CARBON MONOXIDE POISONING

INTRODUCTION

Carbon monoxide (CO) is sometimes called the silent killer, and aptly so. It is a gas that is produced by incomplete combustion of carbon-containing material, it is colorless, odorless, and tasteless and high concentrations of CO in the environment can be lethal. Despite large-scale public education and prevention programs, CO exposure is still a serious public health problem. The pathophysiology, clinical effects, and the best methods for treating CO poisoning have been intensively studied, but much about what CO does and how to treat CO poisoning is still unknown and controversial.

OBJECTIVES

When the student has finished this module, he/she will be able to:

1. Identify the source/cause of most CO exposures.
2. Identify two pathological processes responsible for neurological effects of CO.
3. Identify two ways that CO interferes with oxygen delivery.
4. Identify two ways that CO interferes with oxygen utilization.
5. Identify the relationship between COHb levels and the effects of CO poisoning.
6. Identify three organs susceptible to CO poisoning and the reason why.
7. Identify why it can be difficult to detect CO poisoning.
8. Identify demographic and health factors that increase susceptibility to CO.
9. Identify a delayed clinical effect of CO poisoning and how to identify those at risk.
10. Identify three clinical signs and symptoms of CO poisoning.
11. Identify the important aspects of interpreting a COHb level.
12. Identify the basic treatment/diagnostic tests needed for patients with CO poisoning
13. Identify a common reason why CO poisoning might not respond to oxygen.
14. Identify the rationale for the use of hyperbaric oxygen therapy.
15. Identify two side effects of hyperbaric oxygen therapy.

EPIDEMIOLOGY

As mentioned in the introduction, despite increased public awareness of the dangers of CO and better and more widespread prevention measures, CO poisoning is still very, very common. Many sources consider CO poisoning to be among the leading causes of poisoning deaths in the United States and CO poisoning is perhaps the number one cause of death by poisoning worldwide.\textsuperscript{1,2,3} Carbon monoxide is produced by the incomplete combustion of carbon-containing material, so automobile exhaust and home heating and/or cooking systems (e.g., oil, gas, coal, wood) are common sources of CO and the most common causes of CO poisoning. One unusual source of CO is methylene chloride. Methylene chloride is a chemical that is used in paint strippers, and the inhaled vapor of methylene chloride is converted in vivo to CO. Because it is stored in fat tissues and the metabolizing enzymes are quickly saturated, peak CO levels produced by methylene chloride inhalation are seen 8 hours or longer after an exposure.
CARBON MONOXIDE: PATHOPHYSIOLOGY

The pathophysiology of CO poisoning involves many complex processes.

- **Hemoglobin binding:** Carbon monoxide binds avidly to hemoglobin: it has an affinity for hemoglobin that is 200-250 times greater than that of oxygen.\(^4\) When oxygen is displaced from hemoglobin by CO and the binding sites for oxygen on hemoglobin are occupied by CO, CO and hemoglobin combine to form carboxyhemoglobin (COHb).

- **Oxygen transfer:** Although CO displaces oxygen from hemoglobin, some oxygen will still be bound to hemoglobin. However, the presence of COHB increases the binding of the oxygen that remains attached to hemoglobin. The oxyhemoglobin dissociation curve shifts to the left and this contributes to tissue hypoxia.

**Learning Break:** The oxyhemoglobin dissociation curve indicates how saturated hemoglobin is at any particular level of oxygen tension of the blood and how tightly hemoglobin “holds on” to oxygen (\(P_{O_2}\)). When the curve is shifted to the left, the amount of oxygen attached to hemoglobin that can be released to the tissues decreases. One of the driving forces behind the release of oxygen to the tissues from hemoglobin is the difference in the oxygen needs and saturation of tissues and the amount of oxygen attached to hemoglobin that can be released. When this difference is greatly decreased – as it is with CO poisoning – tissue hypoxia is the result.

For many years, the tissue hypoxia caused by CO binding to hemoglobin and the decreased release of oxygen from hemoglobin were thought to be the critical pathophysiological processes that caused the signs and symptoms of CO poisoning. These are critically important, but there are other ways that CO causes damage.\(^5-8\)

- **Binding to myoglobin:** Myoglobin is an oxygen-transporting and storage pigment that is found inside cells. Carbon monoxide binds to myoglobin – particularly in the myocardium – thus preventing oxygen utilization.

