

# Focus on Smoke Inhalation—The Most Common Cause of Acute Cyanide Poisoning

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**Abbreviations:** CAK = Cyanide Antidote Kit

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**Abstract**

The contribution of smoke inhalation to cyanide-attributed morbidity and mortality arguably surpasses all other sources of acute cyanide poisoning. Research establishes that cyanide exposure is: (1) to be expected in those exposed to smoke in closed-space fires; (2) cyanide poisoning is an important cause of incapacitation and death in smoke-inhalation victims; and (3) that cyanide can act independently of, and perhaps synergistically with, carbon monoxide to cause morbidity and mortality. Effective prehospital management of smoke inhalation-associated cyanide poisoning is inhibited by: (1) a lack of awareness of fire smoke as an important cause of cyanide toxicity; (2) the absence of a rapidly returnable diagnostic test to facilitate its recognition; and (3) in the United States, the current unavailability of a cyanide antidote that can be used empirically with confidence outside of hospitals. Addressing the challenges of the prehospital management of smoke inhalation-associated cyanide poisoning entails: (1) enhancing the awareness of the problem among prehospital responders; (2) improving the ability to recognize cyanide poisoning on the basis of signs and symptoms; and (3) expanding the treatment options that are useful in the prehospital setting.

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**Introduction**

Among prehospital emergency care providers, the term “cyanide poisoning” may evoke associations of homicide or suicide victims poisoned with cyanide salts or of workers exposed to cyanide gas in industrial accidents. Rarely does the term first suggest an association with individuals exposed to smoke from closed-space fires—although the contribution of smoke inhalation to cyanide-attributed morbidity and mortality arguably outstrips all other sources of acute cyanide poisoning. Studies suggest that hydrogen cyanide gas, a nearly ubiquitous toxicant in closed-space fires, is an important factor in many deaths caused by smoke inhalation.<sup>1,2</sup> Firefighters and other first responders, as well as children and the elderly, are at especially high risk for serious injury or death from fires.

Effective prehospital management of smoke inhalation-associated cyanide poisoning is hampered by a lack of awareness of smoke caused by fires as an important cause of cyanide toxicity. Additionally, prehospital management of acute cyanide poisoning is inhibited by the absence of a rapidly returnable diagnostic test to facilitate its recognition and, in the United States, the unavailability of a cyanide antidote that can be used empirically with confidence outside of the hospital. Overcoming these deficiencies is critical to reducing morbidity and mortality from smoke inhalation. Preventing death from cyanide poisoning primarily depends on the time between exposure and treatment. Therefore, the ability of the emergency responders to recognize and intervene rapidly in cyanide poisoning can mean the difference between life and death for smoke-inhalation victims. Addressing the challenges of prehospital management of smoke inhalation-associated cyanide poisoning

<b>Irritants</b>
Hydrochloric acid
Sulfur dioxide
Oxides of nitrogen
Ammonia
<b>Asphyxiants/Toxicants</b>
Carbon dioxide
Hydrogen cyanide
Carbon monoxide
Hydrogen sulfide

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Table 1—Examples of common constituents of fire smoke<sup>7,8</sup>

entails: (1) enhancing the awareness of the problem among prehospital responders; (2) improving their ability to recognize cyanide poisoning on the basis of signs and symptoms; and (3) expanding the intervention options useful in the prehospital setting.

#### Smoke Inhalation-Associated Cyanide Poisoning: The Scope of the Problem

##### *Cyanide as an Often Overlooked Cause of Smoke Inhalation-Associated Injury and Death*

A case report published in the 19 February 2004 issue of the *New England Journal of Medicine*, describes a woman severely burned in the notorious Rhode Island nightclub fire that killed approximately 100 people and injured hundreds more in February 2003.<sup>3</sup> The authors discussed several aspects of managing burn and smoke inhalation-related injury in this patient, but did not consider cyanide toxicity in their report, despite the presence of several signs and symptoms suggesting its presence. This omission, pointed out by readers of the case report in later correspondence published in the *New England Journal of Medicine*, is characteristic of many medical publications on management of smoke inhalation.<sup>4</sup> Why is the potential role of cyanide in smoke inhalation-associated injury and death so often minimized or ignored?

