

You cannot see it, smell it or taste it, but it could be all around you, and it kills! This is the arresting message of a recent television advertising campaign warning of the dangers of carbon monoxide. Dubbed the silent killer, carbon monoxide is present in atmospheric air as a result of the ubiquitous incomplete combustion of hydrocarbons. Common sources in cases of poisoning include motor vehicle exhaust, faulty gas-fired central heating systems, and house fires, but paraffin heaters, gas ovens, wood-burning stoves and even barbeques have been implicated in particular cases. Every year in the UK around 50 deaths and 200 cases of serious illness are caused by accidental or deliberate acute exposure to carbon monoxide. Worldwide it is thought to be responsible for half of all fatal poisonings. Without medical intervention, severe carbon monoxide poisoning causes convulsions, coma and death. However, if hyperbaric oxygen therapy is started before death, even the most deeply comatose patients usually survive with intensive care. The in-hospital mortality rate of severely poisoned patients is just 5%. Previously, it has been supposed that survival following severe exposure to carbon monoxide has no long-term consequences, apart from the variable degree of neurological deficit (eg reduced ability to concentrate, impaired memory etc) that affects a small minority. Now, the results of a recently published US study (*JAMA* 2006; 295: 398–402) suggest that moderate to severe carbon monoxide poisoning may cause the death of patients many years after being discharged from hospital in apparent good health. Thus, the epithet 'silent killer' seems ever more justified.

# The silent killer

**The bad press that carbon monoxide attracts is not entirely justified. We all make a little carbon monoxide and this endogenously produced carbon monoxide has important physiological function.**

## Production, function and elimination

It is more than 50 years since Sjostrand first demonstrated that carbon monoxide (CO) is produced during normal metabolism. In fact, around 0.4 mL carbon monoxide is produced every hour, almost exclusively from the catabolism of haem-containing proteins, including the most abundant of these, haemoglobin.

Haemoglobin released from senescent erythrocytes is degraded to its constituent parts: haem and protein polypeptide. The protein is recycled and haem is metabolised further. In a reaction catalysed by the enzyme haem oxygenase, haem is converted to equimolar quantities of biliverdin, iron and carbon monoxide. Catabolism of haem derived from other haem-containing proteins (eg myoglobin and the cytochromes) contributes to endogenous production of carbon monoxide by the same haem oxygenase-mediated route.

The biological effect of endogenous CO is due largely to the high affinity that haem has for carbon monoxide, and the resultant binding of CO by haem-containing intracellular proteins. By a curious quirk of nature, then, haem is both the source of CO and the mediator of its biological effect. The modulation in function of some haem-containing proteins that results from CO binding has important physiological effect. Thus, endogenous CO is not, as was once supposed, simply a potentially toxic waste product of metabolism, but is involved in many physiological functions, including regulation of respiration, neuronal signalling,

regulation of blood pressure and uterine contraction during pregnancy.

Of all the haem-containing proteins, haemoglobin (Hb) is not only the most abundant but it also exhibits the highest affinity for CO, so that most CO present in blood is bound to Hb. Reversible binding occurs at the same iron atom on the haem site where oxygen binds, and the product of this binding is carboxyhaemoglobin (CO-Hb). This provides the means by which excess endogenous CO can be transported, prior to elimination from the body by the lungs in expired air. A minimum of 0.5–1.0% of the body's haemoglobin is rendered redundant, so far as oxygen transport is concerned, by its combination with endogenously produced CO.

## Environmental sources of CO and normal CO-Hb levels

In addition to the CO produced endogenously, the air we breathe contains CO, partly the result of natural processes but mostly from the incomplete combustion of hydrocarbons. The most significant unnatural sources of environmental CO that we all might be exposed to are motor vehicle exhaust and cigarette smoke. Carbon monoxide in inspired air has an important additive effect on the amount of CO-Hb in blood (Table 1).

The combined effect of endogenous and environmental CO results in a CO-Hb of less than 3% for most non-smoking urban dwellers, and may be just 1–2% for those living in rural areas where air is less

**Table 1.** Carbon monoxide concentration (parts per million) in specific environments and data relating CO exposure to %CO-Hb.