- **Interference with oxidative phosphorylation:** Carbon monoxide binds with mitochondrial cytochrome oxidase, an important enzyme that is needed for proper functioning of the electron transport chain in cellular respiration that produces the bulk of the ATP needed by the body.

- **Vasodilation:** Carbon monoxide increases the formation of cyclic guanosine monophosphate (a second messenger similar to cAMP) and causes the release of nitric acid from platelets and the vascular endothelium. Cyclic guanosine monophosphate and nitric oxide are potent vasodilators, blood is pooled in the vascular bed, and this decreases oxygen delivery to the tissues.
• Free radical formation: High levels of nitric oxide initiate the formation of free radicals, and the tissue damage that is caused by poor perfusion stimulates an inflammatory response and free radical formation. The result is a reperfusion injury that affects the brain.

• Lipid peroxidation: Carbon monoxide poisoning causes lipid peroxidation. Lipid peroxidation refers to damage caused by free radicals to the lipids that are an integral part of cell membranes. This process is thought to be one of the causes of the neurological effects of CO poisoning.

• Leukocyte-mediated inflammation: There is evidence that the oxidative stress induced by free radicals causes neutrophils to adhere to cerebral microvasculature. The result is an inflammatory process that may be the cause of the acute and delayed neurological damage that is a common feature of CO poisoning.

Learning Break: Carbon monoxide is an endogenous compound produced by the breakdown of hemoglobin. It has multiple functions – neural messenger, vasodilation – in normal physiology. In certain circumstances, CO also appears to have anti-oxidant, anti-inflammatory, and other beneficial activities, and there is a lot of research that is being conducted investigating the use of CO as a therapeutic tool.

The mechanisms by which CO poisoning produces signs and symptoms are complex and still not completely understood. Research is ongoing and there are probably other ways that CO causes harm. However, the basic effects of CO poisoning are a) decreased oxygen delivery, b) decreased oxygen utilization, and c) direct toxic injuries to the tissues.

ARE YOU CARING FOR A PATIENT WITH CO POISONING?

The signs and symptoms of CO poisoning are vague, non-specific and often mild (e.g., a slight headache, weakness, dizziness, etc.). Mild CO poisoning can be easily misdiagnosed as influenza, gastroenteritis, food poisoning, influenza, or a migraine headache. Awareness of the situations and circumstances that can cause CO poisoning is the best way to detect CO poisoning in mild cases or when it not obvious or reported that CO poisoning has occurred. If you suspect CO poisoning or want to determine if CO poisoning has occurred, ask the patient these questions.

• Where were you when you began to feel sick? If you were at home, was the heating system on? If these signs and symptoms have occurred before, do they only happen when you are at home? Do they improve when you are out of the house?
• Who do you live with? Has anyone else been sick? If the patient is living with other people, but no one else is sick CO exposure is unlikely.
• Has your heating system, water heater, etc., and the exhaust systems and chimneys in your house been checked recently?
- Do you get sick when you are driving your car? Do your symptoms improve after you leave the car? Has your car’s exhaust system been inspected recently?
- Do the symptoms happen while you are at work? If so, what does the patient do, and what is happening at work when he/she gets sick? Does the patient work inside? If so, are there obvious sources of CO, e.g., mechanics working in a poorly ventilated garage, or is the patient working in a building where gas-powered or gasoline-powered machinery is operating?
- Have you been stripping furniture?
- If there is more than one patient and everyone has essentially the same signs and symptoms, did everyone get sick at the same time (possible CO poisoning) or did the illness start with one person and seem to spread to the others (possible infectious illness).

**SIGNS AND SYMPTOMS OF CARBON MONOXIDE POISONING**

Carbon monoxide poisoning can be difficult to detect because the symptoms may be mild and even in severe cases they are non-specific. Also, the number and intensity of the signs and symptoms of CO poisoning is not always related to the COHB level. Patients with “low” levels may be sicker than patients with “high” levels. If there is no obvious or known exposure to CO, a mild CO exposure can be overlooked or misdiagnosed as a viral illness or some other clinical condition.

**Learning Break:** Remember: Awareness of the situations and circumstances that can cause CO poisoning is the best way to detect CO poisoning in mild cases or when it not obvious or reported that CO poisoning has occurred.

