



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, oxygen competes with carbon monoxide to bind with haemoglobin; the displaced carbon monoxide is predominantly eliminated unchanged via the lungs

Health effects of acute exposure

- the most common symptoms following acute exposure are headache, nausea, vomiting, vertigo, alteration in consciousness and subjective weakness
- symptoms of severe poisoning include confusion, myocardial infarction, respiratory failure, loss of consciousness and death
- 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 lethargy, headaches, nausea, flu-like symptoms and neuropsychological and cardiovascular issues
- adverse outcomes including fetal and neonatal death, congenital malformations and neurological effects have been reported following acute exposure to high levels of carbon monoxide during pregnancy

Summary of Health Effects

The signs and symptoms of carbon monoxide exposure are often non-specific, therefore poisoning can be difficult to diagnose.

The most common symptoms following acute exposure are headache, nausea and vomiting, vertigo, alteration in consciousness and subjective weakness. Severe symptoms include confusion, myocardial infarction, respiratory failure, loss of consciousness and death. The cardiovascular system and the central nervous system (CNS) are the most sensitive target organs for carbon monoxide toxicity. Following an acute exposure, neuropsychiatric features may develop in some individuals; these have been observed up to 40 days after initial exposure.

Blood carboxyhaemoglobin levels are not a reliable indicator of poisoning severity and/or clinical outcome. No significant adverse health effects have been reliably demonstrated in the literature where carbon monoxide exposure resulted in carboxyhaemoglobin levels of below 6% in healthy individuals. A carboxyhaemoglobin level of 30% indicates severe exposure, however significant poisoning effects cannot be excluded at lower concentrations.

Like acute poisoning, chronic carbon monoxide exposure can result in non-specific symptoms (headache, lethargy, syncope, nausea and flu-like symptoms), which may be misdiagnosed. Neurophysiological symptoms including anxiety, psychomotor dysfunction, loss of balance and changes in sleep, memory, vision and smell have also been reported. Epidemiological studies have linked rises in ambient air carbon monoxide and cardiovascular endpoints.

Several adverse outcomes have been reported following acute exposure to high levels of carbon monoxide during pregnancy. These include fetal and neonatal death, congenital malformations and neurological effects and are associated with moderate to severe maternal toxicity. Some studies have reported effects following chronic low level exposure to carbon monoxide during pregnancy, without maternal toxicity.

Kinetics and Metabolism

Following inhalation, carbon monoxide diffuses rapidly across the alveolar and capillary membranes of the lungs, into the blood [1]. Once absorbed, it diffuses through the plasma and enters the red blood cells, where approximately 80 – 90 % binds with haemoglobin, to form carboxyhaemoglobin. Carbon monoxide is also produced endogenously, however this alone is not associated with toxicity [2]. In non-smokers, the baseline carboxyhaemoglobin is around 1-2% while in smokers it is around 5-10% [3].

As exposure to a constant concentration of carbon monoxide continues, the blood carboxyhaemoglobin concentration increases until it reaches equilibrium with the ambient air. For example, exposure to 100 ppm carbon monoxide would result in an equilibrium concentration of carboxyhaemoglobin of 14 % (table 1). As carboxyhaemoglobin levels rise to meet equilibrium, the level is determined by the duration of exposure, pulmonary ventilation and baseline carboxyhaemoglobin levels [1]. When in equilibrium, the level of carboxyhaemoglobin is mainly dependent upon the concentrations of carbon monoxide and oxygen inhaled [1, 4].

Absorbed carbon monoxide is distributed throughout the body. Although it predominantly binds to haemoglobin, carbon monoxide also binds to other haem proteins such as myoglobin, cytochrome P450, dopamine hydroxylase and cytochrome oxidase, leading to a wide distribution [1]. Following autopsies in humans, the highest concentrations of carbon monoxide have been found in the blood, spleen, lung, kidney and skeletal muscle (and detected in the brain and adipose tissue) [2].

Carbon monoxide does not accumulate in the body as carboxyhaemoglobin is fully dissociable. Once exposure has ceased, oxygen competes with carbon monoxide for binding sites and the displaced carbon monoxide is mainly eliminated unchanged via the lungs or undergoes oxidative metabolism [1]. Conversion of carbon monoxide to carbon dioxide by oxidative metabolism is a minor route of elimination. The elimination half-life of carbon monoxide increases with age (with the greatest increase occurring from ages 2 to 20) and is approximately 6% longer in males than females [2]. The half-time elimination of carbon monoxide is 320 minutes when breathing air, 80 minutes when breathing 100% oxygen and 23 minutes with hyperbaric oxygen (at 304 kPa) [1].

