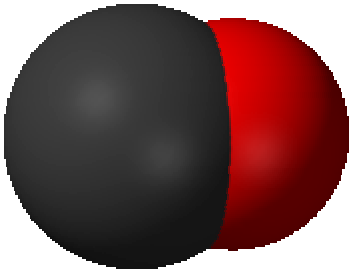
A literature study on Carbon Monoxide

1.0 INTRODUCTION

"You can't **smell** it, **see** it or **taste** it, but it could be there now". Because of this, most people do not understand the nature of the problem from Carbon Monoxide poisoning.

Carbon monoxide is colorless, odorless, tasteless, and non-irritating, making it difficult for people to detect.

Carbon monoxide is a significantly toxic gas with poisoning being the most common type of fatal poisoning in many countries. Carbon monoxide poisoning is the most common type of accidental poisoning in the United States, accounting for thousands of emergency department visits and some 800 deaths annually.



Polluted air often contains unhealthy levels of carbon monoxide. Many areas of the US have struggled to achieve legislated limits. Significant advances have been made since the implementation by 1990 of a vehicle emissions limit of 3.4 gpm (grams per mile), a large reduction from the previous limit of 87 gpm.

The Carbon Monoxide Paradox:

In spite of all the risks of carbon monoxide inhalation, this compound is absolutely essential for the metabolic process required to sustain life.

Carbon monoxide is mainly produced as a waste product from incomplete combustion processes with cigarette smoking, motor vehicles and polluted ambient air as major sources for its presence indoors.

- 0.025 ppm - natural background atmosphere level
- 0.5 to 5 ppm - average background level in homes
- 5 to 15 ppm - levels near properly adjusted gas stoves in homes
- 100-200 ppm - Mexico City central area from autos etc.
- 5,000 ppm - chimney of a home wood fire
- 7,000 ppm - undiluted warm car exhaust
- 30,000 ppm - undiluted cigarette smoke

Under ordinary conditions, it is less dense than air, but during fires, it accumulates on the ground, so that if poisoning causes loss of consciousness, the amount of carbon monoxide inhaled increases and the possibility of fatality is radically increased.

Lethal characteristics of carbon monoxide are:

- Lack of sensory perceptibility, no early warning
- Haemoglobin's high binding affinity ratio
- It is not an irritant, so it does not trigger any defence mechanism like pain, coughing, choking or expectoration
- Early symptoms of poisoning are undefined and often mask as common cold or flu (but no fever), or food poisoning
- It does not alter blood's red hue, nor turns skin bluish, common signs of other suffocating gas inhalation
- It does not build-up in any internal organ, like liver or kidneys, and can mislead routine blood chemistry counts

- There is no medical treatment for CO poisoning. Brain and neurological damages, if not fatal, are irreversible and permanent
- It is a very common pollutant in urban life, readily produced by any combustion process
- Degrees of sensibility vary widely depending on age, physical condition, underlying medical conditions, previous exposure and cumulative concentration levels
- The public general is poorly educated on the effects of carbon monoxide poisoning and usually unaware of high risk common-life situations
- Chronic CO poisoning is more frequent than what it used to be; and
- Simple mistakes, deadly results

Carbon monoxide is not absorbed through the skin or mucous tissue, is hardly soluble in water and it is easy to ventilate. If irreversible damages do not occur, recovery is uneventful and does not build-up sensitivity nor alter tolerance threshold.

It is combustible, burning with a blue-violet flame, and explosive, with a Lower Explosive Limit (LEL) of 12.5% and can be used as fuel (*water or blue gas*). It has a specific weight of 0.96716 - 09736 (air = 1).

The exchangers are the lungs, and the carrier is a special protein contained in red cells called hemoglobin (94% globin, 6% hemo). Each hemoglobin molecule combines with one molecule of oxygen to form oxihemoglobin. This gives blood its bright red color.

1.1 Carbon Monoxide in Cigarettes

Smoking tobacco increases the **CO** content of your blood. The normal level of **CO** for a nonsmoker depends on background levels in the air, but it is usually between 0 and 8 parts per million. The level of **CO** for a smoker is usually much higher. A smoker's level of **CO** varies according to the time of day, the number of tobacco products smoked and how the smoke is inhaled. A person who smokes a pack of **cigarettes** per day will

commonly have a **CO** level of about 20 parts per million. A two-pack-a-day smoker may have a level of about 40 parts per million.

The good news is that after stopping smoking, the **CO** level will return to normal within one or two days. Health effects related to **CO** may vary from person to person.

Carbon Monoxide is a colorless, odorless gas produced from the incomplete burning of virtually any combustible product. It may accumulate indoors as a result of tobacco smoking, poorly ventilated appliances, and attached garages. **Carbon Monoxide** enters the blood from the lungs and combines with hemoglobin, blocking the blood's ability to carry oxygen to body cells. Symptoms of **Carbon Monoxide** exposure may mimic influenza and include fatigue, headache, dizziness, nausea and vomiting, mental confusion, and rapid heart rate. Depending on the level of exposure, Carbon Monoxide can be immediately fatal. Long-term, low-level exposure to **Carbon Monoxide** by pregnant women has the potential to injure the developing fetus.

Carbon Monoxide (CO) is a colorless, odorless, tasteless gas that is a small part of the air we breathe. There are many sources of **Carbon Monoxide** such as incinerators, car exhaust and gas furnaces.

When the level of CO in your blood increases, the ability of your blood to carry oxygen is decreased. It is harmful to your body at any level and it can kill you. Long-term exposure at lower levels can lead to heart disease.

2.0 EPIDEMIOLOGY

Carbon monoxide poisoning is the most common type of fatal poisoning in France and the United States. It has been estimated that more than 40,000 people per year seek medical attention for carbon monoxide poisoning in the United States. In many industrialized countries, carbon monoxide may be the cause of greater than 50% of fatal poisonings. In the U.S., about 200 people die each year from carbon monoxide poisoning associated with home fuel-burning heating equipment. The CDC reports, "Each year, more than 500 Americans die from unintentional CO poisoning, and more than 2,000 commit suicide by intentionally poisoning themselves."

Carbon monoxide is and has been the most common cause of both accidental toxic poisoning and death in the United States for over 100 years. This protocol is meant to assist physicians, respiratory therapists, and other medical professionals in diagnosing and treating cases of chronic low-level CO poisoning as defined by specific symptoms and objective biomarkers. It should not be used for self-diagnosis or self-treatment, or as a substitute for professional medical advice.

3.0 SOURCES

3.1 Exogenous Sources of Carbon Monoxide (from outside the body)

Common sources of CO that may lead to poisoning include house fires, furnaces or heaters, wood-burning stoves, motor vehicle exhaust, and propane-fueled equipment such as portable camping stoves, ice resurfacers, forklifts, and engine-driven generators. Another source is exposure to the organic solvent methylene chloride, which is metabolized to CO by the body.