Perhaps the most important reason for failing to consider a potential role of cyanide is the widely held perception that carbon monoxide is the most prevalent and dangerous of combustion products.<sup>5-7</sup> The focus on carbon monoxide may cause healthcare professionals to overlook other potentially important toxicants. For example, the authors of the *New England Journal of Medicine* case report assessed and treated the fire victim for carbon monoxide intoxication, but did not report evaluating her for toxicity arising potentially from other combustion products.<sup>3</sup> While carbon monoxide intoxication frequently results from exposure to smoke caused by fires, its presence does not imply a lack of toxic contribution from other substances.

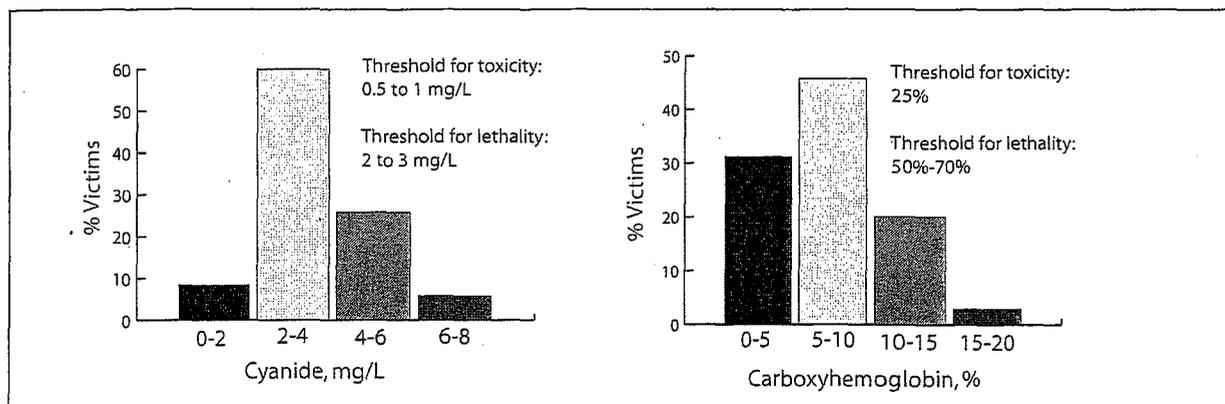
Carbon monoxide is one of several combustion products that can cause human toxicity (Table 1).<sup>7,8</sup> The presence and amounts of specific constituents of smoke vary within and between fires depending on: (1) the nature of the fire substrate; (2) the rate of burning; (3) the temperature of the fire; and (4) the ambient oxygen level.<sup>8</sup>

Substrates for hydrogen cyanide, which is generated by the combustion of nitrogen- and carbon-containing substances, are omnipresent in human dwellings. Burning of paper, cotton, wool, silk, and plastics or other polymers can generate hydrogen cyanide.<sup>1,9,10</sup> With the increasingly widespread use of plastics and other polymers in construction, furnishings, and household implements, the probability of the generation of hydrogen cyanide in a fire also increases.

While the pervasiveness of cyanide substrates alone suggests that cyanide generation is a likely outcome of any modern fire, the degree to which cyanide contributes to smoke inhalation-associated morbidity and mortality has proven difficult to quantify. This difficulty may be attributed mainly to the frequent inability to obtain accurate measures of cyanide concentrations in the blood of fire victims. With a half-life of one hour, cyanide is short lived in the bloodstream.<sup>11</sup> Because blood samples rarely are obtained within the short time required for accurate measurement of peak concentrations of cyanide, measured concentrations often are erroneously low. Furthermore, even when blood samples are obtained promptly after exposure, the influence of various incident- and victim-specific factors (e.g., carboxyhemoglobin saturation of sampled blood, methemoglobin content of sampled blood, time between blood sampling and assay, storage temperature of blood samples) on the measured concentration of cyanide can complicate the interpretation of assay results or introduce sources of error.<sup>2,12</sup> Assessment of carbon monoxide in the blood generally is not associated with these difficulties. The measurement of blood carboxyhemoglobin concentrations, a marker of carbon monoxide poisoning, has become standard practice in caring for smoke-inhalation victims.<sup>13</sup> The common finding in smoke-inhalation victims of carboxyhemoglobin concentrations reflecting carbon monoxide intoxication in the context of the frequent inability to confirm the presence of other toxicants such as cyanide has undoubtedly reinforced the perception of carbon monoxide as the most significant contributor to smoke inhalation-associated morbidity and mortality.

