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Review

Carbon monoxide poisoning — a public health perspective

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Abstract

Carbon monoxide (CO) may be the cause of more than one-half of the fatal poisonings reported in many countries; fatal cases also are grossly under-reported or misdiagnosed by medical professionals. Therefore, the precise number of individuals who have suffered from CO intoxication is not known. The health effects associated with exposure to CO range from the more subtle cardiovascular and neurobehavioral effects at low concentrations to unconsciousness and death after acute or chronic exposure to higher concentrations of CO. The morbidity and mortality resulting from the latter exposures are described briefly to complete the picture of CO exposure in present-day society. The symptoms, signs, and prognosis of acute CO poisoning correlate poorly with the level of carboxyhemoglobin (COHb) measured at the time of hospital admission; however, because CO poisoning is a diagnosis frequently overlooked, the importance of measuring COHb in suspicious settings cannot be overstated. The early symptoms (headache, dizziness, weakness, nausea, confusion, disorientation, and visual disturbances) also have to be emphasized, especially if they recur with a regular periodicity or in the same environment. Complications occur frequently in CO poisoning. Immediate death is most likely cardiac in origin because myocardial tissues are most sensitive to the hypoxic effects of CO. Severe poisoning results in marked hypotension, lethal arrhythmias, and electrocardiographic changes. Pulmonary edema may occur. Neurological manifestation of acute CO poisoning includes disorientation, confusion, and coma. Perhaps the most insidious effect of CO poisoning is the development of delayed neuropsychiatric impairment within 2–28 days after poisoning and the slow resolution of neurobehavioral consequences. Carbon monoxide poisoning during pregnancy results in high risk for the mother by increasing the short-term complication rate and for the fetus by causing fetal death, developmental disorders, and chronic cerebral lesions. In conclusion, CO

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poisoning occurs frequently; has severe consequences, including immediate death; involves complications and late sequelae; and often is overlooked. Efforts in prevention and in public and medical education should be encouraged.

Keywords: Carbon monoxide; Carboxyhemoglobin; Air pollution; Poisoning; Indoor; Health effects; Hyperbaric oxygen

1. Introduction

Carbon monoxide (CO) is one of many ubiquitous contaminants of our environment that requires prevention and control measures to insure adequate protection of public health. A primary focus of air pollution control by industrialized societies has been the regulation of CO in ambient air and occupational settings. The term ambient air is interpreted to mean outdoor air available to the general public. The recommended multi-hour ambient air-quality standard of 9 ppm (10 mg/m^3) CO for 8 h (Federal Register, 1994; World Health Organization, 1999a,b) is intended to protect susceptible population groups from adverse effects resulting from CO exposures in the outdoor environment. The recommended limits for occupational exposure, which range from 25 to 50 ppm (30–60 mg/m^3) CO worldwide (Cook, 1987; Commission of the European Communities, 1993), are intended to protect healthy workers from the adverse effects of CO during a typical 8-h working day. Average monitored exposures from the controlled outdoor and occupational environments, however, represent only part of the total human exposure to CO. Potential exposures that exceed the existing standards may be of greater concern to public health because they increase the total body burden for CO (US Environmental Protection Agency, 1999). For example, the ambient standard outdoors is exceeded as a result of CO emissions from transportation sources, primarily motor vehicles, and from stationary sources producing industrial combustion gases at times or locations that may not be measured. Transient concentrations of CO also can be high in tunnels and parking garages because of the accumulation of engine exhaust fumes; but these locations are not considered to be part of the regulated ambient environment. In addition, the results of time activity/pattern analyses in the United States and other developed countries have indicated that a majority of the public spends most of its time indoors, where exposures to CO emitted from industrial processes, tobacco smoke (see Appendix A), and other combustion sources (such as gas, coal, and wood stoves and fireplaces; and kerosene or other fossil-fuel-burning heaters and appliances) may present problems. Although voluntary standard performance requirements exist for many individual combustion appliances to minimize CO emissions, maintaining healthful CO levels inside homes can present difficulties, especially if multiple combustion sources are located in the same enclosed environment.