Carbon monoxide, an insidious by-product of incomplete hydrocarbon combustion, is generated in toxic amounts by internal-combustion engines, fossil-fuel furnaces, and fires. Carbon monoxide emissions from modern automobiles, though controlled by regulatory standards, are still highly toxic in poorly ventilated spaces.

Carbon monoxide (CO) is produced from the incomplete combustion or burning of any fuel. Indoor exposures obviously are of greater concern than outdoor ones, as they are more likely to pose a risk to human health. The primary sources inside US homes and apartment buildings are smoking, unventilated gas ranges and vehicles started in attached but unventilated garages. Other CO sources include gas and oil furnaces, water and space heaters, ovens, wood and coal stoves, wood and coal fireplaces, gas-log inserts and explosives. Even electric ovens can produce CO when cooking some foods and always do so in self-cleaning mode when baking off spilled food.

3.2 Endogenous Sources of Carbon Monoxide (from inside the body)

The human body also breaks down some inhaled and ingested chemicals into CO, including ubiquitous dichloromethane (a common solvent especially in paint strippers and the most common propellant used in consumer product spray cans).

Stress of any kind induces increased production of heme oxygenase-1 (HO-1), the so-called "universal stress enzyme" found throughout the body, which breaks down heme from heme proteins into iron, biliverdin (which is then converted into bilirubin, a potent anti-oxidant), and carbon monoxide. The stresses that have been shown to induce HO-1 in animals and humans include heat, light, sound, odors, electromagnetic fields, infection, physical trauma and mental or psychological stress. Chronic stress in any of these pathways thus results in chronic destruction of heme and chronic low-level CO poisoning. The ability of so many different types of physical, biological, chemical and mental stressors to induce HO-1 explains why the core symptoms of chronic stress are so similar to CO poisoning regardless of the stressor (see Symptoms, below). Stress-induced HO-1 activity and the relatively constant activity of another isozyme, HO-2, that does not respond to stress, together account for about 75% of the human body's CO production. Other sources of CO include the auto-oxidation of phenols, flavenoids and halomethanes, the photo-oxidation of organic compounds, and the lipid peroxidation of membrane lipids.

HO activity can be directly measured in blood and various organs but of course varies widely, while endogenous CO levels, which also include any exogenous contribution, can be measured directly in breath, blood or muscle. The most commonly measured carboxyhemoglobin level (COHb) only identifies the percent of hemoglobin that is bound to CO, but this is normal in cases of chronic low-level CO poisoning, and even in acute cases not consistently related to symptoms.

4.0 STANDARDS

4.1 Occupational Safety and Health Administration, (OSHA)

- Permissible Exposure Limit (PEL, by TWA) 50 ppm, 8 hours
- Old PEL Standard (by TWA) 35 ppm, 8 hours
- Threshold Limit Value (TLV, by TWA) 25 ppm (29 mg/m^3)

4.2 American Conference of Governmental and Industrial Hygienists (ACGIH)

- Ceiling (max. value, 15 min.) 200 ppm (229 mg/m^3)

4.3 Environmental Protection Agency, (EPA)

- Commercial Indoor Air, all ages (TWA) 9 ppm*, 8 hours
- Domestic Indoor Air, all ages (TWA) 35 ppm, 1 hour

4.4 World Health Organization (WHO)

- Domestic, all ages (TWA) 9 ppm*, 8 hours

4.5 American Gas Association

- Indoor Air 15 ppm

4.6 American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE)

- Indoor Air 9 ppm

5.0 EFFECTS OF EXCESSIVE EXPOSURE

Symptoms of mild poisoning include headaches and flu-like effects; larger exposures can lead to significant toxicity of the central nervous system and heart. Following poisoning, long-term sequelae often occur. Carbon monoxide can also have severe effects on the fetus of a pregnant woman.

The mechanisms by which carbon monoxide produces toxic effects are not yet fully understood, but hemoglobin, myoglobin, and mitochondrial cytochrome oxidase are thought to be compromised. Treatment largely consists of administering 100% oxygen or hyperbaric oxygen therapy, although the optimum treatment remains controversial. Domestic carbon monoxide poisoning can be prevented by the use of household carbon monoxide detectors.

Carbon monoxide is a significantly toxic gas, although patients may demonstrate varied clinical manifestations with different outcomes, even under similar exposure conditions. Toxicity is also increased by several factors, including: increased activity and rate of ventilation, pre-existing cerebral or cardiovascular disease, reduced cardiac output, anemia or other hematological disorders, decreased barometric pressure, and high metabolic rate.

Carbon monoxide is life-threatening to humans and other forms of air-breathing life, as inhaling even relatively small amounts of it can lead to hypoxic injury, neurological damage, and possibly death. A concentration of as little as 0.04% (400 parts per million) carbon monoxide in the air can be fatal. The gas is especially dangerous because it is not easily detected by human senses. Early symptoms of carbon monoxide poisoning include drowsiness and headache, followed by unconsciousness, respiratory failure, and death. First aid for a victim of carbon monoxide poisoning requires access to fresh air; administration of artificial respiration and, if available, oxygen; and, as soon as possible, medical attention.

In addition, a recent report concludes that carbon monoxide exposure can lead to significant loss of lifespan after exposure due to damage to the heart muscle.

Pregnant smokers may give birth to babies of a lower birth mass as foetal haemoglobin takes up carbon monoxide more readily than in an adult, therefore the foetus of a smoker will suffer from mild hypoxia potentially retarding its development.

A sufficient exposure to carbon monoxide can reduce the amount of oxygen taken up by the brain to the point that the victim becomes unconscious, and can suffer brain damage or even death from hypoxia. The brain regulates breathing based upon carbon dioxide levels in the blood, rather than oxygen levels, so a victim can succumb to hypoxia without ever noticing anything up to the point of collapse. Hallmark pathological change following CO poisoning is bilateral necrosis of the pallidum.

The most common signs and symptoms of carbon monoxide poisoning are nonspecific and include headache, dizziness, and confusion. A high index of suspicion is needed to make the diagnosis, particularly when the means of exposure is not evident. The diagnosis is confirmed by measurement of blood carboxyhemoglobin. Indeed, it has been estimated that more than 5 percent of patients in emergency departments who present with influenza-like illnesses during the winter have occult carbon monoxide poisoning. The normal carboxyhemoglobin level is 1 to 3 percent, a result of endogenous carbon monoxide production by heme catabolism and low-level environmental carbon monoxide exposure. Cigarette smokers increase their carboxyhemoglobin level by an average of 5 percent per pack smoked per day, and otherwise healthy smokers tolerate carboxyhemoglobin levels of 10 percent without having symptoms. Overt signs of toxic effects usually appear at carboxyhemoglobin levels of 15 to 20 percent, and a level of 25 percent is an index of severe poisoning, which may lead to sudden loss of consciousness.

Serious consequences occur in half of victims of severe carbon monoxide poisoning and fall into two major categories: acute cardiac or neurologic injuries and late effects. A

delayed neurologic syndrome, typified by memory loss and other, sometimes subtle, cognitive deficits occurs in approximately 15 percent of severely poisoned patients after an interval of 2 to 28 days. Age and loss of consciousness have been identified as independent risk factors. The delayed neurologic syndrome naturally tends to improve gradually, and many patients have normal functional status a year after poisoning, but all require careful follow-up for residual neuropsychological effects.

