War*

**World War I:** France used approximately 4,000 tons of cyanide.

**World War II:** Japan allegedly used cyanide against China.

**World War II:** United States maintained cyanide munitions.

**1980s Iraqi aggression:** Iraq allegedly used cyanide against the Kurds.<sup>9</sup>

incapacitated within seconds to minutes, and death can occur within minutes. Unlike illness or toxicity caused by many other biological and chemical weapons, cyanide poisoning can be effectively treated. Because it progresses so quickly and because no diagnostic test can confirm cyanide poisoning in the time required for initiating intervention, cyanide poisoning must be diagnosed presumptively by first responders on scene at a terrorist attack. Rapid recognition and empiric intervention by first responders are crucial to saving lives and reducing morbidity.<sup>18-19</sup>

In 2000, a CDC taskforce collaborated with other groups to publish strategic recommendations for preparedness for and response to biological and chemical terrorism. The taskforce concluded that preparedness for terrorist attacks constitutes a critical component of the U.S. public health surveillance and response system, and they identified five activities that local, state and federal public health organizations should undertake in order to enhance preparedness for chemical attacks. For the United States to be prepared for a chemical attack involving cyanide, public health organizations need to develop action plans for and allocate resources to each of these preparedness activities.<sup>6</sup>

All of the activities outlined by the CDC taskforce apply to enhancing readiness for chemical terrorism involving cyanide. However, preparedness initiatives involving cyanide antidotes warrant particular attention because, at present, the availability of cyanide antidotes is wholly inadequate to meet the nation's needs. The United States currently lacks an antidote with a risk-benefit ratio that favors empiric administration at the scene of a disaster.<sup>1</sup>

#### INADEQUACY OF CURRENT PREPAREDNESS

With appropriate preparedness, the public health threat posed by a cyanide attack can be contained to an extent. Containment is possible

## PLANNING PARAMETERS to Consider

**There are several parameters emergency responders should consider when preparing for a cyanide attack:**

- Cyanide kills quickly by disabling the blood's mechanism for carrying oxygen;
- It can incapacitate victims within seconds to minutes;
- It causes death within minutes following moderate to high levels of exposure;
- Unlike illness or toxicity caused by many other biological or chemical agents, cyanide poisoning can be effectively treated; and
- Rapid recognition and empiric treatment by emergency responders are necessary to reduce a chemical attack's impact on individuals and the public health system.<sup>18,19</sup>



**Cyanide was used to commit mass suicide in Jonestown, Guyana, where 913 followers of the Reverend Jim Jones died after drinking cyanide-spiked Kool-Aid®.**

AP/Wide World Photos

## CDC-Recommended PREPAREDNESS MEASURES

- Enhance epidemiologic capacity for detecting and responding to chemical attacks;
- Enhance awareness of chemical terrorism among EMS personnel, police officers, firefighters, physicians and nurses;
- Stockpile chemical antidotes;
- Develop and provide bioassays for detection and diagnosis of chemical injuries; and
- Prepare educational materials to inform the public during and after a chemical attack.<sup>6</sup>

in part because signs and symptoms of poisoning manifest instantaneously and dramatically after exposure to moderate to high levels of cyanide, and they elicit the immediate attention of medical personnel and emergency responders trained to recognize chemical poisoning. The absence of significant delay between cyanide exposure and the onset of obvious, attention-commanding signs and symptoms enhances the probability that cyanide poisoning will be recognized—a prerequisite for initiating effective intervention. Unlike cyanide, many other poisons and toxins are associated with a delayed onset of illness and, correspondingly, a delay in diagnosis and intervention. The fact that an effective antidote exists differentiates cyanide from many other chemical and biological weapons that have no known effective countermeasure.<sup>1</sup>

### THE CYANIDE ANTIDOTE KIT

Of several cyanide antidotes available around the world, only one, the cyanide antidote kit, is presently marketed in the United States. The cyanide antidote kit includes three components that are to be administered sequentially: amyl nitrite, sodium nitrite and sodium thiosulfate. The amyl nitrite (available as pearls) is administered via a mechanical ventilation device or by gauze sponge for inhalation to stabilize the victim during the time before an IV line can be

established. The sodium nitrite and thiosulfate are administered intravenously. Sodium nitrite and amyl nitrite neutralize cyanide by binding with it to form methemoglobin. Problematically, nitrite-induced methemoglobinemia reduces the blood's ability to carry oxygen and thus constitutes a dangerous, potentially fatal toxic state. In addition to causing methemoglobinemia, the cyanide antidote kit may cause severe hypotension leading to shock. These liabilities contribute to a sub-optimal risk-benefit ratio of the cyanide antidote kit in empiric prehospital treatment of cyanide poisoning.<sup>1</sup>