Pregnant women produce more endogenous carbon monoxide, typically having carboxyhaemoglobin levels which are 20% higher than non-pregnant values [5]. Carbon monoxide may be transferred across the placenta and into fetal circulation. The elimination half-life of carbon monoxide in the fetus is up to 4 to 5 times longer than in the mother, this is due to fetal haemoglobins greater binding affinity and the relatively small diffusion gradient between maternal and fetal blood [2, 6]. At steady state this may result in fetal concentrations being up to 10-15% higher than maternal concentrations; therefore maternal levels may not accurately represent fetal levels [5, 6].

Table 1: Correlation between carbon monoxide concentration in air and blood carboxyhaemoglobin concentration

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
Reference	
Committee on the Medical Effects of Air Pollutants (COMEAP), Guidance on the Effects on Health of Indoor Air Pollutants, 2004.	

Mechanism

The main mechanism of carbon monoxide toxicity is carboxyhaemoglobin induced hypoxia. The affinity of haemoglobin for carbon monoxide is 245-fold higher than that for oxygen [7]. Therefore haemoglobin will preferentially bind carbon monoxide over oxygen following an exposure. This decreases the oxygen carrying capacity of the blood and alters the dissociation curve of oxyhaemoglobin. As a result, the rate at which oxygen is delivered to cells is reduced, interfering with cellular respiration and causing tissue hypoxia [1].

Non-hypoxic mechanisms may also contribute to the adverse health effects associated with carbon monoxide poisoning. This is thought to be due to the ability of carbon monoxide to bind to other haem proteins that are involved in important physiological regulatory systems [2, 7, 8].

Sources and Route of Human Exposure

Inhalation is the major route of exposure to exogenous carbon monoxide [7]. Therefore, exposure by inhalation will be the focus of this entry. Dermal or ocular exposure to the liquefied gas may occur but the risk is considered to be very low.

Carbon monoxide is released into the atmosphere from both natural and anthropogenic sources [2]. It is formed following the incomplete combustion of carbonaceous fuels/materials such as diesel oils, petroleum products, domestic gas or solid fuels including charcoal [3, 4]. Natural sources of carbon monoxide in the atmosphere include volcanoes, photochemical reactions and natural fires [2]. Small amounts of carbon monoxide are also endogenously produced in the human body [7].

Global background concentrations of carbon monoxide have been recorded between 0.06-0.14 mg/m³. 8 hour averages of ambient carbon monoxide in European cities are typically below 20 mg/m³ with short peaks below 60 mg/m³ [5].

The most important source of exposure to carbon monoxide for the general population is from fuel burning appliances which are poorly installed, faulty or used inappropriately (including inadequate ventilation) [4, 7]. Carbon monoxide poisonings have been reported following the use of barbeques in enclosed areas such as tents and caravans. Carbon monoxide poisoning has been reported following prolonged smoking of shisha/hooka pipes without proper ventilation [3, 4]. Neighbouring premises may also be affected by the carbon monoxide produced by an appliance in an adjoining property [4]. Inhalation of smoke from house fires can result in carbon monoxide exposure and related toxicity [3, 9].

Of 479 suspected or confirmed incidents of carbon monoxide poisoning reported to the UK National Poisons Information Service (NPIS) between 2014-2015, 84% involved exposure at home and 6% in the workplace. A faulty boiler was suspected as the cause of exposure in 62% of those occurring at home (where the source was known) [3].

Other sources of exposure to carbon monoxide include tobacco smoke, from active and passive smoking, car exhausts and incense burning. Tobacco smoke and car engines run in an integral garage may significantly contribute to indoor carbon monoxide exposure [7].

In the absence of indoor sources, outdoor concentration is the main parameter affecting indoor CO concentration, which is generally low in UK houses. Under these conditions, the indoor/outdoor (I/O) ratio of CO concentrations is almost 1.0. With gas cooking and smoking, peak CO concentrations may be increased from background levels (typically <1 mg/m³) and I/O ratios of 1.4 and 1.2 have been reported, respectively [10]. This indicates that gas cooking should not be an issue of concern, under normal ventilation conditions. However, high peaks (>100 mg/m³) can occur with malfunctioning or inappropriately used flued and unflued domestic appliances (boilers, heaters, fires, stoves and ovens), which burn carbon containing fuels (coal, coke, gas, kerosene and wood) [7, 11-13]. Increasing airtightness of dwellings may increase concentrations of CO to levels that could cause poisoning or lead to chronic exposure with subclinical adverse health effects [14].

