

In Focus: Health effects of carbon monoxide intoxication

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INTRODUCTION

Carbon monoxide is a colourless, practically odourless and tasteless gas that is poorly soluble in water, but it is soluble in alcohol and benzene. It is a product of incomplete combustion of carbon-containing fuels. Carbon monoxide burns with a violet flame and it is classified as an inorganic compound. It has a slightly lower density than air.

HEALTH EFFECTS

TOXYCOKINETICS

After reaching the lungs, inhaled carbon monoxide diffuses rapidly across the alveolar and capillary membranes. It also readily crosses the placental membranes. Approximately 80–90% of the absorbed carbon monoxide binds with haemoglobin, which causes a reduction in the oxygen-carrying capacity of the blood. The affinity of haemoglobin for carbon monoxide is 200–250 times that for oxygen, while the relative affinities of other haem proteins (e.g. myoglobin), cytochrome oxidase and cytochrome P-450 for carbon monoxide are much lower.

When in equilibrium with ambient air, the carboxyhaemoglobin (COHb) content of the blood will depend mainly on the concentrations of inspired carbon monoxide and oxygen. If equilibrium has not been achieved, the COHb concentration will also depend on the duration of exposure, pulmonary ventilation and the COHb originally present before inhalation of the contaminated air.

Carbon monoxide is eliminated unchanged via the lungs. The decline in COHb concentration depends on the rate of carbon monoxide release from haem proteins, alveolar ventilation, oxygen concentration in inhaled air, duration of carbon monoxide exposure, and the level of COHb saturation. The formation of COHb is a reversible process, but because of the tight binding of carbon monoxide to haemoglobin, the elimination half-life while breathing room air is 2–6.5 hours depending on the initial COHb level. The elimination half-life of COHb is much longer in the fetus than in the pregnant mother (1).

EFFECTS OF SHORT-TERM EXPOSURE

CO affects health by interfering with the systemic transport of oxygen to tissues (especially the heart and other muscles and brain tissue). The resulting impairment of O₂ delivery cause tissue hypoxia and interferes with cellular respiration. Direct intracellular uptake of CO could permit interactions with haemoproteins such as myoglobin, cytochrome oxidase and cytochrome P-450, and therefore interfere with electron transport processes and energy production at the cellular level. Thus, in addition to observed physiological effects and cardiovascular effects, CO can modify electron transport in nerve cells resulting in behavioural, neurological and developmental toxicological consequences, and may itself play a role in neurotransmission.

The health effects associated with inhaled CO vary with its concentration and duration of exposure. Effects range from subtle cardiovascular and neurobehavioral effects at low concentrations to unconsciousness and death after prolonged exposures or after acute exposures to high concentrations of CO.

Carbon monoxide exposure causes unintentional and suicidal poisonings, and a large number of deaths annually both in Europe and in the United States. It is estimated that more than half of the 6000 annual deaths from fires in the United States is caused by CO poisoning (2). It is obvious that such homes exist where CO concentrations are high enough to increase chronic health effects, especially among sensitive populations such as pregnant women, the fetus, children, the elderly, and individuals suffering from anemia or other diseases that restrict oxygen transport between blood and cells (3).

Annual number of deaths due to indoor CO poisoning has decreased in Europe in the last decades, still they represent a major public health issue. Data from Italy indicate that deaths varied from 135-150 cases per year in the first part of the 80s to 40-105 cases in the very last years (4). Data from France are similar, indicating that deaths attributable to indoor CO poisoning passed from 260/280 cases in the first part of the 80s to 88/107 cases in the first years of this century (5).

First signs and symptoms on healthy individuals, such as decreases in work capacity and decrements of neurobehavioral functions start at [COHb] of 5%, whereas first signs of CO poisoning appear at [COHb] concentrations of 10%.