Depending on the time of exposure symptoms could vary from none, headaches, drowsiness, vomiting, collapse to the extreme irrevocable symptoms of coma and brain damage occurs. Eventually death sets in. **If employees are excessively exposed (depending on the level and length), they should in general be withdrawn from work and only return the next shift.**

5.1 Acute

The earliest symptoms, especially from low level exposures, are often non-specific and readily confused with other illnesses, typically flu-like viral syndromes, depression, chronic fatigue syndrome, and migraine or other headaches. This often makes the diagnosis of carbon monoxide poisoning difficult. If suspected, the diagnosis can be confirmed by measurement of blood carboxyhemoglobin.

The main manifestations of poisoning develop in the organ systems most dependent on oxygen use: the central nervous system and the heart. The clinical manifestations include tachycardia and hypertension, and central nervous system symptoms such as headache, dizziness, confusion, convulsions, and unconsciousness. CO poisoning may also produce myocardial ischemia, atrial fibrillation, pneumonia, pulmonary edema, hyperglycemia, muscle necrosis, acute renal failure, skin lesions, visual and auditory problems, and respiratory arrest.

One of the major concerns following CO poisoning is the severe neurological manifestations that may occur days or even weeks after an acute poisoning. Common

problems encountered are difficulty with higher intellectual functions and short-term memory, dementia, irritability, gait disturbance, speech disturbances, parkinson-like syndromes, cortical blindness, and depression (depression can occur in those accidentally exposed). These delayed sequelae occur in approximately 15 percent of severely poisoned patients after an interval of 2 to 28 days. It is difficult to predict who may develop delayed sequelae; however, advancing age, loss of consciousness while poisoned, and initial neurological abnormalities may indicate a greater chance of developing delayed symptoms. According to the Philadelphia poison control hotline, sequelae are generally not anticipated when exposure is not severe enough to result in loss of consciousness.

5.2 Chronic

Long term, repeat exposures present a greater risk to persons with coronary heart disease and in pregnant patients. Chronic exposure may increase the incidence of cardiovascular symptoms in some workers, such as motor vehicle examiners, firefighters, and welders. Patients often complain of persistent headaches, lightheadedness, depression, confusion, and nausea. Upon removal from exposure, the symptoms usually resolve themselves.

5.3 General

The effects of carbon monoxide in parts per million are listed below:

- 35 ppm (0.0035%) Headache and dizziness within six to eight hours of constant exposure
- 100 ppm (0.01%) Slight headache in two to three hours
- 200 ppm (0.02%) Slight headache within two to three hours
- 400 ppm (0.04%) Frontal headache within one to two hours
- 800 ppm (0.08%) Dizziness, nausea, and convulsions within 45 minutes. Insensible within two hours.

- 1,600 ppm (0.16%) Headache, dizziness, and nausea within 20 minutes. Death in less than two hours.
- 3,200 ppm (0.32%) Headache, dizziness and nausea in five to ten minutes. Death within 30 minutes.
- 6,400 ppm (0.64%) Headache and dizziness in one to two minutes. Death in less than 20 minutes.
- 12,800 ppm (1.28%) Unconciousness after 2-3 breaths. Death in less than three minutes.

Whether arising from exogenous or endogenous sources, CO in the human body may be used or stored in several different ways until it is finally exhaled. CO binds much more aggressively than oxygen to all heme proteins, especially to hemoglobin (Hb). In doing so, it reduces the number of Hb binding sites available for carrying oxygen and makes the remaining oxygen bind more tightly. In muscle, CO binds more aggressively than oxygen to myoglobin (the main heme protein in muscle) and so interferes with oxygen use during exercise, especially in cardiac muscle.

CO activates guanylyl cyclase, which produces cyclic GMP, and nitric oxide synthase, which makes NO, but it also impairs mitochondrial energy metabolism and the function of cytochromes needed for detoxification. CO also triggers oxidative vascular stress (via endothelial cell production of NO and peroxynitrite) and brain lipid peroxidation. Most significantly, CO acts as a gaseous neurotransmitter in modulating many critical functions including respiration rate, heart rate, vasodilation, learning, memory and long-lasting adaptation to sensory stimuli (esp. odors).

Because chronic low-level CO poisoning impairs oxygenation of tissue, any organ may be affected, with the brain, heart and lungs being most sensitive to the effects of CO. The most common symptoms of chronic CO poisoning are actually the same as those of acute poisoning, except that they may vary considerably over time as they wax and wane in response to not just exogenous CO exposures but also in response to any

chronically stressful stimuli, since all such stimuli induce HO-1 to breakdown heme proteins into CO (see Endogenous Sources, above).

5.4 10 Common Symptoms of Carbon Monoxide Poisoning

The 10 common symptoms of CO poisoning are:

1. Headache
2. Fatigue, Weakness
3. Muscle Pain, Cramps
4. Nausea, Vomiting
5. Upset Stomach, Diarrhea
6. Confusion, Memory Loss
7. Dizziness, Incoordination
8. Chest Pain, Rapid Heartbeat
9. Difficult or Shallow Breathing
10. Changes in Sensitivity of Hearing, Vision, Smell, Taste or Touch

Because all these symptoms are common to so many disorders, no single one is considered diagnostic of CO poisoning, but CO should be suspected whenever a majority of these symptoms are reported together and no other cause is determinable, especially if the same symptoms are reported by more than one occupant of the enclosed space (building, vehicle, boat or plane).

A far more discriminating set of 30 symptoms appears in Edgar Allan Poe's classic 1839 tale, *The Fall of The House of Usher*, which we propose may be read as a literal description of chronic CO poisoning. Poe most likely suffered CO poisoning from his exposure to the coal gas that was used in the 1800s for indoor lighting. People with chronic CO poisoning today report having an average of 27 of these 30 symptoms in the last month, compared to healthy normal controls whom average 2.

