

Carbon monoxide

Toxicological overview

Key Points

Kinetics and metabolism

- Following inhalation, carbon monoxide binds with haemoglobin to form carboxyhaemoglobin
- When bound, it reduces the rate at which oxygen is delivered to the tissues, thereby causing hypoxia
- Once exposure has ceased, haemoglobin will bind to oxygen to form oxyhaemoglobin and carbon monoxide is eliminated unchanged via the lungs

Health effects of acute exposure

- Following acute exposure effects such as headache, dizziness, confusion, disorientation, memory loss, fainting, seizures, cerebral oedema, coma and death may arise
- Tachycardia, tachypnoea, hypotension, vasodilation, cyanosis, shock and cardiac arrest may also occur
- Long-term neurological effects may occur following an acute exposure, including cognitive and behavioural changes

Health effects of chronic exposure

- Chronic exposure to low concentrations of carbon monoxide may lead to tiredness, lethargy, headaches, nausea, dizziness, personality changes, memory problems, as well as impairment of visual, auditory or cognitive function
- Low birth weight, perinatal death and behavioural deficits may occur in children exposed to carbon monoxide during pregnancy

Toxicological Overview

Summary of Health Effects

Adverse health effects of carbon monoxide exposure are related to the concentration of carboxyhaemoglobin in the blood. In general, carboxyhaemoglobin concentrations below 2 % are not associated with any adverse effects; 20 - 30 % causes neurological symptoms such as headache, dizziness, weakness, nausea, confusion, disorientation and visual disturbances; over 50 % causes convulsions, respiratory arrest and death.

Following carbon monoxide exposure, tachycardia and tachypnoea may occur as compensatory mechanisms. Hypotension, vasodilation, cyanosis, shock and cardiac arrest may also occur. A decreased maximal oxygen consumption and decreased duration of exercise occurs in patients with impaired blood supply to the heart at lower carbon monoxide concentrations, and in healthy individuals at higher concentrations. Patients with angina are the most sensitive risk group for carbon monoxide intoxication.

The central nervous system is particularly sensitive to carbon monoxide-induced hypoxia and acute effects such as headache, dizziness, confusion, disorientation, memory loss, fainting, seizures, cerebral oedema, coma and death may arise. There is evidence from neurobehavioural studies in volunteers that prolonged exposure to low levels (5-20 % carboxyhaemoglobin), below those causing clinical symptoms, may produce cognitive impairment. Neurological symptoms following severe exposures of acute toxicity may also appear 2 – 40 days after exposure, including headache, lethargy, irritability and lack of concentration.

A range of severe neurotoxic effects may occur following severe poisoning with carbon monoxide including Parkinsonian symptoms, dementia and psychosis. They may not all be related to carbon monoxide-induced hypoxia.

Chronic exposure to carbon monoxide may cause tiredness, lethargy, headaches, nausea, dizziness, personality changes and memory problems.

Studies in patients exposed to carbon monoxide as part of combustion products of wood and coal had a higher frequency of sister chromatid exchanges compared to controls, although effects could not be directly attributed to carbon monoxide. Overall, data on the mutagenicity of carbon monoxide is poor. In addition, no data are available on the carcinogenicity of carbon monoxide.

Pregnant women, the fetus in utero and the newborn infant are at an increased risk from carbon monoxide exposure. Maternal smoking may result in low birth weight, perinatal deaths and behavioural effects in young children.

Kinetics and metabolism

Following inhalation, carbon monoxide diffuses rapidly across the alveolar and capillary membranes of the lungs. Once absorbed, it diffuses through the plasma, passes the red blood cell membrane and enters the red blood cells, where approximately 80 – 90 % binds with haemoglobin in the same way as does oxygen, to form carboxyhaemoglobin. This binding decreases the oxygen carrying capacity of the blood and interferes with oxygen exchange at tissues [1, 2]. The affinity of haemoglobin for carbon monoxide is 234-fold higher than that for oxygen hence the amount of oxygen in the blood becomes greatly reduced. Furthermore, once carbon monoxide is bound it alters the dissociation curve of oxyhaemoglobin, reducing the rate at which oxygen is delivered to the cells. This impaired delivery of oxygen can interfere with cellular respiration and causes tissue hypoxia [2, 3].