However, the variability within the human population must be considered high. A [COHb] of about 15 % only leads to slight symptoms, such as headache, in healthy adults. In contrast, the same [COHb] can cause long-lasting defects in the cognitive development and behavioural alterations in children or even contribute to death from myocardial infarction in individuals with coronary artery disease (6).

Cardiovascular effects

In apparently healthy subjects, the maximal exercise time and the maximal oxygen consumption have decreased at COHb levels as low as 5%. The regression between the percentage decrease in maximal oxygen consumption and the percentage increase in COHb concentration appears to be linear, with approximately a one percentage

point fall in oxygen consumption per one percentage point rise in COHb level above 4% (1).

Patients with cardiovascular disease, especially ischaemic heart disease, are expected to be particularly sensitive to carbon monoxide. Atherosclerotic narrowing of the coronary arteries and impaired dilatation mechanisms restrict blood flow to the myocardium and prevent physiological compensation for lowered oxygen delivery caused by elevated levels of COHb. In exercise, these subjects experience myocardial ischaemia, which can impair myocardial contractility, affect cardiac rate and rhythm, and cause angina pectoris (1).

Early studies have suggested that low level carbon monoxide exposures resulting in COHb levels of 2.5–3.0% shorten the time to onset of exercise-induced chest pain in patients with angina pectoris. Subsequent studies by other investigators have actually given similar results (1).

The design and results of the five most important clinical studies conducted in patients with ischaemic heart disease show that despite the obvious differences between the studies, they all refer to a significant shortening in the time to onset of angina at mean post-exposure COHb levels of 2.9–5.9% which represent mean incremental increases of 1.5–4.4% COHb from the pre-exposure baseline levels (1).

The potential arrhythmogenic effects associated with low-level carbon monoxide exposures have not been fully resolved at COHb levels of $\leq 5\%$ (1). Hinderliter et al. (7) reported no effects at 3.5% and 4.9% COHb levels (post-exercise concentrations) on resting and exercise-induced arrhythmias in ten patients with coronary artery disease and no baseline ectopia. In contrast, Sheps et al. (8) showed in 41 nonsmoking patients with documented coronary artery disease and various levels of baseline ectopia that the frequencies of both single and multiple ventricular depolarizations increased significantly at a mean post-exercise COHb level of 5.0% but not at 3.5%. Dahms et al. (9) found no additional effect of either 3% or 5% COHb over the exercise-induced increases in single or multiple ectopic beats experienced by patients with myocardial ischaemia and baseline ectopia.

According to some epidemiological and clinical data, carbon monoxide from recent smoking and environmental or occupational exposures may contribute to cardiovascular mortality and the early course of myocardial infarction (1). It is not known whether this contribution is due to arrhythmogenic effects or to some longer-term effects, as suggested by some authors. In patients with severe ischaemic heart disease, carbon monoxide poisonings have been lethal at COHb levels of 10–30%, while usual COHb levels in lethal poisonings are around 50–60% (10).

A number of recent epidemiological studies reported associations between levels of ambient air pollutants (CO, PM, O₃, NO_x, SO₂) and hospital admissions for cardiovascular diseases (11). In all the cited studies a positive association was found between CO ambient concentrations and the daily number of cardiovascular disease hospitalizations at the local level.

Often, individuals suffering from CO poisoning are unaware of their exposure because symptoms are similar to those associated with viral illness or clinical depression (2). This may result in a significant number of misdiagnoses by medical professionals. Although the precise number of individuals who suffer from CO poisoning is not known, it is certainly much larger than that indicated by mortality figures. It has been estimated that more than 10 000 people per year in the United States required medical attention or missed at least 1 day of work in the early 1970s because of sublethal exposures to CO. Recent estimates indicate that over 40 000

emergency department visits annually for recognized acute CO poisoning in the United States.