5.5 Edgar Allan Poe's 30 Chronic CO Symptoms

Poe described the following symptoms for chronic CO exposure:

1. "Ghastly pallor of the skin... a cadaverousness of complexion"
2. "Miraculous lustre of the eye"
3. "Gossamer texture" [of hair: soft, silky]
4. "Nervous agitation"
5. "Alternately vivacious and sullen"
6. "Voiced varied from tremulous indecision to ..."
7. "...that species of energetic concision --abrupt, weighty, unhurried, and hollow-sounding enunciation--that leaden, self-balanced, and perfectly modulated guttural utterance, which may be observed in the lost drunkard"
8. "It was, he said, a constitutional and a family evil, and one for which he despaired to find a remedy--a mere nervous affection, he immediately added, which would soon pass off"
9. "It displayed itself in a host of unnatural sensations"
10. "He suffered much from a morbid acuteness of the senses"
11. "Insipid food was alone endurable"
12. "Could wear only garments of certain texture"
13. "The odors of all flowers were oppressive"
14. "Eyes were tortured by even a faint light"
15. "There were but peculiar sounds, and these from stringed instruments, which did not inspire him with horror"
16. "Phantasmagoric conceptions ... wild fantasies"
17. "Fear"
18. "Without having noticed my presence" [oblivious to comings and goings of others]
19. "He arrested and overawed attention ... an intensity of intolerable awe"
20. "Radiation of gloom"
21. "Painted an idea...pure abstractions"

22. "Intense mental collectedness and concentration ...observable only in particular moments"
23. "Roamed from chamber to chamber with hurried, unequal, and objectless step"
24. "Sleep came not near my couch"
25. "Gazing upon vacancy for long hours, in an attitude of the profoundest attention, as if listening to some imaginary sound"
26. "Hysteria in his whole demeanor"
27. "Struggled to reason off the nervousness which had dominion over me"
28. "Irrepressible tremor gradually pervaded my frame"
29. "There sat upon my heart an incubus of utterly causeless alarm"
30. "Overpowered by an intense sentiment of horror, unaccountable yet unendurable"

In large quantities, the effect of COHb is death - known medically as carboxyhaemoglobinemia or carbon monoxide poisoning. However in smaller quantities COHb leads to oxygen deprivation of the body causing tiredness, dizziness and unconsciousness.

COHb increases risk of blood clot. It is thought that through this mechanism smoking increases the risk of having an ischemic stroke.

5.4 Carbon monoxide and Pregnancy

Carbon monoxide poisoning can have significant fetal effects. CO causes fetal tissue hypoxia by decreasing the release of maternal oxygen to the fetus, and by carbon monoxide crossing the placenta and combining with fetal hemoglobin, which has a 10 to 15% higher affinity for CO than adult hemoglobin. Elimination of carbon monoxide is also slower in the fetus, leading to an accumulation of CO. The level of fetal morbidity and mortality in acute carbon monoxide poisoning is significant, so despite maternal wellbeing, severe fetal poisoning can still occur. Due to these effects, pregnant patients

are treated with normal or hyperbaric oxygen for longer periods of time than non-pregnant patients.

6.0 CARBON MONOXIDE POISING MECHANISM

When carbon monoxide is inhaled, it takes the place of oxygen in hemoglobin, the red blood pigment that normally carries oxygen to all parts of the body. Because carbon monoxide binds to hemoglobin several hundred times more strongly than oxygen, its effects are cumulative and long-lasting, causing oxygen starvation throughout the body. When CO combines with hemoglobin in the blood it produces carboxyhemoglobin (COHb). COHb reduces the amount of oxygen in the bloodstream, inhibits blood's ability to absorb oxygen, and essentially chokes human tissue. It increases relative to the amount of CO in the air and the length of exposure.

Prolonged exposure to fresh air (or pure oxygen) is required for the CO-tainted hemoglobin (carboxyhemoglobin) to clear.

A stable gas at physiologic temperatures, carbon monoxide diffuses rapidly across the alveolar capillary membrane and binds tightly to iron centers in hemoglobin and other hemoproteins. Claude Bernard first proposed in 1865 that toxic effects of carbon monoxide resulted from the formation of carboxyhemoglobin.

The precise mechanisms by which toxic effects are induced by CO are not fully understood.

Levels of carbon monoxide bound in the blood can be determined by measuring carboxyhemoglobin, which is a stable complex of carbon monoxide and hemoglobin that forms in red blood cells. Carbon monoxide is produced normally in the body, establishing a low background carboxyhemoglobin saturation. Carbon monoxide also functions as a neurotransmitter. Normal levels of HbCO are approximately 0.8% or 0.0176 ml CO/ml blood for a non-smoker. Normal carboxyhemoglobin levels in an average person are less than 5%, whereas cigarette smokers (two packs/day) may have levels up to 9%.

Serious toxicity is often associated with carboxyhemoglobin levels above 25%, and the risk of fatality is high with levels over 70%. Still, no consistent dose response relationship has been found between carboxyhemoglobin levels and clinical effects. Therefore, carboxyhemoglobin levels are more guides to exposure levels than effects as they do not reliably predict clinical course or short- or long-term outcome.

Carbon monoxide binds to hemoglobin (reducing oxygen transportation), myoglobin (decreasing its oxygen storage capacity), and mitochondrial cytochrome oxidase (inhibiting cellular respiration).

6.1 Hemoglobin

Carbon monoxide has a significant affinity to the iron sites in hemoglobin, the principal oxygen-carrying compound in blood. The affinity between carbon monoxide and hemoglobin is 210 times stronger than the affinity between hemoglobin and oxygen.

CO binds to hemoglobin, producing carboxyhemoglobin (COHb) - the traditional belief is that carbon monoxide toxicity arises from the formation of carboxyhemoglobin, which decreases the oxygen-carrying capacity of the blood. This inhibits the transport, delivery, and utilization of oxygen. Because hemoglobin is a tetramer with four oxygen binding sites, binding of CO at one of these sites also increases the oxygen affinity of the remaining three sites, which interferes with normal release of oxygen. This causes hemoglobin to retain oxygen that would otherwise be delivered to the tissue. COHb will not release the carbon monoxide, and therefore haemoglobin will not be available to transport oxygen from the lungs to the rest of the body. However, animals, such as a human, should survive with very small amounts of COHb in their blood with very little or no observable effects.

Levels of oxygen available for tissue use are decreased. This situation is described as CO shifting the oxygen dissociation curve to the left. Blood oxygen content is actually increased in the case of carbon monoxide poisoning; because all the oxygen is in the blood, none is being given to the tissues, and this causes tissue hypoxic injury. However, despite CO affecting oxygen availability, other mechanisms may contribute to the crucial effects of CO poisoning.

Hemoglobin acquires a bright red color when converted to carboxyhemoglobin, so a casualty of CO poisoning is described in textbooks as looking pink-cheeked and healthy. However, this "classic" cherry-red appearance is not always seen — in one study it was noted in only 2% of cases — so care should be taken not to overlook the diagnosis even if this color is not present.

COHb has a half-life in the blood of 4 to 6 hours.

