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147. Carbon monoxide

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Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical substances. For each document, NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. The document aims at establishing dose-response/dose-effect relationships and defining a critical effect. No numerical values for occupational exposure limits are proposed. Whereas NEG adopts the document by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document.

The evaluation of the literature and the drafting of this document on *Carbon monoxide* were done by Dr Helene Stockmann-Juvala at the Finnish Institute of Occupational Health.

The draft versions were discussed within NEG and the final version was accepted by the present NEG experts on August 21, 2012. Editorial work and technical editing were performed by the NEG secretariat. The following present and former experts participated in the elaboration of the document:

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All criteria documents produced by the Nordic Expert Group may be downloaded from *www.nordicexpertgroup.org*.

Gunnar Johanson, Chairman of NEG

Contents

Abbreviations and acronyms

AEGL	Acute Exposure Guideline Level
ATSDR	Agency for Toxic Substances and Disease Registry
CAD	coronary artery disease
CFK	Coburn-Forster-Kane
CI	confidence interval
CO	carbon monoxide
COHb	carboxyhaemoglobin
ECG	electrocardiogram
EPA	Environmental Protection Agency
GD	gestation day
Hb	haemoglobin
HO	haeme oxygenase
IPCS	International Programme on Chemical Safety
LC_{50}	lethal concentration for 50% of the animals at single inhalation exposure
LOAEL	lowest observed adverse effect level
Mb	myoglobin
NIOSH	National Institute for Occupational and Safety and Health
NO	nitric oxide
NO_2	nitrogen dioxide
NOAEL	no observed adverse effect level
NRC	National Research Council
O_2	oxygen
O_3	ozone
O_2Hb	oxyhaemoglobin
O_2Mb	oxymyoglobin
PD	postnatal day
PMx	particulate matter with aerodynamic diameter up to x μm
pO_2	partial oxygen pressure
US	United States
V_{O2max}	maximal aerobic capacity (also called maximal oxygen uptake)
WHO	World Health Organization

1. Introduction

Carbon monoxide (CO) is an odourless and colourless gas. It is a major atmospheric pollutant in urban areas, chiefly from exhaust of combustion engines, but also from incomplete burning of other fuels. CO is also a constituent of tobacco smoke. Exposure to CO is common in many occupational areas, mainly in those associated with exhaust emissions (229). CO is also an important industrial gas, which is increasingly being used for the production of chemical intermediates (25). CO is formed endogenously and acts as a signalling substance in the neuronal system (249).

The main mechanism behind CO-induced toxicity has for long times been known as the binding of CO to haemoglobin, resulting in carboxyhaemoglobin (COHb) formation and hypoxia. Health effects associated with acute CO poisoning have been extensively documented by others. The present document is focused on examining health effects of low-level CO exposure as this forms the basis for occupational exposure limit setting. The evaluation builds partly on the reviews by the World Health Organization/International Programme on Chemical Safety (WHO/IPCS) from 1999, the United States Environmental Protection Agency (US EPA) from 2000 which was superseded by an update in 2010, the National Research Council (NRC) from 2010, and the Agency for Toxic Substances and Disease Registry (ATSDR) from 2012 (16, 96, 151, 229, 230). Data bases used in search of literature are given in Chapter 19.

2. Substance identification

Table 1. Substance identification data for carbon monoxide (152).

IUPAC name:	Carbon monoxide
Common name:	Carbon monoxide
CAS number:	630-08-0
Synonyms:	carbon oxide, carbonic oxide
Molecular formula:	CO
Molecular weight:	28.01

3. Physical and chemical properties

CO is an odourless and colourless gas with a density close to that of air. General physical properties of CO are given in Table 2.

The CO molecule consists of one atom of carbon and one atom of oxygen, covalently bonded by a double bond and a dative (dipolar) covalent bond. Despite oxygen's greater electronegativity, the effects of atomic formal charge and electronegativity result in a small bond dipole moment with its negative end on the carbon atom. Most chemical reactions involving CO occur through the carbon atom, and not the oxygen. Most metals form coordination complexes containing covalently attached CO (25).

Table 2. Physical and chemical properties of carbon monoxide (152).