Monitoring in the kitchens of UK homes have shown weekly averages of 0.3-2.7 mg/m³, 1-hour averages of 1.9-24.5 mg/m³ and 15-minute averages of around 180 mg/m³ carbon monoxide [8, 11]. Measurements in the living rooms of 168 subjects in the UK yielded carbon monoxide levels of 0-48.1 mg/m³, with the highest being in homes with fuel burning appliances [11]. In a study of 37 newly built homes, two-week mean CO concentrations did not exceed the WHO 8-hour average guideline of 10 mg/m³ (8.6 ppm) in any home, but exceeded the 1-hour and 8-hour WHO guidelines in one home with gas cooking, in the winter peak level study [10].

A range of 0.05-0.6 mg/m³ was measured in offices near a busy street in London. The WHO quotes peak exposures of 60-115 mg/m³ carbon monoxide for non-accidental situations including underground car parks, enclosed ice rinks and homes with gas appliances. Experimental use of a kerosene stove in a tent lead to levels of 200-550 mg/m³ carbon monoxide (and a mean carboxyhaemoglobin concentration of 21.5% in those exposed to it) [7].

Occupational situations in which (construction) workers may encounter significant levels of carbon monoxide include using LPG (e.g. heaters, cookers) or petrol (e.g. generators, cut off saws) powered equipment in enclosed spaces, disruption of gas flues or ventilation during building refurbishment and inadequately installing new gas appliances [15]. Workplace exposure limits (WELs) are enforced to protect workers from the harmful effects of carbon monoxide; in the UK the long term work place exposure limit (WEL) is 35 mg/m³ (30 ppm) and the short term WEL is 232 mg/m³ (200 ppm) [16].

Health Effects of Acute/Single Exposure

Human data

General toxicity

The cardiovascular system and the central nervous system (CNS) are particularly sensitive to carbon monoxide induced hypoxia, due to their high oxygen requirements [2].

The symptoms of carbon monoxide exposure often mimic those of more common illnesses, such as viral infections or food poisoning, resulting in cases of poisoning being difficult to diagnose and often mistaken for infections [4]. Mild exposures are associated with headache, flushing, nausea, dizziness, myalgia or neuropsychological impairment. Moderate toxicity may be associated with dizziness, ataxia and weakness while severe symptoms include confusion, myocardial infarction, respiratory failure, loss of consciousness and death [3, 6]. Skin blisters, rhabdomyolysis, compartment syndrome, acute renal failure, pulmonary oedema, dysrhythmias, retinal haemorrhages, cortical blindness, choreoathetosis, and mutism are less common features [3].

The most common symptom of carbon monoxide poisoning is a headache, with nausea and vomiting, vertigo, alteration in consciousness and subjective weakness, in descending order of frequency reported (see table 2) [4].

Blood carboxyhaemoglobin levels are not a reliable indicator of poisoning severity and/or clinical outcome [3]. This may be due to other non-hypoxic mechanisms contributing to carbon monoxide toxicity, differences in individual sensitivities to carbon monoxide exposures and differences in subjective reporting of symptom type [8].

In non-smokers the baseline carboxyhaemoglobin is around 1-2% while in smokers it is around 5-10% [3]. Beyond a reduction in maximum exercise capacity, no adverse health effects have been reliably demonstrated in the literature where carbon monoxide exposure resulted in carboxyhaemoglobin levels of below 6% in healthy people [7]. Exacerbation of pre-existing cardiovascular disease has been reported in individuals with carboxyhaemoglobin levels ranging from 2-6% [2]. A carboxyhaemoglobin level of 30% or more indicates severe exposure however, significant poisoning cannot be excluded at lower concentrations [3].

Age, anaemia, existing cardio pulmonary diseases and prior exposure to carbon monoxide may determine an individual's susceptibility to carbon monoxide toxicity as well as altitude and activity level [7].

Table 2: The frequency of the most commonly reported symptoms in carbon monoxide poisoning

Symptoms	Frequency of reporting (%)
Headache	90%
Nausea and vomiting	50%
Vertigo	50%
Alteration in consciousness	30%
Subjective weakness	20%
Reference	
National Poisons Information Service (NPIS), TOXBASE. Carbon Monoxide. 2013.	

Neurotoxicity

Acute exposure to carbon monoxide causes symptoms of CNS toxicity, as described in the general toxicity section.

Compensatory mechanisms act to protect the brain from carbon monoxide induced hypoxia. As carboxyhaemoglobin levels increase there is a proportional compensatory increase in arterial blood flow to the brain to prevent hypoxia. Studies have demonstrated that brain tissue metabolism remains constant up to carboxyhaemoglobin levels of 20%, suggesting hypoxia does not occur at CO lower levels [7].