Because CO impairs oxygen delivery and utilization, organs that are very metabolically active – the brain, the heart, the kidneys – suffer the most from exposure to CO. The heart and the brain can be damaged because CO has direct toxic effects on those organs. The elderly, children, people with anemia, cardiovascular disease, or pulmonary disease, and people who smoke have a higher risk of developing CO poisoning than do healthy individuals who are not very young or very old.

The signs and symptoms of CO can be mild or severe, and the severity of any particular case depends on the duration of exposure, the concentration of CO in the air, and the age and health status of the victim. Toxic effects that are possible include:

- Arrhythmias
- Cardiogenic pulmonary edema
- Coma
- Confusion
- Death
- Delayed neurological sequelae
- Dizziness
- Dyspnea
- Flu-like signs and symptoms
- Headache
• Hypotension
• Lactic acidosis
• Myocardial damage
• Myocardial ischemia
• Nausea
• Rhabdomyolysis
• Seizures
• Tachycardia
• Tachypnea
• Vomiting

PERSISTENT AND DELAYED NEUROPSYCHIATRIC SEQUELAE

Many patients with CO poisoning recover completely if they are promptly removed from the source of CO and treated with oxygen and supportive care. However, serious neurological effects are relatively common. Some patients develop neurological signs and symptoms immediately after the exposure, but some patients have an asymptomatic period of days to months and then develop neuropsychiatric sequelae, and this is one of the most serious complications of carbon monoxide poisoning. Complete recovery is possible and most patients do recover, but severe and permanent affective, cognitive, and motor impairments happen, as well.

• Incidence: Neuropsychiatric sequelae appear to be very common and can occur in up to 50% of all patients with a high level of CO. The exact incidence is unknown because the criteria for toxic levels of CO and the criteria used to define, and the testing used to detect and measure neuropsychiatric sequelae are not universal. The incidence of delayed neuropsychiatric sequelae has been estimated to be 2.8%, 14.4%, 30%, and 58%.

• Onset: Neuropsychiatric signs and symptoms can occur immediately after the exposure, but a delayed onset is common: this can be from several days to several months, and the mean time from exposure to the onset of signs and symptoms has been reported to be 4 weeks.

• COHb levels and signs/symptoms: There does not seem to be a correlation between COHb levels and the development of immediate or delayed onset neuropsychiatric sequelae. Patients who are comatose often do, but may not develop neuropsychiatric sequelae, and patients who have not lost consciousness may develop serious neurological problems. Some factors that seem to be consistently associated with an increased risk of developing neuropsychiatric sequelae are age > 36 and a duration of exposure > 24 hours. A more recent study indicated that duration of exposure > 6 hours, seizures, a Glasgow Coma Score < 9, leukocytosis, and elevated CK, or a systolic blood pressure < 90 mm Hg may be factors that predict the development of delayed neurological sequelae.
The signs and symptoms of neuropsychiatric sequelae are divided into affective, cognitive, and motor impairments. Affective impairments that have been reported include anxiety, depression, irritability, and mood swings. Cognitive effects that have been reported include deficits in attention, concentration, memory, and speech, and dementia. Motor impairments that have been reported include chorea, dystonia, incontinence, myoclonus, and parkinsonism signs such as bradykinesia, rigidity, shuffling gait, etc. The neuropsychiatric sequelae can be mild but they can also be profound and disabling. Most patients recover within 3-6 months, but some do not and the older the patient the less likely it is that he/she will recover.

Learning Break: Because COHb levels and signs and symptoms cannot be used to predict which patients are at risk for developing delayed onset neuropsychiatric sequelae, all patients with CO poisoning must be treated as if these effects might happen. Delayed neurological sequelae can occur even in cases of “mild” CO poisoning.

**THE CARBOXYHEMOGLOBIN LEVEL**

The normal level of COHb is 1%-2% in non-smokers. Tobacco combustion produces CO so smokers have COHb levels of 5%-10%. There is a linear correlation between the level of inspired CO and COHb levels, but COHb levels do not correlate well or consistently with the severity of signs and symptoms. This may be because the amount of COHb in the blood does not accurately represent the amount of CO in the tissues. Most people begin to feel ill when their COHb level is 10%-15% or when the CO concentration of the ambient air is > 100 ppm. (Note: The Occupational Safety and Health Administration recommended limit for the workplace is an average of 25 ppm over an 8 hour work day). A COHb level > 25% is generally considered to be serious.