Methemoglobinemia is especially dangerous for smoke-inhalation victims, who often have concurrent carboxyhemoglobinemia due to carbon monoxide exposure. Both carboxyhemoglobinemia and methemoglobinemia reduce the blood's oxygen-carrying capacity, and the additive effects of the two conditions in smoke-inhalation victims can be lethal. Some authorities, therefore, do not recommend the cyanide antidote kit for smoke-inhalation victims, who often have concurrent cyanide and carbon-monoxide poisoning, because of the possibility of causing life-threatening complications.<sup>23</sup>

### IMPROVING PREPAREDNESS: HYDROXOCOBALAMIN

The cyanide antidote kit's potential toxicity and multiple-component

## Cyanide Toxicity

Small amounts of cyanide are metabolized in the liver and excreted in the urine. Cyanide binds to iron (Fe<sup>+++</sup>) in the mitochondria, preventing cells from using oxygen. Without oxygen, cells die. The effects are of progressive tissue hypoxia, and because the heart and brain are the organs most sensitive to hypoxia, they are the first organs to be affected.

## Acute Cyanide Poisoning Symptoms & Signs

### Symptoms

- Nearly immediate loss of consciousness;
- Stupor;
- Giddiness;
- Palpitations;
- Dizziness;
- Nausea/vomiting;
- Hyperventilation;
- Drowsiness; and
- Eye irritation.

### Signs

- Respiratory arrest;
- Cardiac arrest;
- Coma;
- Seizures;
- Pink or red skin color;
- Elevated venous blood oxygen concentration; and
- Metabolic acidosis.<sup>13,20</sup>

administration renders it ill-suited for use in terrorist incident response and other situations requiring rapid prehospital intervention. The Food and Drug Administration is currently evaluating the cyanide antidote hydroxocobalamin for possible introduction in the United States. A precursor of vitamin B12, hydroxocobalamin is currently available in other countries, including France, where it is the cyanide antidote used by the Paris Fire Brigade.

Hydroxocobalamin, which neutralizes cyanide by binding it to form vitamin B12, appears to be at least as effective as the cyanide antidote kit in the treatment of cyanide poisoning but does not appear to be associated with the safety liabilities of the cyanide antidote kit. Hydroxocobalamin does not appear to induce methemoglobinemia or cause hemodynamic instability. Its most common side effects are thought to include discoloration of urine and mucous membranes and abnormalities in specific laboratory tests. These effects are transient (lasting one to two days) and do not appear to reflect clinically meaningful changes.

From the literature, the safety risks of administering hydroxocobalamin appear to be negligible, and the antidote in France is administered at disaster scenes so that intervention is not delayed until hospital care can be provided. Further, because of its favorable risk-benefit ratio, as reported in the literature, hydroxocobalamin need not be reserved for cases of confirmed cyanide poisoning but can be administered in cases of suspected poisoning. Both of these attributes could lead to more rapid initiation of treatment than is possible with the currently available cyanide antidote kit and, thereby, could improve outcomes in a cyanide disaster.<sup>1,13-14,23-25</sup>

In other countries, hydroxocobalamin is recognized as an efficacious, safe and easily administered cyanide antidote with an extremely low adverse effect profile suitable for prehospital use in suspected cyanide intoxication. According to

expert opinion, in order to effectively prepare for a cyanide disaster, the United States should investigate, adopt, manufacture and stockpile hydroxocobalamin to prevent needless morbidity and mortality.<sup>1</sup>

In a June 2001 paper assessing public health readiness for cyanide disasters, authors Samuel Sauer, MD, of the U.S. Army Medical Corp and The School of Public Health at the University of Hawaii and Mark Keim, MD, of the CDC and the Department of Emergency Medicine at Emory University characterized the U.S. state of preparedness for a cyanide disaster as abysmal. In the context of terrorists' continued interest in the use of cyanide as a weapon, the need to implement

**The United States currently lacks an antidote with a risk-benefit ratio that favors empiric administration at the scene of a disaster.**