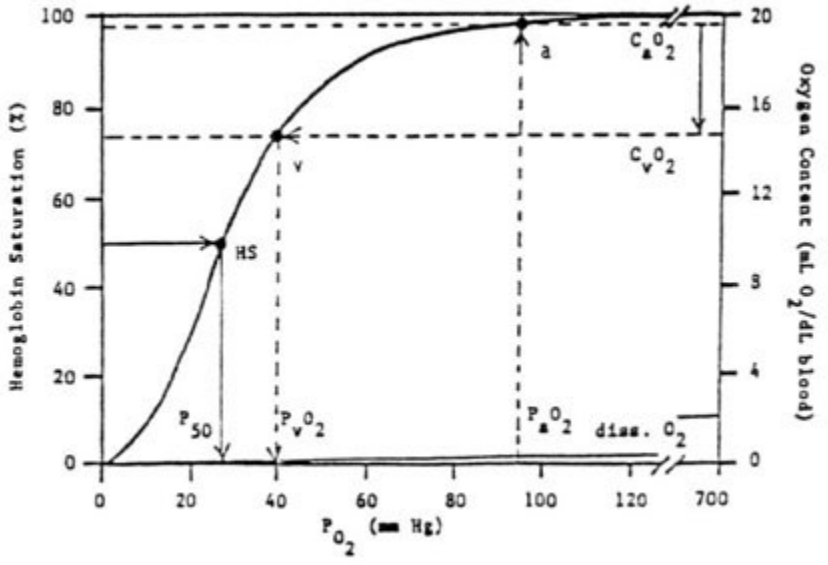
Carboxyhemoglobin decreases the blood oxygen content and hinders the allosteric release of oxygen from hemoglobin to tissues. In patients with severe poisoning, carboxyhemoglobin compromises the delivery of oxygen to tissue and leads to tissue hypoxia and its immediate functional implications, especially for organs with high oxygen demands such as the brain and the heart.

Although an elevated carboxyhemoglobin level is a diagnostic sine qua non of poisoning, it does not predict the severity of clinical signs and symptoms, particularly those affecting the brain. This poor correlation between carboxyhemoglobin levels and neurologic presentation, which has long been recognized, is related to unmeasured tissue uptake of carbon monoxide, which increases during hypoxia because of competition between carbon monoxide and oxygen at the oxygen-binding sites on hemoproteins (see Figure). After cellular uptake of carbon monoxide, nonhypoxic mechanisms, including reoxygenation injury, contribute to pathogenesis.

Carbon monoxide and hemoglobin form carboxyhemoglobin, displacing oxygen and leading to tissue hypoxia. As the partial pressure of oxygen (PO_2) in tissue falls, the amount of carbon monoxide entering the tissues and binding to cell hemoproteins, such as myoglobin and cytochrome oxidase, increases, interfering with their function. After the exposure and during treatment with oxygen, a higher partial pressure of oxygen in the lung and vascular space causes the carboxyhemoglobin level to decrease faster than the level of carbon monoxide bound in tissues, where the partial pressure of oxygen is lower. Thus, the carboxyhemoglobin level may not correlate with the clinical presentation of the patient.

Many errors in clinical medicine revolve around the misunderstanding of COHb - physicians more often than not fail to diagnose CO poisoning when it is actually present. Many more errors in forensic medicine revolve around the misunderstanding of COHb - physicians and others order COHb tests too late, which are certain to show low/normal COHb levels when people have obviously been exposed to CO. The litigation of CO poisoning cases in many instances is thwarted or crippled by a misunderstanding of COHb.

The Oxyhemoglobin Dissociation Curve is depicted in the following diagramme.



The amount of O_2 carried by hemoglobin is a curvilinear function of PO_2

- Sigmoidal curve reflects the four-stage loading of oxygen
- Oxygen loading (lungs) occurs over flat portion of curve
- Oxygen unloading (tissues) occurs over steep portion of curve

Important relationships

- Oxygen capacity (mL O_2/dLblood) =
  (1.36 mL O_2/gram Hb) * (15 gram Hb/dLblood)
- Oxygen content (mL O_2/dLblood) =
  Hb saturation (%) * oxygen capacity (mL O_2/dLblood)
- P50 is the PO_2 corresponding to 50% saturation of Hb
  (half-saturation point = 27 mm Hg)
- CaO_2 - CvO_2 represents the total amount of O_2 extracted
  (mL O_2/dLblood) body wide

Total O_2 content in the blood computes as the sum of O_2 bound to hemoglobin (HbO_2) and O_2 dissolved

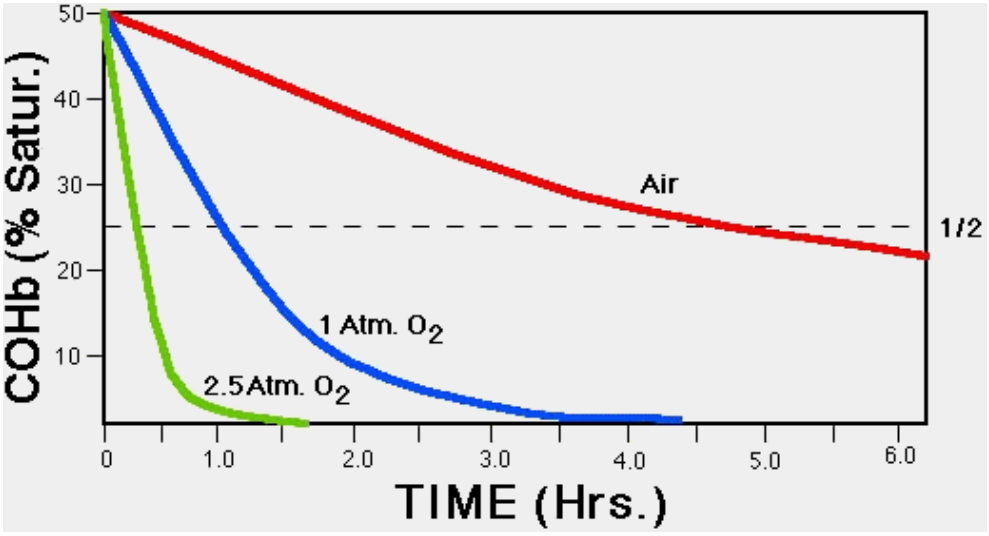
- At PO_2 < 333 mm Hg, O_2 dissolved can be ignored
  (< 1 mL O2/dL is insignificant)
- At PO_2 > 333 mm Hg, O_2 dissolved cannot be ignored
  (> 1 mL O2/dL is significant)

Carbon monoxide is highly toxic, with a rated tolerance level of 50 ppm in air, and can have cumulative effects. COHb has a short 1/2-life in the body, 4-6 hours. Half is gone in 4-6 hours; in most cases the blood CO level is back to background in 24 hours.

Blood oxygen tension is a determinant of the rate of carboxyhemoglobin elimination. This is summarized in the following Table.

% Oxygen	Time (min)
21 (room air)	240-300
80	80-100
100	50-70
100 (at 3 atm)	20-25

Like CO uptake, loss of CO from the body is a slow process at normal atmospheric pressure and concentration of oxygen (21%), with a time to 1/2 the starting concentration of approx. 4.5 hours. CO removal can be speeded up by raising the oxygen concentration, as with bottled gas containing greater fractions of oxygen, or by placing the victim in a pressure chamber where he/she can be treated with oxygen partial pressures of over 2000 mmHg for 30-120 minutes, called hyperbaric oxygen therapy (HBO). This increases the amount of oxygen dissolved in the blood plasma and forces CO off the hemoglobin, allowing it to carry oxygen once again.