Developmental effects

The pregnant mother, the fetus *in utero* and the newborn infant are at high risk of adverse health effects from atmospheric carbon monoxide exposures. During pregnancy, the endogenous production of carbon monoxide can be elevated as much as 3-fold, the concentration of maternal haemoglobin is often reduced, and the mothers have physiological hyperventilation. As a result of these changes, maternal COHb levels are usually about 20% higher than the non-pregnant values. Carbon monoxide diffuses readily across the placental membranes, and the carbon-monoxidebinding affinity of fetal haemoglobin is higher than that of adult haemoglobin. Moreover, carbon monoxide is cleared much more slowly from fetal blood than from maternal blood. At steady state, fetal COHb levels are up to 10–15% higher than maternal COHb levels (1).

There are theoretical reasons and supporting laboratory animal data to suggest that the fetus and the developing organs are especially vulnerable to carbon monoxide. The developing brain seems to have the highest sensitivity of all organs. There is a well established and probably causal relationship between maternal smoking and low birth weight at fetal COHb levels of 2–10%. In addition, maternal smoking seems to be associated with a dose-dependent increase in perinatal deaths and with behavioural effects in infants and young children. Carbon monoxide is probably one of the most important etiological factors for these effects, although there are numerous other toxic pollutants in tobacco smoke.

A case-control study of the association between low birthweight infants and maternal CO exposures in approximately 1000 cases in Denver failed to detect a relationship between CO exposure (estimated from fixed-site outdoor monitoring data) during the last 3 months of pregnancy and lower birth weights. Mean CO levels ranged from 0.6 to 4.1 mg/m³ (0.5 to 3.6 ppm) at 8 monitoring locations in metropolitan Denver. The 5th and 95th percentile concentrations at the site with the highest (4.1 mg/m³) mean were 1.8 and 5.5 mg/m³ (1.6 and 4.8 ppm), respectively. The odds ratio at the highest concentration site was 1.1 and the 95% confidence interval was 0.8-1.6. This study did not directly account for unmeasured sources of CO exposure, such as smoking, emissions from gas appliances and exposures to vehicular exhaust, which are limitations of the study design.

A more extensive study of a cohort of 125573 children born to women living in the Los Angeles area (1989-1993) found that exposure to ambient concentrations > 6.3 mg/m³ (3 mo average) during the last trimester of pregnancy was associated with a significantly increased risk of low birthweight (odds ratio = 1.22; confidence interval = 1.03-1.44) after adjustment for potential confounders (12). Fetotoxicity has been demonstrated in laboratory animal studies. Altered brain neurochemical development and growth retardation have been demonstrated in rats exposed to CO in utero (13).

Neurological and neurobehavioural effects

Central nervous system (CNS) effects in individuals suffering acute CO poisoning cover a wide range, depending on severity of exposure: headache, dizziness, weakness, nausea, vomiting, disorientation, confusion, collapse, and coma.

At low concentrations, CNS effects include reduction in visual perception, manual dexterity, learning, driving performance, and attention level. Earlier work is frequently cited to justify the statement that CO exposure sufficient to produce COHb levels of ca. 5% would be sufficient to produce visual sensitivity reduction and various neurobehavioral performance deficits. In a recent literature re-evaluation, however, the best estimate was that [COHb] would have to rise to 15–20% before a 10% reduction in any behavioral or visual measurement could be observed (2). This conclusion was based on: critical review of the literature on behavioral and sensory effects, review and interpretation of the physiological effects of COHb on the CNS, extrapolation from the effects of hypoxic hypoxia to the effects of CO hypoxia, and extrapolation from rat behavioral effects of CO to humans.