Carbon monoxide is rapidly absorbed. Elimination depends on several factors but the rate of dissociation of COHb is directly proportional to the percentage of inhaled oxygen, so the more oxygen that can be delivered, the faster COHb will be eliminated. The half-life of CO when someone is breathing room air is approximately 4-6 hours, it is approximately 60 minutes when someone is breathing 100% oxygen, and it is approximately 15 minutes if someone is treated with hyperbaric oxygen. When you are interpreting COHb levels, you must always take into account a) how long the patient has been away from the source, and b) how long the patient has been receiving oxygen and how much oxygen he/she has been receiving. A COHb level can be performed on arterial or venous blood. The specimen does not need to be refrigerated or placed in ice.

There are pulse oximeters that can distinguish between oxyhemoglobin and COHb, but some cannot, so you must know the capabilities of the unit you are using. The oxygen saturation measurement of an arterial blood gas is not useful, either, as the saturation is calculated from the PO\(_2\) and the PO\(_2\) is calculated from the oxygen dissolved in plasma, not the oxygen that is bound to hemoglobin. The PO\(_2\) will be normal because it measures the amount of oxygen dissolved in blood and only indirectly provides information on the amount of oxygen attached to hemoglobin.
**Learning Break:** Home CO detectors are designed to alarm depending on concentration and time, e.g., it takes 1-4 hours for the alarm to sound if the level is = 70 ppm, and the unit should alarm within 4-15 minutes if the level is = 400 ppm.

### TREATMENT OF CARBON MONOXIDE POISONING

Treating a case of CO poisoning begins by removing the patient from the source, assessing the ABCs, and assessing the patient’s neurological status. If the patient has suffered a cardiac arrest, is comatose, or is having a seizure or an arrhythmia, administer oxygen in the highest concentration possible and provide basic, supportive care.

**Learning Break:** There are specific therapies that can be used to treat the serious and/or life-threatening complications of CO poisoning that were mentioned above, **but the best initial treatment is high concentration oxygen and basic supportive care.**

If the patient has normal ABCs and no serious signs and symptoms, make sure he/she is receiving high-concentration oxygen, start continuous cardiac monitoring, obtain a 12-lead ECG, and obtain an arterial blood gas, a serum lactate level, and a COHb level. Do **not** withhold high-concentration oxygen if the patient has chronic obstructive pulmonary disease and retains CO$_2$. Consider obtaining blood urea nitrogen (BUN) level, a serum creatinine level, a CK-MB level, a troponin level, and a serum creatinine phosphokinase level. Computed tomography (CT) or magnetic resonance imaging (MRI) scanning of the head should be performed if the patient has any neurological deficits. Perform a basic neurological assessment.

**Learning Break:** Be very careful to document when the patient was last exposed to CO, when and at what percent/flow oxygen therapy was started, and when the COHb level was obtained. These facts will be very important in terms of assessing the severity of the case, the patient’s response to therapy, and the possible need for more aggressive treatment.

The patient should continue to receive high-concentration oxygen until he/she is asymptomatic, the ECG is normal, and the COHb level is < 10%. If the patient has cardiovascular or pulmonary disease, he/she should be treated until the COHb is 2%. The half-life of CO is approximately 60 minutes when a patient is breathing 100% oxygen, so patients with low levels of COHb and mild signs and symptoms on admission to the ED can often be discharged after several hours of treatment.

**Learning Break:** Although it is natural to focus on the pulmonary and neurological effects of CO poisoning – the patients are short of breath, dizzy, unconscious, etc. – myocardial damage is common in patients who have suffered moderate to severe CO poisoning.

If the patient does not respond to normobaric oxygen (oxygen delivered at normal atmospheric pressure), or if the patient has serious complications, or if the patient is considered to have a serious exposure, two issues must be considered: a) the patient may
be suffering from cyanide exposure or methemoglobinemia (the latter is very uncommon), or b) the patient may need hyperbaric oxygen (HBO₂) therapy and/or admission to an intensive care unit (ICU).

What is considered a serious exposure to CO? There is no universally agreed upon definition. However, if the patient has any of the following signs or symptoms or demographic characteristics, most clinicians would consider the exposure to be serious.