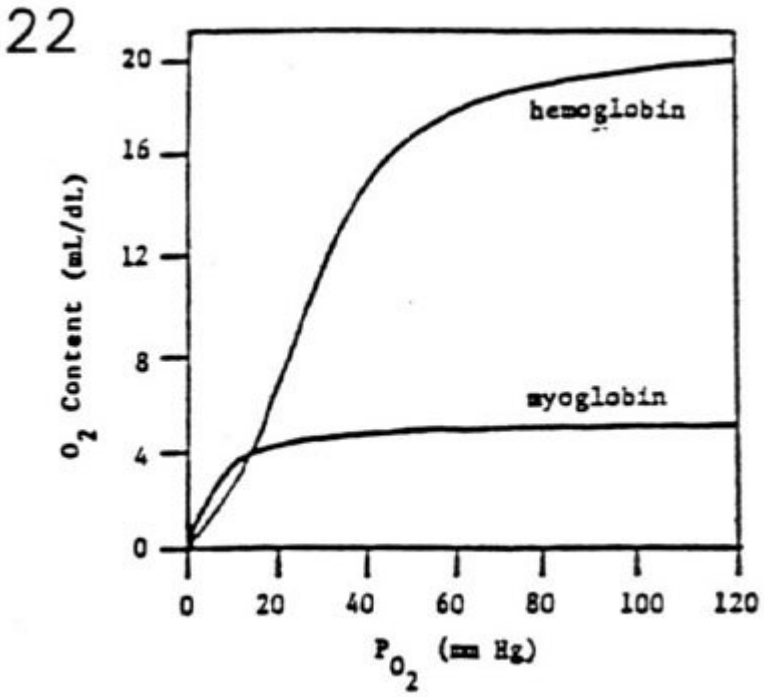


CO Elimination Time Chart under Different O_2 Pressures

6.2 Myoglobin

Carbon monoxide also has a high affinity for myoglobin. CO bound to myoglobin may impair cardiac output and result in cerebral ischemia. A delayed return of symptoms has been reported and appears to result following a recurrence of increased carboxyhemoglobin levels; this effect may be due to late release of CO from myoglobin, which subsequently binds to hemoglobin.

The Myoglobin Dissociation Curve is depicted in the following graph.



Myoglobin is a muscle protein with oxygen carrying characteristics

- each myoglobin molecule has one site for reversible oxygen binding
- hyperbolic curve reflects one-stage loading of oxygen
- P50 of 5 mm Hg indicates high oxygen affinity at low PO2 values

Myoglobin provides an important source of O2 for exercising muscle

6.3 Cytochrome oxidase

A second mechanism involves co-effects on the mitochondrial respiratory enzyme chain that is responsible for effective tissue utilization of oxygen. CO does not bind to cytochrome oxidase with the same affinity as oxygen, so it likely requires significant intracellular hypoxia before binding. This binding interferes with aerobic metabolism and efficient adenosine triphosphate (ATP) synthesis. Cells respond by switching to anaerobic metabolism, causing anoxia, lactic acidosis, and eventual cell death.

6.4 Other mechanisms

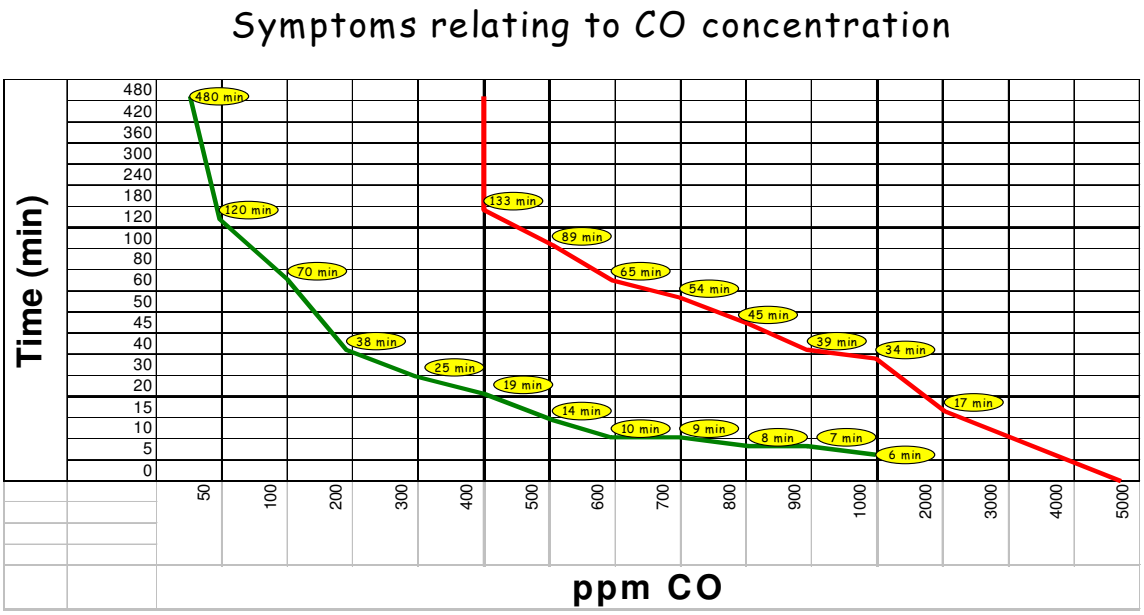
Another mechanism that is thought to have a significant influence on delayed effects involves formed blood cells and chemical mediators, which cause brain lipid peroxidation.

CO causes endothelial cell and platelet release of nitric oxide, and the formation of oxygen free radicals including peroxynitrite. In the brain, this causes further mitochondrial dysfunction, capillary leakage, leukocyte sequestration, and apoptosis. The end result is lipid peroxidation (degradation of unsaturated fatty acids), which causes delayed reversible demyelinization of white matter in the central nervous system, and can lead to edema and focal areas of necrosis within the brain. This brain damage occurs mainly during the recovery period and results in cognitive defects (especially affecting memory and learning) and movement disorders. The movement disorders are related to a predilection of CO to damage the basal ganglia. These delayed neurological effects may develop over days following the initial acute poisoning.

7.0 CONTROL OF CO

No employee should be allowed to conduct any work in a CO-area unless continuous monitoring is conducted.

Guidelines with regard to the time exposure to CO are provided. As an alternative, employees should only enter the CO-area with a Breathing Apparatus (BA-set).



Area	Symptoms of Exposure
Below GREEN line	None
Between GREEN & RED line	Headache, Nausea, Drowsy, Vomiting, Collapse
Above RED line	Coma, Brain damage, Death

Once an exposure scenario reach es the GREEN line (within a 24 hr period), further work in CO areas may only continue provided a BA set is used.

Figure 2: Exposure time and CO exposure

A policy should be compiled specifically addressing the management of CO. The policies should cover at least the following aspects:

1. Overview
2. Policy Statement
3. Procedures/Protocol/Equipment

3.1 Medical surveillance

8.0 TREATMENT AND PROTOCOLS

8.1 Biomarkers

There are several biomarkers capable of identifying the impaired oxygen delivery associated with CO exposure and tracking its response to 100% oxygen treatment. Qualitatively, a ***SPECT scan of the brain*** shows the most dramatic evidence of decreased blood flow in various areas of the brain that all improve with oxygen treatment. Unfortunately, high-resolution 3-camera SPECT scans are hard to find and expensive, with scans costing thousands of dollars each and most health insurers unwilling to pay for them.