Carbon monoxide is impossible to detect by an exposed person because it is colorless, tasteless, odorless, and nonirritating. When inhaled, CO is readily absorbed from the lungs into the bloodstream, where it forms a tight but slowly reversible complex with hemoglobin (Hb) known as carboxyhemoglobin (COHb). The presence of COHb in the blood decreases the oxygen carrying capacity, reducing the availability of oxygen to body tissues and resulting in tissue hypoxia. A reduction in oxygen delivery because of the elevated COHb level, exacerbated by impaired perfusion resulting from hypoxic cardiac dysfunction, potentially will impair cellular oxidative metabolism. This occurs because hypoxia and reductions in blood flow may allow CO to bind to cytochrome *c* oxidase, which inhibits aerobic adenosine triphosphate synthesis (Brown and Piantadosi, 1990). The disturbance in mitochondrial electron transport also causes generation of oxidative stress, measured as an increase in the hydroxyl-like radical fraction, and causes generation of hydroxyl-like radicals (Chance et al., 1970; Brown and Piantadosi, 1992; Piantadosi et al., 1997). Energy production and mitochondrial function are restored slowly after COHb levels decrease because of continued inhibition of respiration (Brown and Piantadosi, 1992).

A proposed pathological mechanism of CO, which may be independent of hypoxic stress, is related to an elevation in the steady-state concentration of the free radical, nitric oxide (•NO). This phenomenon has been documented in vitro with human and rat platelets, and bovine lung endothelial cells, and in vivo in both lung and brain of experimental animals (Thom et al., 1997, 1999a,b). The elevation of •NO can occur with exposures as little as 22 nM CO, which is the concentration expected with an interstitial CO partial pressure of about 20 ppm and a COHb level of 7% (Thom and Ischiropoulos, 1997; Thom et al., 1997). The mechanism for enhanced •NO release appears to be based on competition between CO and •NO for intracellular hemoprotein binding sites, rather than on a net increase in enzymatic production of •NO (Thom et al., 1994; Thom and Ischiropoulos, 1997; Thom et al., 1997). Vascular oxidative stress from •NO can cause leakage of high-molecular-weight substances into organ parenchyma and trigger leukocyte adherence/activation (Ischiropoulos et al., 1996; Thom et al., 1999a,b).

The health risks associated with CO vary with its concentration and duration of exposure. Effects range from subtle cardiovascular and neurobehavioral effects at low concentrations to unconsciousness and death after prolonged exposures or after acute exposures to high concentrations of CO. Risks associated with the relatively low ambient concentrations found in the environment and in contaminated work places have been reviewed in several excellent reports (US Environmental Protection Agency, 1991; Kleinman, 1992; Bascom et al., 1996; Penney, 1996; US Environmental Protection Agency, 1999).

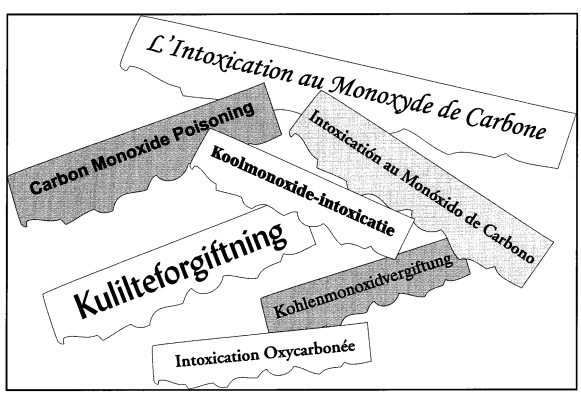

Fig. 1. Carbon monoxide poisoning is truly an international problem — examples of titles of articles on carbon monoxide poisoning published in the scientific literature.

2. History

Carbon monoxide poisoning is a major public health problem and mat be responsible for a significant percentage of all poisoning deaths. In fact, CO may be responsible for more than one-half of all fatal poisonings that are reported worldwide each year (National Safety Council, 1982; Cobb and Etzel, 1991; Mathieu et al., 1996). The frequency of health problems associated with sublethal levels of CO is difficult to quantify. Certain indoor and outdoor environments exist where the risk of exposure to dangerous levels of CO can be anticipated. Outdoors, concentrations of CO are highest near traffic intersections, in congested traffic, near exhaust gases from internal combustion engines and from industrial combustion sources, and in poorly ventilated areas such as parking garages and tunnels. Indoors, CO concentrations in the workplace and in homes with faulty or unvented combustion appliances or downdrafts and backdrafts, have been measured in excess of 100 ppm, which is estimated to result in COHb levels of greater than 10% after 8 h of exposure (US Environmental Protection Agency, 1999). In addition, CO is found in the smoke produced by all types of fires. Of the 6000 deaths from fires in the United States each year, the COHb levels of victims are sufficiently high to suspect that deaths in more than one-half were caused by CO poisoning (Heimbach and Waeckerle, 1988). Because of the risk of occult poisoning, some communities now require the installation of CO detectors in residences, along with smoke detectors and fire alarms (see Section 5). Despite efforts in prevention, and in public and medical education, CO intoxication remains frequent, severe, and too often overlooked (Barret et al., 1985; Balzan et al., 1996; Roy and Crawford, 1996; Molitor, 1997).