- Age > 50 years
- Arrhythmias
- Cardiac ischemia
- COHb > 25
- Loss of consciousness
- Metabolic acidosis
- Persistent depressed level of consciousness
- Seizure

**HYPERBARIC OXYGEN THERAPY**

Hyperbaric oxygen therapy delivers 100% oxygen at atmospheric pressures that are 2 to 3 times above normal. The therapeutic mechanisms by which hyperbaric oxygen work include increased dissociation of COHb, increased plasma concentration of oxygen, increased dissociation of CO from cytochrome oxidase, increasing free radical production, and decreasing leukocyte-mediated inflammation.²³,²⁴

Hyperbaric oxygen is routinely used for patients with serious CO poisoning (remember the signs, symptoms, and patient demographic from the previous section) or patients who do not respond to normobaric oxygen therapy. The goal of hyperbaric oxygen therapy is to prevent the development and/or reduce the severity of neurological sequelae. Hyperbaric oxygen therapy has been used for many years and is commonly prescribed for patients with moderate to severe CO poisoning. However, some basic issues about using it are still controversial.

- The effectiveness of hyperbaric oxygen therapy: There is no doubt that hyperbaric oxygen has many beneficial physiological effects and given the pathological processes of CO poisoning, it makes sense that hyperbaric oxygen therapy would be an effective treatment for CO poisoning. There is a lot of evidence that hyperbaric therapy does reduce the incidence and severity of neurological sequelae. Some studies have failed to find a beneficial effect from hyperbaric oxygen therapy, but these studies had serious methodological flaws.

- Patient selection: There are no universally accepted criteria for selecting patients who should/should not receive hyperbaric oxygen therapy. There is no agreed upon definition of what constitutes a “serious” CO poisoning, no one knows what level of COHb is dangerous, there is disagreement about what signs and symptoms should be considered to be definite indicators for the need for
hyperbaric oxygen therapy, and no one what patients are at risk for developing
delayed neuropsychiatric sequelae.

- When, how often, end-point of therapy: No one knows if there is a point after
which hyperbaric oxygen therapy will not be effective, and there are no standard
protocols for how often someone should receive it, and when it should be
 discontinued. The effectiveness of hyperbaric oxygen therapy may decrease if the
patient is treated > 6 hours after the exposure\textsuperscript{25}, but it may be effective if it is
given 16 hours to 21 day after CO poisoning.\textsuperscript{26,27} Some hyperbaric oxygen
centers will use several treatments, some use only one, and different hyperbaric
therapy centers have different endpoints for therapy.

Learning Break: \textit{Patients with a COHb of $> 25\%$, patients who have serious
arrhythmias, cardiac ischemia, or metabolic acidosis, or patients who have lost
consciousness, have a persistent depressed level of consciousness, or who have had a
seizure should receive hyperbaric oxygen therapy.}

Hyperbaric oxygen therapy (often called a \textit{dive}) is done in a “dive” chamber: these can
be small “monoplace” chambers or a multi-place sealed room that can accommodate one
or more patients, a ventilator, monitoring equipment, and (occasionally) a nurse. The
mono-place chamber is filled with 100\% oxygen which is compressed to the desired
atmospheric pressure. In the multi-place chamber, the patient breathes 100\% oxygen
from an outside source and the ambient air in the chamber is compressed.

Most large cities have a hyperbaric oxygen treatment center, but the patient may
be far away from one of these and deciding whom is stable enough to be transferred
and when he/she should be transferred should be considered very carefully.

Patients who have been intubated may need sedation and occasionally neuromuscular
paralysis during hyperbaric oxygen treatment. The cuff of the endotracheal tube should
be deflated and refilled with sterile saline before the patient enters the chamber; the high
atmospheric pressure can collapse the cuff if it is filled with air. The patient’s pulmonary
status and blood pressure must be monitored carefully when he/she is in the chamber.
Hypercapnia can increase the risk of seizures, so the P\textsubscript{a}CO\textsubscript{2} should be maintained at a
normal level. Hyperbaric oxygen therapy can lower the blood pressure, so blood pressure
should be checked frequently, especially if the patient has cardiovascular disease or is
receiving an IV vasopressor.