As exposure to carbon monoxide continues, the carboxyhaemoglobin concentration increases and reaches equilibrium. For example, exposure to 100 ppm carbon monoxide would result in an equilibrium concentration of carboxyhaemoglobin of 14 % (table 1). Furthermore, the increase in carboxyhaemoglobin concentration is largely dependent on the persons breathing rate, with the uptake of carbon monoxide increasing the faster one breathes [4].

Table 1. Correlation between carbon monoxide concentration in air and blood carboxyhaemoglobin concentration [4]

Carbon monoxide concentration (ppm)	Equilibrium carboxyhaemoglobin concentration (%)
10	1.6
15	2.4
20	3.2
25	3.9
30	4.7
40	6.1
50	7.6
100	14.0

Although carbon monoxide is predominantly bound to haemoglobin, it also binds to other haem proteins such as myoglobin, cytochrome P450, dopamine hydroxylase and cytochrome oxidase [1]. Concentrations of carboxyhaemoglobin in the blood are determined by factors such as the amount of inhaled carbon monoxide, blood production volume, diffusion capacity of the lungs, breathing rate and endogenous carbon monoxide. Pregnant women produce nearly twice as much endogenous carbon monoxide [1].

Carbon monoxide does not accumulate as carboxyhaemoglobin is fully dissociable. Once exposure has ceased, oxygen competes with carbon monoxide for binding sites and the carbon monoxide is lost from haemoglobin in the lungs [2]. Due to the high affinity of carbon monoxide for haemoglobin, the elimination half life is between 2 and 5 hours, the elimination becoming slower as the concentration decreases [1].

Sources and route of human exposure

Inhalation of carbon monoxide is the major route of exposure. Vehicle emissions, cigarette smoke, gas cookers, fires and boilers, paraffin heaters, solid fuel heaters and wood and coal fires are the major sources of carbon monoxide production, hence for the majority of people, the largest exposure occurs in cars or at home [5]. Poorly installed or faulty appliances, resulting in poor combustion of fuel, as well as poor ventilation causing an inadequate removal of waste products results in increased carbon monoxide exposure.

Ambient background levels of carbon monoxide are approximately $0.01 - 0.23 \text{ mg m}^{-3}$ (0.009 – 0.2 ppm). In urban traffic the 8-hour mean concentrations are higher but still less than 20 mg m^{-3} (17.5 ppm) and 1-hour average concentrations are not usually greater than 29 mg m^{-3} (25 ppm). In the average UK home with carbon monoxide sources, peak concentrations of up to 60 mg m^{-3} (52.4 ppm) have been recorded [1, 6]. In homes with faulty appliances or poor ventilation, it has been reported that carbon monoxide concentrations have reached 182 mg m^{-3} (160 ppm) for prolonged periods. Such high exposures are rarely encountered by the general public [6]. The majority of the population are exposed long-term to very low concentrations of carbon monoxide and their carboxyhaemoglobin is largely dependent on their endogenous production.

Outdoor emissions of carbon monoxide have already declined by 33 % between 1990 and 1999, and it is estimated that emissions from transport should decline by 40 % between 1995 and 2005 [7]. Exposure to ambient concentrations of carbon monoxide may particularly affect workers exposed to vehicle exhausts, such as mechanics, garage and petrol station attendants, police, fire fighters, street vendors, street cleaners, cyclists or construction workers. Vehicle drivers are also exposed to carbon monoxide as car interiors produce the highest concentrations of carbon monoxide, on average $10 - 29 \text{ mg m}^{-3}$ (9 - 25 ppm) [1].

In the UK, the Expert Panel on Air Quality Standards (EPAQS) recommended an air quality standard of 10 ppm (8-hour time-weighted average (TWA) [8]. This aims to limit exposure of the population, especially individuals that are susceptible such as those with angina or coronary artery disease. Regular smokers are unlikely to be affected by normal environmental concentrations of carbon monoxide as their blood levels of carboxyhaemoglobin are already higher than would be reached by breathing polluted air [8].

Dermal or ocular exposure to the liquefied gas may occur but the risk is considered to be very low.

Health Effects of Acute / Single Exposure

Human Data

General toxicity

Adverse health effects of carbon monoxide exposure are related to the concentration of carboxyhaemoglobin in the blood.