More attention to CO poisoning has been addressed recently in both the scientific literature (for example, Ernst and Zibrak, 1998) and the popular media (for example, Brown, 1995; Tipton, 1998) (Fig. 1). The first scientific studies of the hypoxic effects of CO were described by Claude Bernard (1865) and John Haldane (1895). The attachment of CO to Hb (producing COHb) was evaluated by Douglas et al. (1912); this study provided the necessary tools for studying human response to CO. During the next half-century, numerous studies were conducted with the principal emphasis being on high concentrations of COHb (see Haldane, 1927; Lilienthal, 1950). Carbon monoxide poisoning as an occupational hazard (Grut, 1949) received the greatest attention because of the increased use of natural gas and the potential for leakage of exhaust fumes in the workplace. Other indoor sources of CO have become more important and more insidious. The clinical picture of CO poisoning, as described by Grut (1949), relates primarily to alterations in cardiac and central nervous system function caused by CO.

The incidence of mortality and morbidity from CO exposure is similar worldwide. In 1985, 1365 deaths from CO exposure were reported in England and Wales (Meredith and Vale, 1988). In the United States, a report from the early 1970s suggested that more than 3800 people died annually from accidental and intentional CO poisoning (Schaplowsky et al., 1974). The rate of unintentional deaths from CO decreased from 1513 to 878 deaths per year between 1979 and 1988 (Cobb and Etzel, 1991) and to 600 deaths annually in the 1990s (Cook et al., 1994; Miller et al., 1995; Koontz and Niang, 1997). Per-capita mortality and morbidity statistics for CO are similar for the Scandinavian countries and Canada. The decline in unintentional CO deaths is speculated to result, in part, from transportation-related emission controls, improved safety of heating and cooking appliances, and public awareness of the dangers of CO poisoning. However, not all instances of CO poisoning are reported or diagnosed, and complete, up-to-date data are difficult to obtain, particularly from developing countries. In some places, continuous surveillance is performed through the recording of all cases hospitalized in the region, yielding annual epidemiological reports at the local level (Litovitz et al., 1992; Mathieu et al., 1996). Often, individuals suffering from CO poisoning are unaware of their exposure because symptoms are similar to those associated with viral illness or clinical depression. This may result in a significant number of misdiagnoses by medical professionals (Grace and Platt, 1981; Fisher and Rubin, 1982; Barret et al., 1985; Dolan et al., 1987; Kirkpatrick, 1987; Heckerling et al., 1987, 1988, 1990). Although the precise number of individuals who suffer from CO poisoning is not known, it is certainly much larger than that indicated by mortality figures. Schaplowsky et al. (1974) estimated that more than 10 000 people per year in the United States required medical attention or missed at least 1 day of work in the early 1970s because of sublethal exposures to CO. A recent study (Hampson, 1998) estimated over 40 000 emergency department visits annually for recognized acute CO poisoning in the United States.

3. Health effects

The symptoms, signs, and prognosis of acute CO poisoning correlate poorly with the level of COHb measured at the time of arrival at the hospital (Garland and Pearce, 1967; Winter and Miller, 1976; Okeda et al., 1982; Choi, 1983; Klees et al., 1985a,b; Myers et al., 1985; Meredith and Vale, 1988; Thom et al., 1995). This observation has created two concerns. The first is that investigators must be extremely careful when attempting to study patient populations because determination of the severity of poisonings and, therefore, the efficacy of one's treatment will be difficult. The second concern is that this observation raises questions regarding the presence of mechanisms for toxicity beyond that caused by hypoxic stress from COHb. A brief overview on mechanisms of CO toxicity already has been presented in Section 1. Mechanisms unrelated to hemoglobin binding may be especially relevant when considering the health risks associated with low CO levels, as found in the ambient environment. Pulmonary