Quantitatively, and much less expensively, one can order standard arterial and venous blood gases to compare the ***partial pressure of oxygen in venous blood*** (PvO_2) with that of oxygen in arterial blood (PaO_2). PaO_2 is usually normal or low-normal in cases of CO poisoning but PvO_2 is abnormally high, indicating substantial impairment of oxygen delivery from arterial blood plasma into tissue. Venous blood for the PvO_2 analysis should be drawn at the elbow without a tourniquet. The optimum PvO_2 level in healthy non-smoking adults is about 25mm Hg, while levels in CO poisoning (and CFS/FMS/MCS) patients are commonly in the range of 30 to 50. The optimum atereo-venous gap is 70 to 60mmHg: a smaller $P(a\text{-}v)O_2$ gap is clear evidence that oxygen delivery to tissues and/or its uptake is impaired.

For screening adults, the fastest, least invasive and least expensive biomarker to assess is the concentration (in ppm) of ***CO in exhaled breath***, which measures the total rate of CO excretion from all sources and correlates closely with COHb in healthy controls. This is commonly measured in smoking cessation clinics and some emergency rooms using handheld, battery powered, electro-chemical CO sensors with digital readouts designed for this purpose (see Resources, below). Because a 23-second breath hold is optimal (to allow time for CO exchange in the lungs), this test is not easily done by young children or people with significant respiratory impairments. In normal healthy adults, breath CO levels range from 0-6ppm, while smokers range from 7ppm

(after 24 abstinence) to over 70ppm (immediately after smoking). Elevated levels may be due to exogenous CO poisoning but are also associated with a variety of chronic diseases, including asthma, bronchitis, cystic fibrosis and diabetes. The amount of CO exhaled also increases when breathing enriched oxygen, so recording this immediately before and after 100% oxygen treatment provides a simple way to quantify the impact of each session on CO elimination.

Most commonly measured but least helpful is the ***carboxyhemoglobin level*** that gives the percent of hemoglobin (Hb) binding sites occupied by CO, arterial and venous COHb are the same because CO binds so tightly to Hb). The CO bound to Hb is much less active biologically than the CO that is less tightly bound to other heme proteins such as myoglobin and cytochromes or that circulating freely in blood plasma. Although COHb is usually significantly elevated in the hours immediately following an acute high level CO exposure--with minor symptoms starting around 10% COHb according to most textbooks–it usually normalizes within a few days of exposure (if not fatal) because the biological half life of COHb is only 4 to 6 hours. COHb levels measured weeks and months after a single acute CO exposure are usually normal (under 2% for non-smokers, under 10% for smokers) and rarely correlate with any residual chronic symptoms. ***So while a high COHb level confirms significant exposure to one or more sources of CO, a normal value cannot rule out chronic low-level exposure***. The symptoms in chronic cases are more likely due to the myriad effects of CO in other more biologically active pathways (binding with cytochromes, for example) than to its interference with oxygen-binding on hemoglobin.

COHb can adjust to great variation in CO exposure and oxygen demand, although it may take weeks to habituate to new conditions. This is evident in how long it takes non-smoking coast dwellers to habituate to the lower oxygen pressures found at high altitudes compared to smokers, whose higher COHb levels are more like those of people who live at high altitude year round and who are more aerobically fit in such low-oxygen environments than visitors with lower COHb levels.

8.2 First aid

First aid for carbon monoxide poisoning is to immediately remove the victim from the exposure without endangering oneself, call for help, and apply CPR if needed. The main medical treatment for carbon monoxide poisoning is breathing 100% oxygen by a tight fitting oxygen mask. Oxygen hastens the dissociation of carbon monoxide from hemoglobin, improving tissue oxygenation by reducing its biological half-life. Hyperbaric oxygen is also used in the treatment of CO poisoning; hyperbaric oxygen also increases carboxyhemoglobin dissociation and does so to a greater extent than normal oxygen. Hyperbaric oxygen may also facilitate the dissociation of CO from cytochrome oxidase.

A significant controversy in the medical literature is whether or not hyperbaric oxygen actually offers any extra benefits over normal high flow oxygen in terms of increased survival or improved long term outcomes. There have been clinical trials in which the two treatment options have been compared; of the six performed, four found hyperbaric oxygen improved outcome and two found no benefit for hyperbaric oxygen. Some of these trials have been criticized for apparent flaws in their implementation. A recent robust review of all the literature on carbon monoxide treatment concluded that the role of hyperbaric oxygen is unclear and the available evidence neither confirms nor denies a clinically meaningful benefit. The authors suggested a large, well designed, externally audited, multicentre trial to compare normal oxygen with hyperbaric oxygen.

Further specific treatment for other complications such as seizure, cardiac abnormalities, pulmonary edema, and acidosis may be required. The delayed development of neuropsychiatric impairment is one of the most serious complications of poisoning, with extensive follow up and treatment often being required.

8.3 General

It is the best that blood is drawn for COHb measurements within a few hours leaving the site in susspected CO poisoning.

If you, your furnace maintenance man, your physician, etc. suspect you have been exposed to CO, INSIST that blood be drawn immediately **(venous will be as good as arterial blood** and it is a lot less painful to obtain). Once drawn, blood for COHb assay can be stored for days/weeks without loss of testing accuracy. If medical personnel or others tell you the draw time can be delayed, they are wrong! Refer them to this website and the Webmaster for re-education.

Attempt to keep track of exactly how long it was from the time you left the site of the CO exposure until your blood was drawn. Second: keep track of how long and when were given 100% oxygen by EMS or ER physicians before blood was drawn. While this may be challenging if you are in an altered state of consciousness from the CO, the numbers are invaluable later in re-constructing your t_o COHb concentration.

Breathlyzer Equipment can be used to determine blood COHb level with great accuracy. The test does not require that blood be drawn.

Pulse Oximeters, as found in EMS vans and in hospital ERs, should not be use to determine whether you have abnormally high levels of CO in your blood. They lie!

There are many **reasons why Carboxyhemoglobin may be unexpectantly low**.
* If the blood is drawn many hours after leaving the site of the poisoning, it may be possible to back-calculate to determine the COHb level at t_o. This depends on the length of time (number of 1/2 lives) between time of blood draw and t_o, and on the difference in COHb between the measured value and background COHb value.

8.4 Hyperbaric treatment

The cornerstone of treatment for carbon monoxide poisoning is supplemental oxygen, which hastens the dissociation of carbon monoxide from hemoproteins in direct relation to the partial pressure of oxygen. Hyperbaric oxygen at a pressure of 2.5 to 3.0

atmospheres absolute, with which an arterial partial pressure of oxygen above 1800 mm Hg can be achieved, greatly facilitates carboxyhemoglobin dissociation as compared with normobaric oxygen at sea level. In experimentally induced carbon monoxide poisoning, hyperbaric oxygen also benefits the brain more than normobaric oxygen does, by improving energy metabolism, preventing lipid peroxidation, and decreasing neutrophil adherence.