In general, carboxyhaemoglobin concentrations below 2 % are not associated with any significant health effects; 20 - 30 % causes neurological symptoms such as headache, dizziness, weakness, nausea, confusion, disorientation and visual disturbances; over 50 % causes convulsions, respiratory arrest and death (table 2) [4, 8]. The cherry red skin colour observed when carboxyhaemoglobin concentrations exceed approximately 20 % is rarely observed [5].

Table 2. Summary of toxic effects following acute exposure to carbon monoxide [4, 8]

Carboxyhaemoglobin in blood (%)	Signs and symptoms
<2	No significant health effects
2.5-4.0	Decreased short-term maximal exercise duration in young healthy men
2.7-5.2	Decreased exercise duration due to increased chest pain (angina) in patients with ischaemic heart disease
2.0 – 20.0	Equivocal effects on visual perception, audition, motor and sensorimotor performance, vigilance and other measures of neurobehavioural performance
4.0-33.0	Decreased maximal oxygen consumption with short-term strenuous exercise in young healthy men
20-30	Throbbing headache
30-50	Dyspnoea, dizziness, nausea, weakness, collapse, coma
> 50	Convulsions, unconsciousness, respiratory arrest, death

Cardiovascular toxicity

The heart is one of the most sensitive organs to hypoxia caused by carbon monoxide. As a compensatory mechanism against cellular hypoxia, increased coronary blood flow and tachycardia may occur. At the point where blood flow cannot meet oxygen demand, the myocardium becomes ischaemic resulting in chest pain and reduced myocardial functioning. Other changes such as hypotension, vasodilation, cyanosis, shock and cardiac arrest may occur [6].

Decreased oxygen uptake leading to a decreased work capacity under maximum exercise conditions has been demonstrated in healthy adults with 5 % carboxyhaemoglobin, although

some studies have reported small decreases when exposed to concentrations of 2.3 – 4.3 % [1].

Chronic angina patients are the most sensitive risk group for effects following carbon monoxide exposure. Exposure to 50 ppm for 2 – 4 hours, causing a blood carboxyhaemoglobin concentration of 2 – 5 % aggravates symptoms of angina and the duration of exercise was significantly decreased by the onset of chest pain [9]. Carboxyhaemoglobin concentrations of 50 - 60 % have been associated with death, although some fatalities have been reported in individuals with coronary heart disease with a carboxyhaemoglobin concentration of as low as 10 % [1].

Neurotoxicity

The central nervous system is particularly sensitive to carbon monoxide-induced hypoxia and acute effects such as headache, dizziness, confusion, disorientation, memory loss, fainting, seizures, cerebral oedema, coma and death may occur [1].

Many studies have demonstrated that an increase in carboxyhaemoglobin to above 20 % is associated with a compensatory increase in blood flow in the brain, which may lead to behavioural changes. Elevation in carboxyhaemoglobin concentration produces small decrements in tracking (fine motor behaviour and hand-eye coordination) whereas fine motor control is unaffected by concentrations less than 20 % [1].

Delayed effects following an acute exposure

Carbon monoxide toxicity occurs predominantly due to hypoxia. However, in some cases of severe poisoning symptoms persist when carboxyhaemoglobin levels return to normal. In such cases, neuropsychological sequelae may appear 2 – 40 days after exposure including headache, lethargy and lack of concentration [3, 10]. Glycosuria and heart irregularities have been reported as well as cerebral congestion and oedema, the latter possibly resulting in long-term mental or nervous damage [6]. Other effects include apraxia, visual impairment and in cases of severe poisoning Parkinsonian-type symptoms, dementia and psychosis may occur [3, 10]. The cause of such delayed neurological symptoms are largely unknown, although it has been speculated that free radical production and lipid peroxidation during the reperfusion phase, when oxygen becomes available, may contribute [10].

Although there are no epidemiological data to support lasting effects occurring at low levels of exposure, there is experimental evidence to suggest that carbon monoxide can affect the brain even at very low concentrations, leading to effects on cognitive function prior to the clinical symptoms occurring [3].

Health Effects of Chronic / Repeated Exposure

Human Data

General toxicity

Chronic carbon monoxide poisoning may not necessarily give typical symptoms associated with acute exposure. Chronic symptoms may include tiredness, lethargy, headaches, nausea, dizziness, personality changes, memory problems, Parkinsonian symptoms, visual loss and dementia [1, 11].