Table 1
Equilibrium carboxyhemoglobin levels resulting from steady-state exposure to increasing concentrations of carbon monoxide in ambient air[a]

CO in atmosphere		Estimated COHb in blood (%)
%	ppm	
0.001	10	2
0.007	70	10
0.012	120	20
0.022	220	30
0.035–0.052	350–520	40–50
0.080–0.122	800–1220	60–70
0.195	1950	80

[a] Source: adapted from Winter and Miller (1976), Ellenhorn and Barceloux (1988).

cell injuries could arise with direct uptake of dissolved CO in the blood, without need for delivery by blood-borne hemoglobin. Elsewhere in the body, it is likely that CO will be delivered by hemoglobin and, therefore, the concentrations experienced by cells in perivascular and extravascular sites are estimated using calculations first described by Coburn (1970). Neurological symptoms of CO poisoning are generally more severe with higher COHb levels and include headache, dizziness, weakness, nausea, vomiting, confusion, disorientation, and visual disturbances. Exertional dyspnea, increases in pulse and respiratory rates, and syncope are observed with continuous exposure. With extreme exposures, coma, convulsions, and cardiorespiratory arrest may occur. There are numerous tables giving symptom-associated COHb levels; however, most physicians recognize the weak relationship between COHb levels and clinical presentation of the poisoned patient. Table 1 gives examples of CO concentrations in the atmosphere and estimated COHb levels that might result from steady-state exposure (see Ellenhorn and Barceloux, 1988).

Individuals may experience very different clinical manifestations of CO poisoning and, therefore, have different outcomes, even under similar exposure conditions. Norkool and Kirkpatrick (1985) found that COHb levels in individuals who had not lost consciousness at hospital arrival ranged from 5 to 47%. In individuals who were found unconscious, but regained consciousness at hospital arrival, the range was 10–64%; for those remaining unconscious, COHb levels varied from 1 to 53%. The large differences in COHb levels found in these individuals may have been related to the time elapsed between removal from exposure to CO and drawing blood for COHb determination. Alternatively, variations in clinical presentation could be related to the duration of exposure, the concentration of CO, or the amount and duration of supplemental oxygen administration prior to drawing the blood sample (Sokal, 1985; Sokal and Kralkowska, 1985).

The level of CO in the tissues may have an equal or greater impact on the clinical status of the patient than does the blood level of CO (Broome et al., 1988). The extent of tissue injury clearly is influenced by the length of exposure, based on laboratory animal studies (Thom, 1990a; Ischiropoulos et al., 1996; Thom et al., 1999a,b). Hypoxic stress related to elevations of COHb appears to be responsible for fatalities, cardiac injuries, and the acute neurological abnormalities which develop in approximately 14% of survivors from serious CO poisoning (Anderson et al., 1973; Ginsberg and Myers, 1974; Cramlet et al., 1975). Rhythm disturbances include sinus tachycardia, atrial flutter and fibrillation, premature ventricular contractions, and ventricular tachycardia and fibrillation. Other documented electrocardiographic changes include a decrease in the magnitude of the R wave, ST elevation, T-wave inversion, and heart block. Coronary hypoperfusion can lead to myocardial infarction, especially if coronary artery disease is present; however, myocardial infarction may result from CO poisoning even if coronary arteries are normal (Marius-Nunez, 1990).

Pulmonary edema is a relatively uncommon feature in CO poisoning unless smoke inhalation is involved, making a chest X-ray mandatory in such patients (Mathieu and Wattel, 1990). Other systemic complications, such as skeletal muscle necrosis, renal failure, pancreatitis, and hepatocellular injury, also can occur as a result of CO poisoning.