Whether to use hyperbaric oxygen clinically and, if so, when to use it are matters that have been debated since it emerged as a treatment for carbon monoxide poisoning in 1960. Practice guidelines were developed on the basis of clinical experience and inferences of efficacy in uncontrolled studies. Results of past controlled trials comparing hyperbaric-oxygen and normobaric-oxygen therapy have been inconclusive because of methodologic difficulties. However, in this issue of the *Journal,* Weaver et al. (pages 1057–1067) clearly demonstrate, in a carefully designed, double-blind, randomized trial involving 152 patients, that hyperbaric-oxygen therapy at 3 atmospheres absolute is superior to normobaric-oxygen therapy in reducing the incidence of cognitive dysfunction at 6 weeks and 12 months after acute carbon monoxide poisoning.

These findings strengthen the rationale for hyperbaric-oxygen therapy in patients with acute carbon monoxide poisoning, but important clinical issues remain. First, we need better predictive tests or criteria for determining the risk of delayed and permanent effects of carbon monoxide poisoning. Second, practical questions remain concerning optimal hyperbaric-oxygen regimens — for example, the optimal number of treatments and the maximal delay after which hyperbaric oxygen is no longer useful. Most trials have enrolled patients as soon as possible after poisoning, yet Weaver et al. leave open the question of whether some patients benefit from hyperbaric oxygen after the often-quoted therapeutic window of 6 to 12 hours. A third unresolved issue is that of mild carbon monoxide poisoning: how should patients who do not need hyperbaric-oxygen therapy be treated? Many practitioners recommend six hours of 100 percent normobaric oxygen delivered by face mask, although the efficacy of this treatment has not been validated. Finally, it must be emphasized that neither hyperbaric oxygen nor any other

therapy can be expected to prevent cognitive deficits due to cell death sustained during the episode of poisoning. Therefore, prevention remains a vital public health issue.

For the treatment of chronic low-level CO poisoning evidenced by high PvO_2 (regardless of COHb level), MCS Referral & Resources recommends ***Extended Normobaric Oxygen Therapy (ENOT)***. **Three to four months of daily 2-hour sessions breathing 100% oxygen from a tank or concentrator while supine via a nasal canulus at 6 to 10 liters per minute are usually sufficient to normalize PvO_2 and obtain lasting relief from the most common symptoms of chronic CO poisoning.** ENOT is less expensive and more widely available than hyperbaric oxygen, which is the recommended treatment for acute CO cases (for information on this option, contact the Undersea & Hyperbaric Medicine Society, 301-942-2980). ENOT has fewer risks of adverse side effects than hyperbaric therapy and may be carried on by the patient at home after training by a respiratory therapist. Both Medicare and private insurers are usually willing to pay for home delivery of supplemental oxygen regardless of the source (compressed O_2, liquid O_2 or concentrator O_2) as long as the need is documented and consistent with a diagnosis of CO poisoning. This protocol has not been evaluated in children (whose normal PvO_2 range is unknown) but they clearly are more sensitive to both CO and 100% oxygen.

8.5 ENOT Indications

This protocol was developed for treating adults with at least 5 of the 10 most common symptoms of CO poisoning listed above (usually including chronic fatigue, sensory changes and cognitive dysfunction) who also have an abnormally elevated partial pressure of oxygen in venous blood. When drawn from the antecubital fossa without a tourniquet, the optimal PvO_2 in healthy controls is about 25mmHg, so any PvO_2 over 30, or a $P(a\text{-}v)O_2$ gap of less than 60, may be considered abnormal. These admittedly arbitrary cutoffs are primarily for research purposes, however, and need not be strictly followed in clinical practice, where physicians may want to consider other factors in assessing the potential risks vs. benefits of oxygen treatment. Since PaO_2 is rarely

significantly decreased in CO cases and more painful to obtain than venous samples, arterial testing may be omitted unless documentation of the arterial-venous oxygen gap is needed.

Regardless of the initial PvO_2 level, this should be rechecked weekly or biweekly during treatment. Daily oxygen should continue until PvO_2 either falls below normal (25mmHg) and stays there or stops falling for two successive measurements. Of course, if a patient is still reporting subjective improvements at this point without adverse side effects, the treatments may be continued until the patient no longer reports any additional benefit or need. While no long-term studies have yet been done, anecdotal reports suggest PvO_2 levels remain in the normal range and substantial symptom relief persists for months with no need for further daily oxygen treatment. However, physicians should consider prescribing a continuing supply of oxygen for use as needed to relieve symptoms of any new CO exposures (most insurance covers oxygen "as needed" for migraine if not for CO).

8.6 ENOT Contraindications

Extended normobaric oxygen therapy should not be attempted in anyone who has reacted poorly to 100% oxygen in the past. When first trying 100% oxygen, patients should be monitored closely by their physician for sudden or dramatic changes in heart rate, respiration, blood pressure and any reports of adverse effects associated with oxygen toxicity (especially any respiratory, neurologic or sensory complaints). If no adverse reactions are noted, patients may be taught how to continue daily treatments at home on their own, with a warning that they should immediately discontinue treatment and notify their physician if they notice any poorly-tolerated effects.

8.7 Medications, Supplements and Diet

Although no medications are needed to supplement extended normobaric oxygen therapy, the treatment theoretically works best if the patient's exposures to CO are

minimized. This requires reducing exposures not just to exogenous CO but also to all the many types of physical, biological, chemical and mental stresses that increase endogenous CO production (via stress-induced HO-1 catabolism of heme). Since medications and supplements are a source of chemical stress and poorly tolerated by most people with chronic CO poisoning and related syndromes (Autism, ADHD, CFS, FMS, MCS etc), the protocol urges doctors to consider weaning their patients off all non-essential supplements and medications prior to starting ENOT (including anti-depressants except in potentially suicidal cases). While many of these patients have significant deficiencies in vitamins (particularly the B series), minerals (particularly magnesium and zinc) and hormones (particularly thyroid), we recommend testing for but not treating these deficiencies until PvO_2 has been normalized and the oxygen therapy concluded, as some may self-correct with the improved oxygenation of tissue that ENOT provides. The only exception is for buffered vitamin C or some other buffered anti-oxidant, which should be taken daily during oxygen treatment to boost the body's ability to deal with the free radicals formed by oxidative metabolism.

Low plasma volume should be treated concurrently with high water consumption (at least one glass per hour except when sleeping). Since chlorinated water, alcohol, caffeine and processed foods are all common sources of chemical stress in these patients, they should be avoided as much as possible during the oxygen treatment. If food intolerances have not already been identified and eliminated, this should be done with a rotation diet prior to starting ENOT. After their PvO_2 normalizes, patients may try reintroducing a broader range of foods one at a time.