**Firefighters emerge after cleaning toxic gas-contaminated cars at Tokyo's Kodemmacho subway station in March 1995. Although it received little press attention, the precursors of cyanide were found in the subway bathrooms.**



AP/Wide World Photos

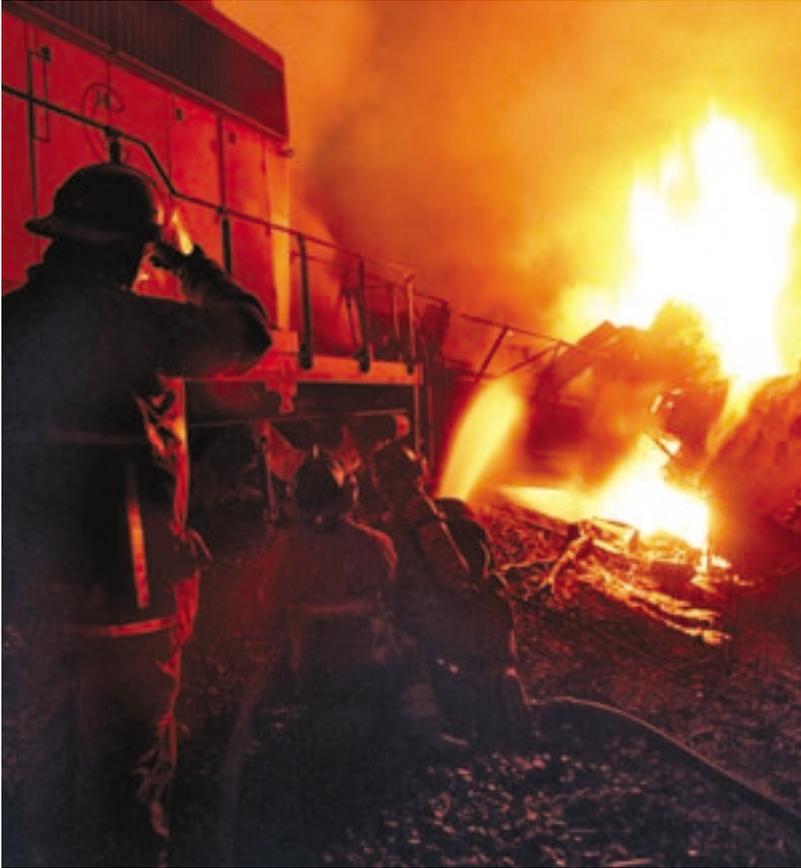


Photo: Glen E. Ellman

**Any terrorist attack that involves explosions or fire in a structure or other enclosed space, such as a train, will likely involve the release of hydrogen cyanide.**

The safety risks of administering hydroxocobalamin are believed to be negligible, & the antidote is administered at disaster scenes so that **intervention is not delayed** until hospital care can be provided.

the imperatives set forth by Sauer and Keim seems even more pressing today than when their paper originally appeared.<sup>1</sup>

What would constitute adequate preparedness for a chemical attack? First, antidotes that are effective and safe for empiric prehospital use should be made available in the United States. Progress has been made on that front since the time of Sauer and Keim's paper in that regulators are evaluating hydroxocobalamin for possible introduction in the United States.

To realize the potential benefits of hydroxocobalamin, parallel progress needs to occur in other aspects of readiness, including but not limited to developing plans for ensuring local and regional availability of antidote and educating emergency responders and health-care professionals in the recognition and management of cyanide poisoning. Many U.S. hospitals cur-

rently stock one or fewer currently available cyanide antidote kits, and many emergency responders and other health-care providers are poorly informed in the use of the antidote and the recognition of cyanide poisoning.

In conclusion, the recent history of use and planned use of cyanide suggests that a terrorist attack involving cyanide is quite possible in the United States. Cyanide poisoning can be treated effectively if it is treated quickly. The ability to manage a cyanide attack's effect on individuals and public health depends on the speed of recognition and fast intervention. The potential introduction in the United States of hydroxocobalamin, an antidote with a promising risk-benefit ratio for empiric treatment, may help to enhance preparedness for a cyanide attack. However, progress is also necessary in other areas, including educating emergency responders and health-care professionals in the recognition and management of cyanide poisoning, and raising public awareness of the potential for a chemical weapons attack and how to respond. 🔥

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