##### *Research Assessing the Contribution of Cyanide to Death from Smoke Inhalation*

A growing number of studies in which blood concentrations of cyanide and carboxyhemoglobin were assessed systematically contradicts this perception by showing that: (1) cyanide exposure from smoke caused by fires appears to occur as often as exposure to carbon monoxide; (2) cyanide is found at toxic-to-lethal levels in approximately 33% to 90% (depending on the fire) of victims dying in closed-space fires; and (3) cyanide sometimes appears to be the primary cause of death from smoke inhalation.<sup>2,11,14-25</sup> In a recent study, cyanide and carboxyhemoglobin concentrations were measured from the blood of 35 Argentinian inmates who died



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Figure 1—Percentage of smoke-inhalation victims with specific levels of cyanide and carboxyhemoglobin in blood<sup>23</sup>

Database	% Victims at $\geq 1$ mg/L Cyanide	% Victims at $\geq 3$ mg/L Cyanide	Median Cyanide, mg/L	% Victims at $>50\%$ HbCO	Median HbCO, %
<i>Dupont Plaza Hotel fire deaths, 1986:</i> -97 deaths -Blood samples from 53 burned victims were analyzed several months after the fire, and some samples had deteriorated.	48%	5%	1	5%	33%
<i>Happy Land Social Club fire deaths, 1990:</i> -87 deaths -Blood samples were described as being promptly collected (specific timings not reported), and the Office of the City of New York Medical Examiner completed autopsies within 2 days of the fire.	87%	25%	2.1	98%	78%
<i>Manchester aircraft fire deaths, 1985:</i> -54 deaths Blood sampling timing and methods were not described. -Cyanide was found in every victim, but HbCO levels were relatively low (median 39%).	87%	33%	2.3	21%	39%

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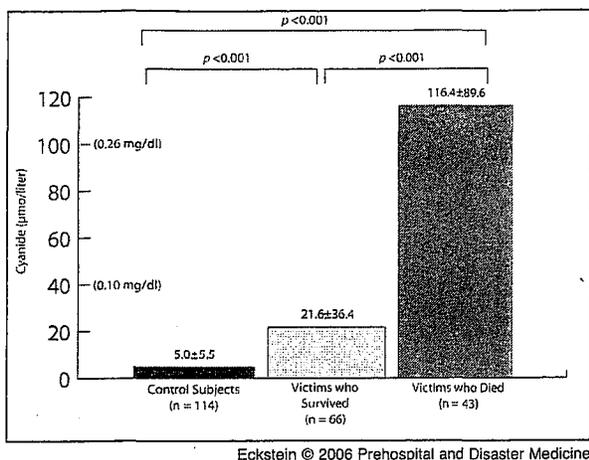
Table 2—Cyanide and carboxyhemoglobin in the blood of smoke-inhalation victims in selected\* major fires<sup>2</sup>

\*Incidents reported in the medical literature, resulting in  $>50$  deaths, involving structural or other closed-space fires, and having assessments of both cyanide and carboxyhemoglobin concentrations in victims' blood are shown. In the Dupont Plaza Hotel fire, many of the victims were burned severely, and the relative contributions of smoke inhalation and burns to their deaths are difficult to determine.

within 3–5 minutes after the onset of a prison fire produced by the pyrolysis of polyurethane mattresses.<sup>23</sup> The results show that none of the 35 victims had toxic levels of carboxyhemoglobin, but  $>90\%$  had toxic-to-lethal levels of blood cyanide (Figure 1).<sup>23</sup> The toxic and lethal values quoted in the published literature for blood cyanide and carboxyhemoglobin vary.<sup>2,15</sup> Generally, toxic and lethal thresholds for blood cyanide are described as 0.5–1 mg/L and 2–3 mg/L, respectively. The corresponding thresholds for carboxyhemoglobin are 25% and 50%–70%. Blood concentrations of cyanide averaged 3.5 mg/L (range 2.0–7.2

mg/L), and blood concentrations of carboxyhemoglobin averaged 9% (range 4%–18%). The authors concluded that hydrogen cyanide was the main cause of death in these 35 victims.