CO concentration in specific environments	
<ul style="list-style-type: none"> <li>• Global background CO – 0.12 ppm</li> <li>• Urban traffic environmental CO – 17 ppm overall, with peaks of up to 53 ppm</li> <li>• Underground car parks, road tunnels – up to 100 ppm, may peak even higher</li> <li>• Environmental tobacco smoke (offices, public houses etc) – 20–40 ppm (eight-hour average)</li> <li>• Workplace safety limit – 50 ppm (averaged over eight hours)</li> </ul>	
CO concentration of inspired air (ppm)	%CO-Hb
70	10
120	20
220	30
350–520	40–50
800–1200	60–70
1950	80
To maintain %CO-Hb below 2.5% at all times, CO exposure cannot exceed 10 ppm.	

## SCIENCE REVIEW

polluted. Cigarette smoke contains a high concentration of CO and smokers are exposed to an estimated 400–500 ppm CO while smoking and consequently have much higher CO-Hb. A necessary consensus, given the variability in %CO-Hb due to environmental CO, suggests an absolute upper limit of normal CO-Hb of 3% for non-smokers and 10% for heavy smokers.

### Sources in cases of CO poisoning

The most common source of CO in cases of fatal poisoning is motor vehicle exhaust. In the confines of a closed garage, potentially lethal concentrations of CO can be achieved in a matter of minutes. The combination of a faulty car exhaust system and poor bodywork allows CO to enter the driving compartment.

Driving and riding passenger in such a car with the windows closed can result in CO poisoning.

Incomplete combustion of gas and consequent release of CO occurs in poorly maintained gas central heating boilers. This common cause of CO poisoning in the home is potentiated by poor ventilation. Carbon monoxide poisoning is also a common feature among those overcome by smoke inhalation in, for example, house fires. In particular circumstances of poor ventilation, combustion of most hydrocarbon fuels (paraffin, propane, methane etc) can give rise to CO levels sufficient to cause symptoms of poisoning.

Clearly, a closed or poorly ventilated environment is an important contributory

factor in most cases of CO poisoning but it remains possible to suffer severe, even fatal CO poisoning outdoors if one is close enough to a rich source of CO. For example, there are several recorded cases of fatal CO poisoning as a result of swimming in marinas close to motor-boat exhausts.

### Toxicity

Toxicity of CO is due to the effect that hemoglobin binding of CO has on the oxygen carrying capacity of blood. Affinity of haemoglobin for CO is 200–250 times greater than that for oxygen, so CO displaces oxygen from haemoglobin as CO-Hb is formed.

Carboxyhaemoglobin reduces the oxygen carrying capacity of blood in a dose-dependent manner. In addition, binding of CO by Hb at the first of the four haem sites has an effect on its quaternary structure, which results in increased affinity for oxygen at the remaining three sites. This effect is evident in a shift of the haemoglobin dissociation curve to the left and results in reduced release of oxygen from haemoglobin at the tissues.

The combined effect of reduced oxygen carrying capacity and reduced release of oxygen leaves tissues effectively starved of oxygen (hypoxic). Organs such as the brain and heart whose normal oxygen consumption, compared with other organs, is relatively high are particularly sensitive to the relative anoxia induced by increased CO-Hb.

Fetal Hb exhibits an even higher affinity for CO than does adult Hb. Therefore, as CO diffuses readily across the placental membrane, the developing fetus is particularly vulnerable to tissue anoxia in cases of maternal CO exposure during pregnancy.

**Table 2.** Relationship between symptoms of carbon monoxide poisoning and %CO-Hb.

Carboxyhaemoglobin in blood (%)	Symptoms
10	No appreciable effect except shortness of breath on exertion; tightness across forehead
20	Shortness of breath on moderate exertion; occasional headache
30	Headache; easily fatigued, judgement disturbed; dizziness; dimness of vision
40–50	Headache; confusion; fainting; collapse
60–70	Unconsciousness; convulsions; respiratory failure; death if exposure continues
80	Immediately fatal

If increased production of CO-Hb were, as was once supposed, the only mechanism involved in CO toxicity, then severity of symptoms would be accurately predicted by %CO-Hb, but this is not always the case. It is now clear that 'free' CO dissolved in blood plasma enters tissues and competes with oxygen for sites on intracellular haem-containing proteins such as myoglobin, peroxidase and the cytochrome enzymes, with a variety of pathological effects independent of haemoglobin-CO binding.