In controlled human studies involving patients with documented coronary artery disease, mean postexposure COHb levels of 2.9–5.9% (corresponding to postexercise COHb levels of 2.0–5.2%) have been associated with a significant shortening in the time to onset of angina, with increased electrocardiographic changes and with impaired left ventricular function during exercise. In addition, ventricular arrhythmias may be increased significantly at the higher range of mean postexercise COHb levels (8). Epidemiological and clinical data indicate that carbon monoxide from recent smoking and environmental or occupational exposures may contribute to cardiovascular mortality and the early course of myocardial infarction (1). According to one study there has been a 35% excess risk of death from arteriosclerotic heart disease among smoking and nonsmoking tunnel officers, in whom the long-term mean COHb levels were generally less than 5% (14). Current data from epidemiological studies and experimental animal studies indicate that common environmental exposures to carbon monoxide do not have atherogenic effects on humans (1).

During pregnancy, endogenous production of carbon monoxide is increased so that maternal COHb levels are usually about 20% higher than the non-pregnant values. At steady state, fetal COHb levels are up to 10–15% higher than maternal COHb levels (1). There is a well established and probably causal relationship between maternal smoking and low birth weight at fetal COHb levels of 2–10%. In addition, maternal smoking seems to be associated with a dose-dependent increase in perinatal deaths and with behavioural effects in infants and young children.

Subpopulations at increased risk of adverse effects

At CO levels typically encountered in indoor and outdoor environments, health effects are most likely to occur in individuals who are physiologically stressed, either by exercise or by medical conditions that can make them more susceptible to low levels of CO. Subpopulations at increased risk of adverse effects are:

1. *Individuals with cardiovascular diseases*: COHb levels of 2–6% may impair the delivery of oxygen to the myocardium causing hypoxia and increasing coronary blood flow demand by nearly 30%. When myocardial oxygen demands are increased, as in exercise, the hypoxic effects of CO may exceed the limited coronary reserve producing adverse health effects including earlier onset of myocardial ischaemia, reduced exercise tolerance in persons with stable angina pectoris, increased number and complexity of arrhythmias, and increased hospital admissions for congestive heart failure.

2. *Fetuses* are more susceptible to CO exposure for several reasons: CO crosses the placenta; fetal Hb has greater affinity for CO than maternal Hb; the half-life of COHb

in fetal blood is three times longer than that of maternal blood, and the fetus has high rate of oxygen consumption and lower oxygen tension in the blood than adults. Also, maternal smoking during pregnancy exposes the fetus to greater than normal concentrations of CO leading to a decrease in birth weight.

3. *Children* develop acute neurotoxic effects (e.g. headaches, nausea), long-lasting neurotoxic effects (e.g. memory deficits) and impaired ability to escape (i.e. syncope) at lower [COHb] than adults. Children have greater activity levels and smaller body masses than adults and should therefore experience higher levels of CO uptake than will adults for the same average exposure concentration.

4. *Pregnant women* have increased alveolar ventilation, increasing the rate of CO uptake from inspired air. Also, a pregnant woman produces nearly twice as much endogenous CO.

5. *Individuals with chronic obstructive pulmonary disease* such as chronic bronchitis, emphysema and chronic obstructive pulmonary disease are more susceptible to CO effects, since their lungs are less efficient at oxygenating the blood.

6. *Individuals with reduced blood haemoglobin concentrations*, or with abnormal haemoglobin, will have reduced O₂ carrying capacity in blood. In addition, disease processes that result in increased destruction of red blood cells (haemolysis) and accelerated breakdown of haemoproteins accelerate endogenous production of CO, resulting in higher COHb concentrations than in normal individuals. For example, patients with haemolytic anemia have COHb concentrations 2 to 3 times those seen in normal individuals.

7. *Certain occupational groups* are at risk from ambient CO exposure including those who work on city streets (street repairmen, street cleaners, street vendors, deliverymen, and garage attendants, taxi and bus drivers). Individuals who work in industrial processes including those exposed to other chemical substances (e.g. methylene chloride) that increase endogenous CO formation.

8. *Individuals who have not adapted to high altitude* and are exposed to a combination of high altitude and CO.

A synthesis of adverse health effects of CO exposure is presented in Table 1.