Neuropathology following CO poisoning may include neuronal death in the cortex, hippocampus, substantia nigra and globus pallidus (LaPresle and Fardeau, 1967). One of the most common abnormalities is demyelination of cerebral cortex, which occurs in a perivascular distribution along with evidence of a breach in the blood–brain barrier (Meyer, 1928; Courville, 1957; LaPresle and Fardeau, 1967; Putnam et al., 1991). Blood flow and perivascular abnormalities have been shown using several clinical neuroimaging techniques, but their relevance to progression of neuropathology is unknown (Bianco and Floris, 1988; Maeda et al., 1991; Shimosegawa et al., 1992; De Reuck et al., 1993; Silverman et al., 1993; Ducassé et al., 1995). Acute vascular and perivascular changes also have been found in brains of experimental animals (Funata et al., 1982; Okeda et al., 1982; Ischiropoulos et al., 1996). Clinical and experimental findings suggest that the effects of CO are systemic, and variations in the clinical manifestations following poisoning arise because each brain region responds differently to the stresses. Neurological manifestations of acute CO poisoning include disorientation, confusion, cogwheel rigidity, opisthotonic posturing, extremity flaccidity or spasticity, extensor plantar response, and coma. Perhaps the most insidious effect of CO poisoning is the development of delayed neuropsychiatric impairment, also known as delayed neurological syndrome. Within 2–28 days after poisoning, 3–40% of patients will manifest new cognitive difficulties such as impaired judgment, poor concentration, memory loss, and relative indifference to obvious neurological deficits.

4. Treatment and prognosis

Management of CO-poisoned patients first consists of removing the patient from exposure to the toxic atmosphere and supplying pure oxygen to accelerate the elimination of CO and improve tissue oxygenation. Respiratory and circulatory conditions are assessed rapidly, and resuscitative measures are performed, if needed. Evaluation includes the neurological status of conscious level, motor response and reflectivity, and a complete physical examination looking for complications, associated trauma or intoxication, and previous disease. Laboratory examinations should include a blood gas analysis to assess acid–base status and a COHb measurement. Carboxyhemoglobin levels over 5% in a nonsmoker and over 10% in a smoker confirm the diagnosis but not the severity of intoxication (Ilano and Raffin, 1990).

Patients with mild CO poisoning respond to treatment with 100% oxygen at normal barometric pressure (NBO_2). If available, treatment with hyperbaric oxygen (HBO_2) at 2.5–3 atm abs (AZA) for 90 min is preferable in more severely poisoned individuals (Myers, 1986; National Heart, Lung, and Blood Institute, 1991). However, the precise conditions requiring treatment with either NBO_2 or HBO_2 and their respective outcomes have been topics of debate in the literature (Mathieu et al., 1985; Norkool and Kirkpatrick, 1985; Broome et al., 1988; Brown and Piantadosi, 1989; Gorman et al., 1989; James, 1989; Neubauer and Gottlieb, 1989; Raphael et al., 1989a,b; Roy et al., 1989; Thom and Keim, 1989; Van Hoesen et al., 1989; Brown et al., 1992; Gorman et al., 1992; Raphael et al., 1993; Hardy and Thom, 1994; Tibbles and Perrotta, 1994; Ducassé et al., 1995; Thom et al., 1995; Scheinkestel et al., 1999). It has been suggested that, if COHb is above 25%, HBO_2 treatment should be initiated (Norkool and Kirkpatrick, 1985), although data to support any specific COHb level requiring HBO_2 are lacking (Myers and Britten, 1989; Thom and Keim, 1989). Approximately 50% of North American hyperbaric oxygen treatment facilities identify a COHb level above which HBO_2 therapy is recommended (Hampson et al., 1995). Among these, 25–30% is the COHb level most commonly identified. Most hyperbaric centers treat patients with CO intoxication when they manifest loss of consciousness or other neurological signs and symptoms, regardless of the amount of COHb present (Piantadosi, 1990; Hampson et al., 1995). The first European Consensus Conference on hyperbaric medicine concluded that hyperbaric oxygen is highly recommended for every comatose patient, every patient who lost consciousness during exposure, every patient with

abnormal neuropsychologic manifestation, and every pregnant woman (Mathieu et al., 1996).

Emergency treatment emphasizes the use of supplemental oxygen because this intervention will hasten removal of CO from the body. The half-time elimination of CO while breathing air is approximately 320 min; when breathing 100% oxygen at normobaric pressure, it is 80 min; and, when breathing oxygen at 3 ATA, it is 23 min (Myers et al., 1985). In case of normobaric oxygen treatment, the length of oxygen administration is also controversial, but it appears that it must be long enough to ensure total CO detoxification. Proposed durations are often between 5 and 48 h. Additional mechanisms associated with hyperbaric oxygen therapy, but not exposure to ambient pressures of oxygen, include improvement of mitochondrial oxidative metabolism (Brown and Piantadosi, 1992), inhibition of lipid peroxidation (Thom, 1990b), and impairment of leukocyte adhesion to injured microvasculature (Thom, 1993).