This finding is not surprising, given that mattresses made of the cyanide substrate polyurethane were the source of this fire. Cyanide also has been implicated to a greater extent than carbon monoxide in deaths occurring in other closed-space fires characterized by conditions facilitating generation of both hydrogen cyanide and carbon monoxide. For example, the majority of victims of the 1985 Manchester aircraft fire, in which smoke inhalation rather



**Figure 2**—Mean±SD blood cyanide concentrations in the control subjects, the fire victims who died, and the victims who survived in the Paris Fire Study. Blood cyanide concentrations of 5.0 µmol/L, 21.6 µmol/L, and 116.4 µmol/L correspond to values of 0.01 mg/L, 0.58 mg/L, and 3.14 mg/L, respectively From Baud *et al*, 1991<sup>11</sup> [Permission pending.]

than burns, accounted for the fatalities, had toxic-to-lethal blood levels of cyanide in the presence of nontoxic blood levels of carboxyhemoglobin.<sup>2,25</sup> In other fires, such as the Happy Land Social Club fire, large proportions of victims had toxic to lethal blood levels of both cyanide and carboxyhemoglobin (Table 2).

The role of cyanide in smoke inhalation associated mortality is elucidated further by the 1988–1989 Paris Fire Study,<sup>11</sup> perhaps the most rigorous assessment of blood cyanide in fire victims to date. The Paris Fire Study was designed prospectively to assess blood cyanide concentrations from samples obtained promptly after cyanide exposure, in a consistent manner from patient to patient, and before victims received antidotal treatment that could affect laboratory results.<sup>3</sup> Unlike many other studies of the consequences of smoke inhalation, this study included contemporaneous control groups. Data from 109 fire victims (66 of whom survived and 43 of whom died) were compared with those from 114 control individuals (40 hospital inpatients with drug intoxication, 29 patients with carbon monoxide poisoning caused by malfunction of a heating appliance, and 45 patients with major trauma).

The results show that mean blood cyanide concentrations were inversely related to probability of survival (Figure 2),<sup>11</sup> a finding consistent with a possible causal role of cyanide in the deaths. Furthermore, in corroboration of data from several other studies, blood levels of cyanide in some victims were in the toxic-to-lethal range, while blood levels of carbon monoxide were in the nontoxic range. This suggests that cyanide poisoning may predominate over carbon monoxide poisoning as a cause of death in some fire victims. Finally, several patients died despite having nontoxic levels of both cyanide and carbon monoxide. Most of these patients had life-threatening burns that may have been the cause of death. Alternatively or additionally, additive toxicity of cyanide and carbon monoxide, which has

been demonstrated in several experimental models, may have contributed to these deaths.<sup>26–28</sup>

Considered in aggregate, data from the Paris Fire Study and investigations of other incidents such as the Manchester aircraft fire and the prison fire in Argentina suggest that cyanide toxicity from smoke inhalation is at least as important as carbon monoxide toxicity as a cause of death by smoke inhalation. The frequent presence of toxic concentrations of cyanide in the blood of smoke-inhalation victims suggests that emergency responders to the scene of a closed-space fire should expect to encounter cyanide toxicity in fire victims.

#### *Cyanide-Induced Incapacitation as an Indirect Contributor to Smoke Inhalation-Associated Injury and Death*

Even when it is not present in immediately lethal concentrations, cyanide indirectly can lead to injury or death by causing confusion and incapacitation that delay or prevent escape from a fire.<sup>29,30</sup> In all likelihood, the resultant prolonged exposure to toxicants, including many in addition to hydrogen cyanide, can cause injury or death. In animal research, exposure to sublethal levels of cyanide caused rapid loss of consciousness even in the absence of toxic levels of blood cyanide measured hours after exposure.<sup>29</sup> The degree to which sublethal concentrations of cyanide may contribute to smoke inhalation-associated injury and death in humans has not been quantified because of challenges in measuring blood cyanide and the difficulty in defining possible independent contributions of multiple concurrent asphyxiants to incapacitation.

#### *Recognition of Cyanide Poisoning Arising from Smoke Inhalation*

Cyanide primarily causes toxicity by preventing cells from using oxygen. Signs and symptoms of cyanide poisoning primarily are nonspecific (Table 3)<sup>1,9,31</sup> and reflect largely the effects of oxygen deprivation on the heart and brain, which require a high, continuous supply of oxygen.

The time between cyanide exposure and the onset of signs and symptoms depends upon: (1) the form of cyanide; (2) the route by which cyanide enters the body; and (3) the concentration of exposure.<sup>1</sup> Among the forms of cyanide, gas is most rapidly toxic. Signs and symptoms appear seconds to minutes after the exposure of moderate to high concentrations, and death can occur within minutes.