The duration of most dives is about 2 hours. Most side effects are mild and temporary.
Middle ear barotrauma such as bleeding, pain, and perforation of the eardrum happen in
about 2\% of all patients. Barotrauma to the lung and air embolization are rare adverse
effects. Seizures are possible, but they do not cause residual damage; the rate of seizures
during hyperbaric oxygen therapy has been reported to be 0.3\% to 2.5\%\textsuperscript{28}

\textbf{CARBON MONOXIDE POISONING IN THE PREGNANT PATIENT}

Carbon monoxide can be very dangerous to a fetus because even a relatively small
decrease in maternal PO\textsubscript{2} can cause a sharp drop in fetal PO\textsubscript{2}, and fetal hemoglobin has a
higher affinity for binding to CO than maternal hemoglobin. Severe carbon monoxide
poisoning has been associated with fetal mortality rates of 36% to 67%, and serious complications such as limb deformities, microcephaly, motor and neurological disabilities, and persistent seizures are possible if the child survives. The recommendations for treating pregnant patients are the same as for any other patient, but some hyperbaric oxygen treatment centers may adjust the criteria and have a lower threshold for treating this population. Children may show signs and symptoms of CO poisoning sooner than adults (they have a higher metabolic arte and a higher minute ventilation rate), but their risk for suffering harm or complications is no greater than the risk of adults and the treatment of CO poisoning is the same for children and adults.

WHAT IF THE PATIENT DOES NOT RESPOND TO TREATMENT?

There are several reasons why a patient who has been poisoned with CO does not respond to treatment, but the most common cause of a lack of response would be cyanide poisoning. Cyanide is a highly toxic gas that is produced when there is incomplete combustion of nitrogen-containing material. Cyanide is a chemical asphyxiant. It interferes with aerobic production of ATP by binding to cytochrome oxidase and preventing the use of oxygen by the electron transport chain.

The exact incidence of cyanide poisoning caused by fire and smoke inhalation is not known, but it is thought to be common. Since these situations (house fires, etc.) very often cause CO poisoning as well, the patient is at great risk for hypoxic injury and there may be a synergistic effect between CO and cyanide that increases the toxicity of each one.

However, cyanide poisoning will not respond to oxygen therapy. The pathologic mechanism of cyanide poisoning and CO are different, and patients with cyanide poisoning must be given the cyanide antidote kit or hydroxocobalamin. Patients with combined CO and cyanide poisoning may also benefit from hyperbaric oxygen therapy but there is no evidence that proves it is effective for CO and cyanide poisoning. Some people feel that hydroxocobalamin should be given empirically to most fire victims: these patients should be evaluated on a case by case basis for the use of this antidotal therapy.

Learning Break: Cyanide poisoning should be suspected in all fire victims and especially if the patient is comatose, or has an acidosis with an elevated lactate level, or has an elevated venous saturation level.

FOLLOW-UP AFTER CARBON MONOXIDE POISONING

People who have had CO poisoning should be followed closely after discharge. The onset of delayed neuropsychiatric sequelae can occur weeks after an exposure to CO so the patient and the physician who is providing follow-up care must be aware of this. If these complications do occur, there are no treatments that have been evaluated with clinical trials. Symptomatic and supportive care should be provided, and this can include (when appropriate) occupational therapy, physical therapy, and speech therapy. Cognitive symptoms have been treated with donepezil, but there is very, very little experience using the drug for this purpose and the results have equivocal. Stimulants such as
dextroamphetamine, methylphenidate and modafanil might be helpful to treat attention and memory deficits, but there is no clinical experience with them as yet. If the patient has signs and symptoms of Parkinsonism, standard therapy with anticholinergics and levodopa can be used, but as with the other pharmacological therapies mentioned, there is very little clinical experience and the results have been equivocal.\textsuperscript{34}

The survival rate of patients with CO exposure who survive long enough to reach an emergency room has been estimated to be 2.6%. If the patient had lost consciousness, had a high COHb level, had developed an acidosis, or needed endotracheal intubation, the risk of death was increased.\textsuperscript{35} People who survive CO poisoning appear to have a significantly higher rate of death than the general population: one study found the increase in deaths in this population to twice what would be expected.\textsuperscript{36}

**CHRONIC CARBON MONOXIDE POISONING**

Air pollution and cigarette smoke – inhaled and second-hand – are serious and widespread sources of carbon monoxide exposure. There is evidence that chronic exposure to low/moderate carbon monoxide may contribute to the development of vascular and cardiovascular disease.\textsuperscript{37} There is also evidence from animal studies that this type of carbon monoxide exposure can affecting the developing nervous system. However, research in this area is not extensive, it is ongoing, and the results so far regarding the toxic effects of chronic, low level exposure to carbon monoxide have been conflicting.
REFERENCES