Successful removal of CO from the blood does not ensure an uneventful recovery with no further clinical signs or symptoms. Neurological problems may develop insidiously weeks after recovery from the acute episode of CO poisoning (Meredith and Vale, 1988). These late neurological sequelae include intellectual deterioration; memory impairment; and cerebral, cerebellar, and mid-brain damage. Up to 40% of patients develop memory impairment, and more than 30% suffer deterioration of personality. Smith and Brandon (1973) published a study in which they found 10% of cases with immediate gross neurological sequelae, 33% with delayed personality deterioration, and 43% with memory disturbances. In a literature review, Ginsburg and Romano (1976) found 15–40% of late cases with neurological sequelae. The explanation for neurological problems may be misdiagnosis (30% in a French Poison Control Center study; Mathieu et al., 1985), inadequate therapy (40% of the patients of Smith and Brandon (1973) did not receive any oxygen in the emergency treatment), or delayed therapy. Complete recovery is obtained more often if supplemental oxygen is given within 6 h following exposure (Barois et al., 1979). These same issues are present in the literature pertaining to efficacy of hyperbaric oxygen therapy.

Since 1960, hyperbaric oxygen has been used with increasing frequency for severe CO poisoning because clinical recovery has appeared to be more rapid and complete than with ambient pressure oxygen therapy (Smith and Sharp, 1960; Mathieu et al., 1985; Myers et al., 1985; Gorman et al., 1992). However, the first prospective clinical trial involving hyperbaric oxygen failed to find it to be superior to ambient pressure treatment (Raphael et al., 1989a). This study has been criticized because the authors used a low oxygen partial pressure (2 ATA versus the more usual protocols with 2.5–3 ATA) and because nearly one-half of the study population received hyperbaric oxygen treatments more than 6 h after patients were discovered (Brown and Piantadosi, 1989). In 1969, a retrospective study indicated that hyperbaric oxygen reduced mortality and morbidity only if administered within 6 h after CO poisoning (Goulon et al., 1969).

Some centers have proposed using psychometric screening tests to identify patients with subtle neurological compromise and as a method to identify patients needing HBO_2. Results from a prospective, randomized investigation involving 60 CO-poisoned patients suggest that this approach may not be useful. Patients in this study appeared to suffer from mild to moderately severe poisoning because they had symptoms such as headache, nausea, and lethargy, but none of the signs or symptoms presumed to be associated with severe poisoning, such as ischemic changes on electrocardiogram or a history of unconsciousness (Thom et al., 1995). Delayed neurological sequelae were defined as development of new neurological symptoms and also reductions from original scores on a standardized psychometric battery of tests. The initial test scores were not helpful in identifying those who went on to suffer delayed sequelae, but do lend support to the concept that HBO_2 therapy is more efficacious than NBO_2. Twenty-three percent of patients (seven of 30) treated with ambient pressure oxygen developed neurological sequelae 6 ± 1 (S.E.) days after poisoning, and sequelae persisted for 41 ± 8 days. No patients (0 of 30)

($P < 0.05$) treated with HBO_2 (2.8 ATA) developed sequelae.

Hyperbaric oxygen also was found to have a significant benefit in other prospective, randomized trials (Ducassé et al., 1995; Mathieu et al., 1996). In Ducassé's report, 26 patients were hospitalized within 2 h of discovery and they were equally divided between two treatment groups — ambient pressure O_2, or 2.5 ATA O_2. Three weeks later, patients treated with HBO_2 had significantly fewer abnormalities on electroencephalogram, and SPECT scans showed that cerebral vessels had nearly normal reactivity to CO_2, in contrast to diminished reactivity in patients treated with ambient pressure O_2. Mathieu et al. (1996) conducted a study on the long-term consequences of CO poisoning and treatment by hyperbaric oxygen therapy on 774 patients who were divided into five groups: Group 0, where patients suffered only from headache or nausea; Group I, with abnormality in neurological examination; Group II, where patients had lost consciousness, regardless of their clinical state of admission; Group III, where patients were comatose (Glasgow Coma Scale 6); and Group IV, where patients were deeply comatose. Group 0 received only normobaric pure oxygen, where as Groups I–IV received hyperbaric oxygen. At 1 year, only 4.4% of the patients suffered from persistent manifestations, and only 1.6% had major functional impairment. However, persistent neurological manifestations occurred only in patients from Groups I and IV.