Lesions of the basal ganglia and white matter have been observed in patients with acute carbon monoxide poisoning [2].

Cardiovascular toxicity

Similarly to the brain, compensatory mechanisms act against cellular hypoxia, by increasing blood flow rate to the heart to ensure a constant delivery of oxygen. At the point where blood flow cannot meet oxygen demand, the myocardium becomes ischaemic resulting in chest pain and reduced myocardial functioning [8].

In clinical studies, acute controlled low-level exposures to carbon monoxide sufficient to cause carboxyhaemoglobin levels of 2.4-5.9% exacerbated existing cardiovascular disease. Carbon monoxide exposure exacerbated exercise induced myocardial ischemia including reduced time to angina, increased duration of angina symptoms and in some cases time to ST-depression (indication of myocardial ischemia) in individuals with exertional angina. In healthy subjects, acute controlled exposure to carbon monoxide has resulted in reduced exercise performance (but not adverse cardiovascular effects) [2].

Delayed effects following an acute exposure

In some cases of severe poisoning, symptoms persist when carboxyhaemoglobin levels have returned to normal [17, 18]. Some individuals may develop neuropsychiatric features; this is more likely following, severe poisoning, loss of consciousness during exposure or in those aged over 40 [3]. Reported features include headache, memory and language impairment, disorientation, visual changes, apathy, irritability, inappropriate euphoria, inability to concentrate, personality change, neuropathy, incontinence, chorea, apraxia, psychosis, dementia and parkinsonism [3, 7].

Delayed features following acute high level exposure to carbon monoxide may develop up to 40 days after exposure [3]. 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 [18].

Cardiac damage during poisoning increases the risk of mortality for the 10 years following exposure [19].

Health Effects of Chronic/Repeated Exposure

Human data

General toxicity

Long-term low level exposure to carbon monoxide is frequently associated with faulty domestic heating appliances. Chronic carbon monoxide poisoning is often misdiagnosed or in some cases undiagnosed because the symptoms are non-specific. Features include headache, lethargy, nausea and flu-like symptoms [3].

Epidemiological studies indicate that environmental exposure to ambient levels of carbon monoxide in air may be associated with respiratory and cardiovascular morbidity [2, 7].

Respiratory

There is inconclusive evidence for an association between increasing ambient air concentrations of carbon monoxide and respiratory outcomes (e.g. exacerbation of asthma, hospitalisations and emergency room visits related to respiratory complaints) [2, 7].

Neurotoxicity

Chronic exposure to carbon monoxide has been reported to cause neurological impairments [3]. However, it has not been fully elucidated whether chronic exposure to low concentrations of carbon monoxide produces long lasting effects on the brain. Individuals may often experience short periods of acute carbon monoxide poisoning in addition to long-term low level exposure. Therefore, it can be difficult to determine the type of exposure responsible for the adverse health effects. Neuropsychological symptoms reported include anxiety, psychomotor dysfunction, loss of balance and changes in sleep, memory, vision and smell [17].

Cardiovascular toxicity

Chronic epidemiology studies have demonstrated a positive association between ambient air carbon monoxide exposure and cardiovascular morbidity (emergency department visits and hospitalisation for ischemic heart disease, congestive heart failure and cardiovascular disease) in several locations where carbon monoxide levels ranged from 0.6 to 10.9 mg/m³ [7].

There is some evidence that chronic exposure to carbon monoxide may lead to the onset of atherosclerosis [18].

Genotoxicity

There are inadequate data available to assess the genotoxicity of carbon monoxide [2]. It would not be expected, from its structure, to have any significant mutagenic properties.

Carcinogenicity

There are limited data available on the carcinogenicity of carbon monoxide in humans. Epidemiological studies of populations exposed to ambient air concentrations of carbon monoxide have failed to show an association with increased cancer risk [2].

Reproductive and developmental toxicity

Several adverse birth outcomes have been reported following acute exposure to high levels of carbon monoxide poisoning during pregnancy. These include fetal and neonatal death, congenital malformations and neurological effects and are associated with moderate to severe (loss of consciousness/coma) maternal toxicity [6].

The risk of adverse outcomes following carbon monoxide exposure is greater in the presence of maternal toxicity; however risk to the fetus cannot be ruled out following less severe maternal toxicity or low level exposures with no maternal toxicity. Adverse outcomes following in-utero exposure to chronic low levels (e.g. smoking, ambient air pollution) of carbon monoxide, without maternal toxicity have also been investigated. Some studies have reported an association between environmental carbon monoxide exposure and pre-term delivery, low birthweight, congenital malformations (including heart defects), sudden infant death and neurodevelopmental problems [6].

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