Freezing point at 101.3 kPa:	-205 °C
Boiling point at 101.3 kPa:	-191.5 °C
Vapour density (air = 1):	0.968
Vapour pressure at 20 °C:	> 101 kPa (1 atm)
Flammability range in air (vol/vol):	12–75%
Solubility in water at 20 °C:	2.4 ml/100 ml
Conversion factors at 25 °C:	1 ppm = 1.145 mg/m^3
	1 mg/m^3 = 0.873 ppm

4. Occurrence, production and use

4.1 Occurrence

CO is a minor atmospheric constituent. The ambient concentrations range from a minimum of about 30 ppb during summer in the Southern Hemisphere to about 200 ppb in the Northern Hemisphere during winter. CO originates chiefly as a product of volcanic activity but also from natural and man-made fires and the burning of fossil fuels. It occurs dissolved in molten volcanic rock at high pressures in the earth's mantle. CO is a major atmospheric pollutant in urban areas, chiefly from exhaust of combustion engines, but also from incomplete burning of other fuels (including wood, coal, charcoal, oil, kerosene, propane, natural gas and trash). It reacts photochemically to produce peroxy radicals, which react with nitric oxide (NO) to increase the ratio of nitrogen dioxide (NO_2) to NO. This reaction reduces the quantity of NO that is available to react with ozone (O_3) (229).

CO is also a constituent of tobacco smoke. In various studies, the CO emission has been estimated to vary between 0.5 and 78 mg per cigarette, and 82–200 mg for large cigars (229).

The CO levels in indoor air vary depending on whether there are CO producing sources, like gas stoves, kerosene heaters or smoking in the building. In a study including 400 homes in the US, the average CO concentration was 2.23 ± 0.17 ppm (measured in 203 homes). Use of gas stoves and kerosene space heaters was associated with increased CO levels (229).

Small amounts of CO are formed endogenously in the human blood as a result of breakdown of haemoglobin and other haemoproteins (myoglobin, cytochromes, peroxidases and catalase) (see Section 7.2).

4.2 Production and use

CO is formed by the incomplete combustion of carbonaceous materials, by the reduction of carbon dioxide, or by the decomposition of organic compounds (e.g. aldehydes). CO may also be recovered from the off-gas of industrial processes, like blast furnace processes or calcium carbide synthesis (25).

In industrial production of CO, the initial product is usually a gas mixture containing CO. The three most important processes include gasification of coal, steam reforming/carbon dioxide reforming (for light hydrocarbons), and partial

oxidation of hydrocarbons (for hydrocarbons heavier than naphtha). CO can then be separated, or the CO-hydrogen ratio can be adjusted, by various procedures. The most common procedures for separation are: a) Copper ammonium salt wash (reversible complexation) at elevated pressure, followed by desorption at lower pressure, b) Cryogenic separation, including low-temperature partial condensation and fractionation, and liquid methane scrubbing and separation, c) Pressure-swing adsorption, and d) Permeable membranes (25).

Laboratory scale production of CO can be based on the slow addition of concentrated formic acid to concentrated sulphuric acid, followed by removal of traces of sulphur dioxide and carbon dioxide by passing the gas through potassium hydroxide pellets (25).

Syngas (synthesis gas) is a gas mixture that contains varying amounts of CO and hydrogen. The name comes from their use as intermediates in creating synthetic natural gas (SNG) and for producing ammonia or methanol. Most of the syngas production is nowadays based on natural gas and sulphur-rich heavy vacuum residues. Other usable raw materials include naphtha, coal, heavy fuel and residual oil (25).

CO is an important industrial gas which is increasingly being used for the production of chemical intermediates (25).

CO is frequently used as a reducing agent in the production of inorganic chemicals e.g. in the direct reduction of iron to sponge iron and in the preparation of very pure metals, like nickel metals. The reaction of CO with chlorine yields phosgene which can be used to prepare aluminium chloride by the chlorination of bauxite (25).

The major use of CO is in the production of acetic acid, by catalytic carbonylation of methanol. Other organic chemicals formed in reactions including pure CO are formic acid, methyl formiate, acrylic acid and propanoic acid.

The most important chemicals produced using syngas are methanol, hydrocarbons and linear aliphatic aldehydes (25).