Scheinkestel et al. (1999) reported no benefit from HBO_2 therapy in a prospective trial of 191 patients. This report has garnered substantial discussion among toxicologists and emergency physicians because many concerns about the experimental protocol and data analysis severely diminish the potential impact of this investigation. Therefore, despite several contradictory reports, use of hyperbaric oxygen in every CO-poisoned patient who has suffered loss of consciousness during CO exposure, who has a neurological abnormality on clinical examination, or who displays evidence of myocardial ischemia continues to be advocated.

5. Prevention

One way to avoid dangerous CO exposures is to prevent high concentrations of CO from occurring in residences and other indoor environments. This can be accomplished by: (1) frequent inspection and routine maintenance of vented combustion appliances and fireplaces; (2) not allowing automobiles to idle in closed or open garages; (3) not using unvented combustion sources indoors, such as space heaters, cooking devices (e.g., charcoal grills and hibachis), and tobacco products, or not misusing properly vented sources (e.g., using a gas oven/range for heating); and (4) installation of CO alarms.

Electronic carbon monoxide alarms have been designed like residential smoke detectors — to be low cost, yet provide protection from a catastrophic event by sounding an audible alarm. The CO alarm industry is young and in a stage of rapid growth. In the United States, an estimated 15 million alarms have been purchased since the early 1990s, and the numbers used in residences and commercial buildings will continue to rise as local municipalities change building codes to require the installation of CO alarms in new structures containing combustion-source appliances, stoves, or fireplaces.

Currently available electronic CO alarms are based on an interactive-type sensor (e.g., metal oxide, electrochemical, artificial hemoglobin) that relies on direct interaction between CO and the sensitive element to generate a response. They are battery powered, a.c. powered, or both. The most popular a.c.-powered alarms at the present time have a heated metallic sensor that reacts with CO, whereas the battery-powered detectors have a chemically treated gel disk that darkens with exposure to CO. Small, inexpensive CO detection cards or tablets that require frequent visual inspection of color changes do not sound an alarm and are not recommended as primary detectors.

Carbon monoxide alarms are sensitive to location and environmental conditions, including temperature, relative humidity, and the presence of other interfering gases (e.g., hydrogen, nitrogen oxides); they also may become less stable with time. For example, they should not be installed in

dead-space air (i.e. near ceilings) or near windows or doors where air movement is high. They should not be exposed to temperature or humidity extremes. Excessive heat or cold will affect performance, and humidity extremes will affect the activation time. Utilization of noninteractive infrared technology (e.g., nondispersive infrared analysis) in indoor CO detection would overcome these shortcomings of currently available CO alarms.

In the United States, a voluntary standard for CO alarms was published in 1992 by Underwriters Laboratories (UL Standard 2034), revised in 1995, and again in 1997 and 1999. This standard provides alarm requirements that are based on both CO concentration and exposure time. It is designed so that an 85-decibel alarm must activate within 189 min of exposure to 70 ppm, within 50 min of exposure to 150 ppm, or within 15 min of exposure to 400 ppm (i.e. when exposures in a highly active nonsmoker would be expected to result in COHb levels approaching $\approx 10\%$). The British standard for domestic CO alarms (BS 7860:1996) recommends no response within 1 h of exposure to 45 ppm CO, and requires alarm activation within 15 min of exposure to 150 ppm CO and within 5 min of exposure to 350 ppm CO. More than 15 manufacturers currently produce commercially available detectors (Consumers Union, 1995; Federal Register, 1995; Underwriters Laboratories, Inc., 1995; Consumers Union, 1996).

Because the recommended standards cover a wide range of exposure conditions, there has been some ambiguity about their interpretation. In addition, alarm sensitivities are still a problem for the industry, and further discussion and direction is needed. Part of the controversy centers on the population the standards are trying to protect. To be in compliance with the U.S. Environmental Protection Agency and World Health Organization ambient air standards, it would be necessary to set alarms to register exposures to 9 ppm CO for 8 h or 25 ppm for 1 h. Current alarms provide warning only against CO levels that protect most healthy persons from experiencing the adverse effects of acute CO exposure (e.g., loss of ability to react). Despite these limitations, CO alarms can be reliable and effective, continue to improve, and should be recommended for use in homes in addition to smoke detectors and fire alarms.