Neurotoxicity

To date it has not been fully elucidated whether chronic exposure to low concentrations of carbon monoxide produces long lasting effects on the brain [3]. A chronic flu-like syndrome has been described in such conditions, including headache, irritability and malaise [10]. It is however difficult to distinguish between the effects of carbon monoxide and damage caused by free radical production during the reperfusion phase when oxygen becomes available again [12].

Recent studies have demonstrated that prolonged exposure to concentrations of carbon monoxide concentrations that do not produce adverse symptoms, may produce subtle effects on the CNS. Neuropsychological symptoms reported included anxiety, psychomotor dysfunction, loss of balance and changes in sleep, memory, vision and smell [3]. Older studies reported an association between exposure to 100 ppm carbon monoxide (causing a carboxyhaemoglobin concentration of 5%) and neurological changes such as loss of visual, auditory or cognitive function [9].

Cardiovascular toxicity

In contrast to acute exposure to carbon monoxide that causes myocardial arrhythmias, chronic exposure to carbon monoxide may lead to the onset of atherosclerosis [10].

Long-term exposure to ambient concentrations of carbon monoxide is unlikely to increase the carboxyhaemoglobin concentrations above 5 %. Patients with inadequate coronary arterial blood flow may experience angina-type symptoms upon exposure to carbon monoxide. In volunteer studies, exposure to carbon monoxide concentrations causing 5 % carboxyhaemoglobin may reduce the time to onset of angina brought on by exercise [10].

Genotoxicity

The genotoxic effect of exposure to combustion products of coal or wood was investigated by analysing the frequency of sister chromatid exchange in individuals presenting with carbon monoxide intoxication. Authors reported a statistically significant increase in sister chromatid exchange frequency in the exposed group compared to controls, although there was no correlation with blood carboxyhaemoglobin hence such effects could not be directly ascribed to carbon monoxide exposure [13]. Overall, there is little data available on the mutagenicity of carbon monoxide in humans [2, 14].

Carcinogenicity

No data are available on carcinogenicity following carbon monoxide exposure [2, 14]. Carbon monoxide is not generally regarded as carcinogenic.

Reproductive and developmental toxicity

Pregnant women, the fetus in utero and the newborn infant are at an increased risk from atmospheric carbon monoxide exposure. During pregnancy the endogenous carbon monoxide may be elevated as much as three-fold and the maternal haemoglobin is often reduced, leading to physiological hyperventilation. As a consequence less oxygen is available to be transported to the fetus. Carbon monoxide readily crosses the placenta by simple diffusion and binds to fetal haemoglobin with a higher affinity than for maternal haemoglobin. Furthermore, carbon monoxide is cleared from fetal blood slower than from maternal blood, leading to the accumulation of carbon monoxide which, at steady state, may be up to 10 – 15 % higher than maternal concentrations [1, 2].

The developing brain appears to be the most sensitive organ to the effects of carbon monoxide. Maternal smoking, resulting in fetal carboxyhaemoglobin concentrations of 2 – 10 % may result in low birth weight, perinatal deaths and behavioural effects in young children [2].

Animal and In-Vitro Data

Genotoxicity

No data are available on the genotoxicity following carbon monoxide exposure. Carbon monoxide would not be expected, from its structure, to have any significant mutagenic properties.

Carcinogenicity

No data are available on carcinogenicity following carbon monoxide exposure [2, 14]. Carbon monoxide is not generally regarded as carcinogenic.

Reproductive and developmental toxicity

Studies in experimental animals have demonstrated that maternal exposure to 150 – 200 ppm carbon monoxide resulting in carboxyhaemoglobin concentration of 15 – 25 % cause a reduction in birth weight, cardiomegaly and delayed behavioural development and cognitive function [1].

Mice exposed to concentrations of 65 – 500 ppm carbon monoxide on days 7 – 18 of gestation showed a dose-dependent effect on the fetus. Exposure to 500 ppm resulted in a significantly increased mortality and exposure to 125 ppm caused a decrease in birth weight. No signs of maternal toxicity were observed [15].

Offspring of rats exposed to 150 ppm for the duration of gestation had minor reductions in birth weights, decreased growth rates and persistent memory deficits that became more pronounced in adulthood. In addition, exposure of rats to 30 and 90 ppm led to a decrease in pregnancy rate to 69 and 38 %, respectively [15].

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This document will be reviewed not later than 3 years or sooner if substantive evidence becomes available.