### Clinical signs and symptoms

A high index of suspicion is required to entertain a diagnosis of CO poisoning unless CO exposure is certain, because the most common symptoms, which include headache, weakness, dizziness, confusion and nausea are non-specific and are often mistaken for a 'flu-like' or other common 'viral' illness.

Affected patients may be breathless, particularly on exertion, and have clinical signs (tachycardia, tachypnoea) to indicate compensation for the oxygen deficit. In more severe cases there are frank signs and symptoms of cardiac involvement, including palpitations, hypotension and a lowering of the ischaemic chest pain threshold in patients with a history of angina. Convulsions and coma occur in severe toxicity. Exposure to CO concentration greater than 1900 ppm is almost immediately fatal.

An unequivocally raised CO-Hb is diagnostic of CO poisoning, with the peak level correlating with severity of symptoms in most, but not all, cases (Table 2).

Carboxyhaemoglobin has a half-life of just four hours, which is shortened further by oxygen therapy. Consequently, if there is a delay between exposure and blood sampling,

particularly if oxygen therapy is instituted, measured CO-Hb will not accurately reflect the level of exposure, and it may in fact be normal.

Haemolytic anaemia is associated with increased endogenous production of CO and a resultant increase in CO-Hb. Invariably, this is slight and a patient with a haemolytic anaemia who has not been exposed to excess CO is very unlikely to have a CO-Hb greater than 5–10%.

### Long-term effects of CO poisoning

Most severely poisoned patients survive if they are brought to hospital alive (in-hospital mortality is of the order of 5%). However, these patients often require hyperbaric oxygen therapy in specialised intensive care units. Recovery may be slow and in a third of cases may be complicated by development of neuropsychiatric problems (loss of memory/cognition, personality change etc) as a result of anoxia-mediated brain injury. These problems gradually resolve in most patients, but a small and unpredictable minority are left with permanent neurological deficit (eg Parkinsonism). Apart from this caveat, CO poisoning has always been considered a condition not associated with long-term consequences. Survival to discharge from hospital generally represents a clean bill of health.

However, such a view is now challenged by the results of recently published study (*JAMA* 2006; **295**: 398–402). According to the authors, this is the first published investigation of long-term mortality among survivors of CO poisoning.

The work was conducted at a US regional referral centre for treatment of CO poisoning and focused on 230 patients with moderate to severe poisoning admitted between 1994 and 2002. A qualification of entry to the study was that the patient's

condition on admission was sufficiently severe to warrant hyperbaric oxygen therapy.

Of the 230 patients, 12 (5.2%) died in hospital before discharge, leaving 218 who were discharged apparently well. During median seven-year follow up, a further 42 patients died. Analysis of US population mortality statistics revealed that this cohort of CO poisoning survivors were three times more likely to die than others of the same age and sex.

Blood samples were taken during initial assessment from all the study patients for measurement of cardiac markers, troponin and CK(MB) to detect myocardial damage induced by CO exposure. Eighty-five patients (ie 37% of the total study group) had sustained myocardial damage according to the results of this blood testing. Of these, 32 (38%) died subsequently during follow up. Only 15% of those who did not sustain myocardial damage died.

This statistically significant difference in death rates between the two groups allowed the authors to conclude that myocardial damage sustained during CO poisoning increases the risk of premature death. In fact, only age and myocardial damage were found to be independent predictors of death.

To summarise, this study has shown that survivors of moderate to severe CO poisoning have a poorer outlook than was previously supposed, as they are three times more likely to die during the following seven years than would have been the case had they not been exposed to CO. The study has also shown that around a third of patients suffer myocardial damage during CO exposure, and this increases the risk of death. The authors advise that measurement of serum cardiac markers should be included in the routine assessment of all patients presenting with CO poisoning.