6. Summary

Carbon monoxide is responsible for a large percentage of the accidental poisonings and deaths reported throughout the world each year. Certain conditions exist both in the indoor and outdoor environments that cause a small percentage of the population to become exposed to dangerous levels of CO. Outdoors, concentrations of CO are highest near street intersections, in congested traffic, near exhaust gases from internal combustion engines and industrial sources, and in poorly ventilated areas such as parking garages and tunnels. Indoors, CO concentrations are highest in workplaces or in homes that have faulty or poorly vented combustion appliances or downdrafts or backdrafts.

The symptoms, signs, and prognoses of acute CO poisoning correlate poorly with the level of COHb measured at the time of arrival at the hospital. Carboxyhemoglobin levels below 10% usually are not associated with symptoms. At higher COHb levels, neurological symptoms of CO poisoning can occur (headache, dizziness, weakness, nausea, confusion, disorientation, and visual disturbances). Exertional dyspnea, increases in pulse and respiratory rates, and syncope are observed with continuous exposure. With extreme poisoning, coma, convulsions, and cardiopulmonary arrest may occur.

Complications occur frequently in CO poisoning (immediate death, myocardial impairment, hypotension, arrhythmias and pulmonary edema). Perhaps the most insidious effects of acute CO poisoning are the delayed development of neuropsychiatric impairment within 2–28 days and the neurobehavioral consequences. Carbon monoxide poisoning during pregnancy results in high risk for the mother by increasing the short-term complications rate and for the fetus by causing fetal death, developmental disorders, and cerebral anoxic lesions. Furthermore, the severity of fetal intoxication cannot be assessed by the mother's clinical status.

In conclusion, CO poisoning remains frequent and severe throughout the world, with a relatively high risk of immediate death, complications, and late sequelae; furthermore, CO poisoning also often is overlooked. Although studies on CO poisoning are not adequate for evaluating the quantitative relationship between dose and effect or for recommending CO standards in ambient air, they suggest that, under some circumstances and meteorological conditions, CO poisoning can occur in the population. This possibility has to be taken into account in defining standards for the protection of public health. Efforts in prevention and in public and medical education should continue to be encouraged.

7. Disclaimer

The technical discussion in this paper is based on a review of the scientific literature and the best professional judgement of the authors. It does not necessarily represent official policy of the US Environmental Protection Agency or any other governmental health agency.

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Appendix A. Cigarette smoke contains carbon monoxide

A common source of CO for the general population is tobacco smoke. The actual quantity of CO entering the lung depends on the form of tobacco smoked, the pattern of smoking, and the depth of inhalation. Very little CO is absorbed in the mouth and upper airways; therefore, most of the CO available for binding to hemoglobin in blood must reach the distal respiratory tract to raise the level of COHb present in blood. The CO concentration in tobacco smoke is approximately 4.5% (45 000 ppm). A cigarette smoker may be exposed to 400–500 ppm CO for the approx. 6 min that it takes to smoke a typical cigarette, producing an average baseline COHb of 4%, with a typical range of 3–8%. Heavy smokers may achieve COHb levels as high as 15%. In comparison, nonsmokers average about 1% COHb in their blood. Exposure to tobacco smoke not only increases COHb concentrations in smokers, but, under some circumstances, it also can affect nonsmokers. For example, acute exposure (1–2 h) to smoke-polluted environments has been reported to cause an incremental increase in nonsmokers' COHb of about 1%.

In addition to being a source of CO for smokers and nonsmokers, tobacco smoke also is a source of other chemicals (e.g. nitrogen dioxide, hydrogen cyanide, polyaromatic hydrocarbons, nicotine) with which environmental CO could interact. Available data strongly suggest that acute and chronic CO exposure attributed to tobacco smoke can affect the cardiopulmonary system, but the potential interaction of CO with other products of tobacco smoke confounds the results. Further research is needed to determine the toxicological importance of CO alone, and in combination with the other components of tobacco smoke.

In many of the studies currently cited to justify ambient air standards for CO, neither the smoking habits of the subjects nor their exposure to passive smoking have been taken into account. In addition, as the result of higher baseline COHb levels, smokers actually may be exhaling more CO into the air than they are inhaling from the ambient environment. Smokers may even show an adaptive response to the elevated COHb levels, as evidenced by increased red-cell volumes and reduced plasma volumes. As a consequence, it is not clear if incremental increases in COHb caused by environmental exposure actually would be addi-

tive to the chronically elevated COHb levels caused by tobacco smoke. Thus, the standards are recommended primarily for the protection of nonsmokers.

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