Table 1 - Carboxyhaemoglobin levels resulting from steady-state exposure to increasing concentrations of CO in ambient air and associated symptoms in healthy adult humans and susceptible (adapted from U.S.EPA, 2000; Ellenhorn and Barceloux, 1988)

[CO] in atmosphere		[COHb]	Signs and symptoms	
ppm	mg/m	%	Healthy adults	Susceptible subpopulations
0	0	0.4 – 0.7	Physiologic background concentration	
10	11.5	2	Asymptomatic	
17	19.5	2.9		during physical exertion reduced time to onset of angina and electrocardiogram signs of myocardial ischaemia in subjects with

				coronary artery disease
		5-6	Decreases in work capacity and decrements of neurobehavioral function	Increase in cardiac arrhythmias in subjects with coronary artery disease
42	48	7		Headache, nausea in children
		3-8	Background concentration in smokers	
70	80	10	No appreciable effect, except shortness of breath on vigorous exertion; possible tightness across the forehead; dilation of cutaneous blood vessels.	
		13		Cognitive development deficits in children
		15		Myocardial infarction in subjects with coronary artery disease
120	137	20	Shortness of breath on moderate exertion; occasional headache with throbbing in temples	
		25		syncopes in children - stillbirths
220	252	30	Decided headache; irritable; easily fatigued; judgment disturbed; possible dizziness; dimness of vision	
350-520	401-595	40-50	Headache, confusion; collapse; fainting on exertion	
800-1220	916-1400	60-70	Unconsciousness; intermittent convulsion; respiratory failure, death if exposure is long continued	
1950	2230	80	Rapidly fatal	

EFFECTS OF LONG-TERM EXPOSURE

There is not enough reliable information on effects of chronic exposures to low concentrations from either controlled human studies, ambient population-exposure studies, or from occupational studies (1). Chronic exposures to low CO concentrations may not pose as much a problem as high, acute exposure due to physiological compensation, tolerance, or adaptation.

EMISSION SOURCES AND EXPOSURE LEVELS

The most common cause of high carboxyhaemoglobin concentrations in man is the smoking of tobacco and the inhalation of the products by the smoker. Faulty domestic cooking and heating appliances, inadequately vented to outside air, may cause high indoor concentrations of CO. Also gas stoves, water heaters, and exhaust from vehicles in attached garages might be important indoor sources.

The most important source of carbon monoxide in ambient air is the exhaust of gasoline-powered motor vehicles. The emission rate depends on the type of vehicle, its speed, and its mode of operation.

Other common ambient sources include heat and power generators, especially when using coal, industrial processes such as the carbonisation of fuel, and the incineration of refuse (6).

The EXPOLIS project (15) found indoor concentrations typically lower in Northern Europe than in Central Europe, where they were again lower than in Southern Europe. Average residential indoor concentration in Helsinki was 1.2 mg/m^3 for non-ETS population. Average 48-hour exposure to CO, being 1.4 mg/m^3 , was slightly higher than the respective indoor concentration. In Basle and Prague average exposures to CO were higher than in Helsinki, but lower than in Milan and Athens. The highest geometric mean exposure concentrations were found in a subpopulation of smokers in Athens, being 4.0 mg/m^3 (15). Average residential indoor CO concentrations in Milan vary from 2.1 to 3.9 mg/m^3 .

Based on the EXPOLIS results average residential indoor CO concentrations in Milan were the lowest when no special indoor sources were present and the highest if gas cooking and environmental tobacco smoke (ETS) were present (16;17). The highest short-time peak concentration was found during gas cooking, 7.4 mg/m^3 . Average 15-min ambient CO concentration, 2.6 mg/m^3 , was higher than the respective indoor concentration when no indoor sources were present, but lower if gas cooking or ETS was present. Average 1-hour exposures to CO were higher, 8.4 mg/m^3 , than the respective ambient concentrations, 5.7 mg/m^3 . Instead, average 8-hour and 48-hour ambient concentrations were at the same level than the respective exposures, being 3.8 and 2.4 mg/m^3 , respectively.