Rapid recognition of cyanide poisoning is essential for initiating intervention in time to prevent death. Because laboratory tests cannot return results within the time required for initiating intervention, the prehospital responder must diagnose cyanide poisoning on the basis of signs and symptoms. Given the need for a rapid, presumptive diagnosis and the high likelihood of cyanide exposure in a closed-space fire, the prehospital emergency responder should consider cyanide poisoning to be present by default in individuals exposed to smoke in closed-space fires and having soot in the mouth and/or nose (Table 3). Suspicion of cyanide poisoning is heightened by the findings of altered mental status (ranging from confusion or drunken behavior to coma) and hypotension.<sup>1</sup> In all probability, cyanide-poisoned victims of a closed-space fire also may

Nonspecific Signs and Symptoms	
Early cyanide poisoning	-Giddiness -Headache -Vertigo -Confusion -Drunken behavior -Shortness of breath
Advanced cyanide poisoning	-Nausea/vomiting -Hypotension -Generalized seizures -Coma -Cardiac arrhythmias -Asystole -Apnea -Noncardiac pulmonary edema
Other, More Specific Findings (Not Always Present)	
- Normal-to-pink skin color (because of high arterial and venous levels of oxygen in the presence of the cellular inability to utilize oxygen)	
-Bright red retinal veins and arteries (because of inability of tissues to extract oxygen from the blood)	
-Breath smelling of bitter almonds (a smell that cannot be detected by a significant number of people)	
Findings in Fire Victims	
-Exposure to fire smoke in a closed-space fire	
-Soot in the mouth and/or nose	
-Altered mental status	
-Hypotension	

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Table 3—Acute cyanide poisoning: Manifestations assessable in the prehospital setting<sup>1,9,31</sup>

suffer from concurrent poisoning with other asphyxiants, particularly carbon monoxide.

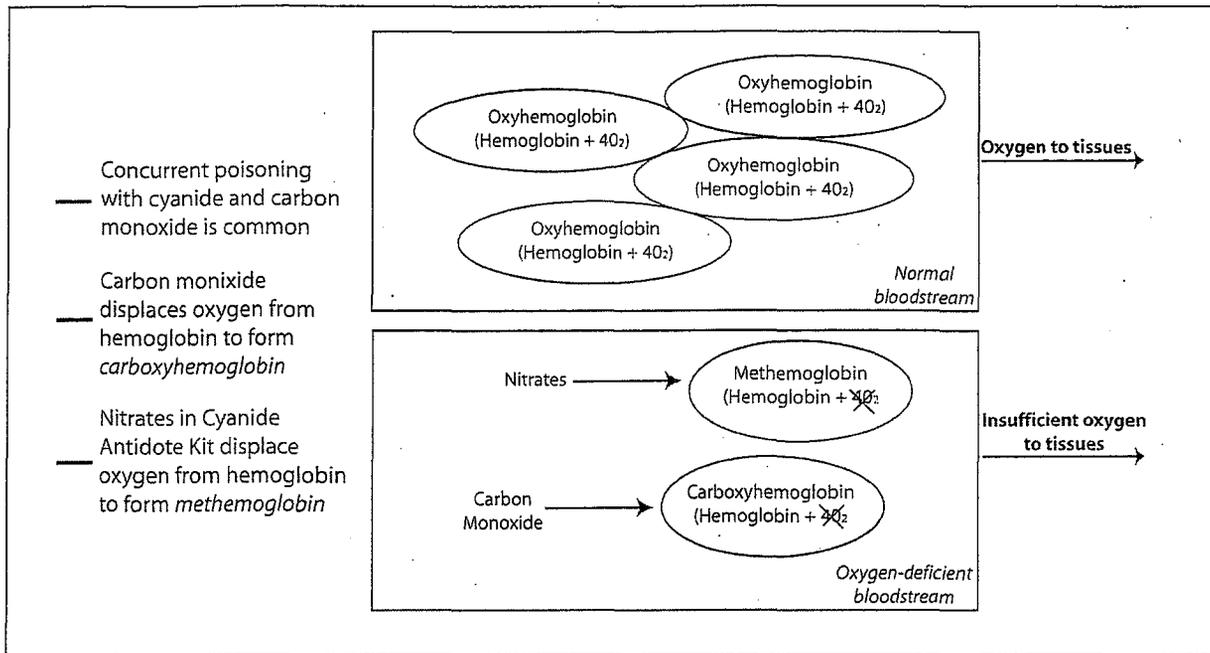
#### Prehospital Management of Smoke Inhalation-Associated Cyanide Poisoning

The prehospital treatment of acute cyanide poisoning entails: (1) removing the patient from the source of cyanide; (2) implementing supportive measures including administering 100% oxygen and providing cardiopulmonary resuscitation and/or support; (3) administering sodium bicarbonate (to correct metabolic acidosis), anti-convulsants, epinephrine, and antiarrhythmics as needed; and (4) providing antidotal treatment.<sup>1,9,31</sup> Additionally, emergency responders must take measures to protect themselves from secondary contamination.

The provision of antidotal treatment is associated with unique concerns in victims exposed to cyanide from smoke inhalation as opposed to other cyanide sources. The typical practice of administering antidotal treatment on the basis of a presumptive diagnosis of cyanide poisoning in the prehospital setting is discouraged in smoke-inhalation victims

because the only antidote available in the United States—a kit containing amyl nitrite, sodium nitrite, and sodium thiosulfate, known as the Cyanide Antidote Package, the Cyanide Antidote Kit (CAK), the Taylor kit, the Lilly kit, and the Pasadena kit—can be dangerous for smoke-inhalation victims with concomitant carbon monoxide poisoning. Carbon monoxide reduces blood oxygenation by displacing oxygen from hemoglobin.<sup>14,32</sup> Like carbon monoxide, the nitrite components of the CAK displace oxygen from hemoglobin. Carbon monoxide displaces oxygen from hemoglobin to form carboxyhemoglobin, whereas nitrites in the Cyanide Antidote Kit displace oxygen from hemoglobin to form methemoglobin (Figure 3). The additive oxygen-depriving effects of nitrites and carbon monoxide can be lethal.<sup>33,34</sup>

The increased lethality of amyl nitrite and sodium nitrite in the presence of carboxyhemoglobinemia caused by carbon monoxide is demonstrated in a study in which mice were exposed to carbon monoxide immediately after they were poisoned by an injection of potassium cyanide and then were either given antidotal treatment with amyl



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Figure 3—Additive effects of carbon monoxide and antidotal nitrates on the ability of blood to carry oxygen in smoke-inhalation victims

or sodium nitrite or were not given any antidotal treatment.<sup>34</sup> The results show that the probability of death was higher in the animals given antidotal treatment with nitrites compared with those given no antidotal treatment after concurrent poisoning with cyanide and carbon monoxide. Compared with control animals given no antidotal treatment, those given antidotal treatment were 43% more likely to die when exposed for one minute to amyl nitrite, 59% more likely to die when exposed for two minutes to amyl nitrite, and 25% more likely to die when exposed to sodium nitrite.

In addition to causing methemoglobinemia, the sodium nitrite in the CAK can cause severe hypotension, which can be dangerous, especially in fire victims with compromised hemodynamic status.<sup>33,35</sup> Administration of just sodium thiosulfate in order to avoid these risks is not an ideal alternative because of its slow onset of action.<sup>35,36</sup>

Partly in response to the need for a safer, effective antidote for victims of smoke inhalation, the vitamin B12 precursor hydroxocobalamin is being developed for potential introduction in the United States.<sup>35</sup> Hydroxocobalamin detoxifies cyanide by binding with it to form vitamin B12, which is excreted in urine, without compromising the oxygen-carrying capacity of the blood or causing hypotension.<sup>9,35,37</sup> Hydroxocobalamin has been used for decades in some European countries to treat acute cyanide poisoning, and in 1996, received regulatory approval in France for this use. The apparently low risk of causing harm by adminis-

tering hydroxocobalamin potentially could render prehospital empiric treatment of smoke inhalation-associated cyanide poisoning a reality in the United States. The ability to treat cyanide poisoning empirically in the prehospital setting could lead to more rapid initiation of treatment and thereby improve the chances of saving lives.

### Conclusions

Cyanide exposure is an expected outcome of smoke inhalation in closed-space fires. Research establishes that cyanide poisoning can be an important cause of incapacitation and death in victims of smoke inhalation, and suggests that cyanide can act both independently of, and perhaps synergistically with carbon monoxide to cause morbidity and mortality. Because cyanide gas in smoke caused by fires can turn lethal rapidly, early recognition and management of smoke inhalation-associated cyanide poisoning in the prehospital setting are critical for saving lives. Although the United States currently lacks a cyanide antidote well suited for use in prehospital first-responder care of smoke-inhalation victims, one that may allow prehospital intervention in this patient population is being studied for potential introduction in this country.

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