Short time carbon monoxide concentrations related to some typical indoor sources such as tobacco smoke, gas cooking and commuting in five European cities showed that much higher levels were found in a Finnish study determining personal exposures of preschool children in Helsinki. The highest exposures to carbon monoxide were as high as 80 mg/m^3 , 69 mg/m^3 and 28 mg/m^3 for 15-min, 1-hour and 8-hour averages, respectively. Elevated exposures were related to gas stoves, mothers' smoking and living in high rise buildings.

The highest maximum values ranging 121 – 182 mg/m³ were measured in homes when using a gas grill attached to the gas stove (3), in the underground parking facilities and in a home with a faulty boiler. Elevated concentrations were also found in other microenvironments such as motor vehicles, indoor ice arenas, bars and restaurants.

Lately attention is being paid to incense burning in homes and other public buildings including stores and shopping malls. Jetter et al (18) reported emission rates of 23 different types of incense such as incense rope, cones, sticks, rocks, powder etc. that are typically used indoors. The measured emission rates of carbon monoxide ranged 144 - 531 mg/h. The authors estimated a peak concentration of 9.6 mg/m³ caused by incense burning and, therefore concluded that carbon monoxide concentrations could exceed the US EPA's National Ambient Air Quality Standard (NAAQS) 10 mg/m³ for an 8-hour average depending on the room volume, ventilation rate and the amount of incense burned. Especially, incense burning might be a significant contributor to population exposure in such cultures, where incense is burned frequently, for example in religious rituals.

INDEX STANDARDS

The INDEX project “Critical appraisal of the setting and implementation of indoor exposure limits in the EU (2002–2004)” was funded by the European Commission' DG SANCO and JRC was given the assignment to identify priorities and to assess the needs for a Community strategy and action plan in the area of indoor air pollution (19).

CO was included in a list of five priority compounds with potential of high indoor concentrations, uncontested health impacts, and effective risk management were selected to be regulated with priority.

Available exposure data from the INDEX project confirmed that Carbon Monoxide (CO) sources in EU-residences are contributing to short-term rather than to long-term exposures. Personal exposure outcomes averaged over 1-hour were considered of moderate concern even for the most susceptible subpopulations. Increased exposures could be expected for residences in the vicinity of busy city streets. In addition, there was no evidence that long-term CO exposures in EU residences contribute to carboxyhaemoglobin levels in blood higher than the baseline levels resulting from endogenous production in normal, non-smoking individuals.

On the other hand carbon monoxide causes a considerable number of deaths and acute poisonings in the general population (with complications and late sequelae). Also, individuals suffering from CO poisoning are often unaware of their exposure because symptoms are similar to those associated with viral illness or clinical depression. In indoor environments, these health risks are nearly completely associated with the incorrect use of combustion devices or faulty unvented gas appliances.

As to carbon monoxide, proposed guideline values are 10 mg/m³ (8-hour) and 30 mg/m³ (1-hour). Management options suggested were to connect each combustion equipment/appliance to chimney or vented hood, to ensure sufficient local extract

ventilation in kitchens with gas stove, mandatory inspection and maintenance of indoor combustion devices, and CO alarms.

Following general recommendations have been suggested: • Restrict tobacco smoking in all indoor spaces; • Restrict the construction of attached garages, or isolate them from living and working spaces; • Ensure that ventilation dilutes predictable indoor emissions below the guideline levels; • Raise public awareness about indoor air risks.

CONCLUSIONS

CO sources in EU-residences are contributing to short-term rather than to long-term exposures. CO health effects vary from very light effects to death. Some groups of subjects (pregnant women, children, elderly and individuals with anemia, peripheral vascular disease or chronic obstructive lung disease) are more susceptible to adverse effects of CO. Recommendations and management options are necessary to avoid the development of adverse effects due to CO exposure.

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