In 2009, the total reported use of CO in preparations in Sweden, Norway and Finland was 2.4 million tonnes. In 2001, the corresponding value was 2.3 million tonnes, indicating a stable use, although the number of reported preparations decreased from 48 in 2001 to 28 in 2009. The main use categories included manufacture of basic metals, chemicals, and chemical products, scientific research, as well as the category “electricity, gas, steam and air condition supply” (207).

Based on studies showing that CO is acting as a secondary messenger molecule in the cell, research is ongoing on the potential use of CO as a therapeutic gas, using doses of 3 mg/kg body weight (resulting on COHb 12%) (145). It has been suggested that CO could be used in order to obtain anti-apoptotic or anti-inflammatory effects through modulation of protein kinase pathways (187, 229). A large number of experimental studies show promising results, but so far the number of clinical trials is low, and do not show any clear anti-inflammatory or other protective effects (18, 116).

5. Measurements and analysis of workplace exposure

5.1 Air samples

The most commonly used techniques for CO detection in air samples are based on the principle of non-dispersive infrared detection (NDIR), and they may include a gas filter correlation (GFC) methodology. The most sensitive versions of these instruments can detect CO at a level of about 0.04 ppm. These techniques are also the federal reference methods recommended by the US EPA (96, 229).

If a more sensitive technique is needed, gas chromatography with flame ionisation detector is the best choice (detection limit 0.02 ppm) (96, 229).

The US National Institute for Occupational Safety and Health (NIOSH) method for the occupational hygienic measurement of CO uses a portable direct reading monitor. The limit of quantification is reported to be 1 ppm and the working range is 0–200 ppm (147).

5.2 Biological samples

The exposure to CO is usually estimated by measuring carboxyhaemoglobin (COHb) in blood (for a definition of COHb, see Section 7.3). CO in exhaled breath can be used to reflect CO levels in blood.

5.2.1 Blood carboxyhaemoglobin measurement

COHb in blood can be measured using a variety of methods. The majority of clinical measurements are carried out using direct-reading spectrophotometers, such as CO-oximeters. Traditionally, these instruments utilised 2–7 wavelengths in the visible region, but modern instruments use up to 128 wavelengths, thus allowing for the determination of proportions of oxyhaemoglobin, COHb, reduced haemoglobin and methaemoglobin. The detection limits of the currently available oximeters are well below the COHb concentrations of unexposed persons (see Section 8.1) (26, 96, 193).

Among new methods for CO measurement are the pulse oximeters, which enable non-invasive measurement of COHb. The pulse oximeters emit near-infrared and long-wavelength visible light, which diffuse through the tissue. COHb levels measured using fingertip pulse-oximetry correlate well with blood COHb results obtained by traditional blood CO-oximetry, but may slightly overestimate the CO levels. This device can be used in clinical practise for screening purposes, but could in theory also be used in field studies at workplaces (26, 96, 193, 214).

The most sensitive techniques measuring COHb are based on gas chromatography (limit of detection 0.005% COHb). The basis for these methods is the analysis of the CO gas released from the blood when COHb is dissociated. The detection methods include infrared absorption, flame ionisation and thermal conductivity (17, 44, 75, 121, 131, 229).

5.2.2 Carbon monoxide in expired breath

CO in breath can be measured using any of the techniques used to measure ambient CO concentrations. The main techniques include portable analysers with electrochemical detection, infrared spectrometry, gas chromatography and tuneable diode laser spectrometry. Method development has recently focused on creating linear and reliable techniques working at a broad range of CO concentrations. The sample detection limits are low, even below 1 ppb (106, 118, 119, 150, 229).

In the measurement of CO in exhaled air, it is important to consider the dead-space gas volume, as it serves to dilute the alveolar CO concentration. Different methods for taking the dead-space dilution into account have been developed. The breath-hold technique (20 seconds breath-hold was found to provide almost maximal values for CO pressures) is the mostly used technique, the others being the Bohr computation (mathematical determination of the dead space) and the rebreathing technique (5 litres of oxygen are re-breathed for 2–3 minutes while the carbon dioxide is removed) (96, 229).

6. Occupational exposure data

Occupational exposure to CO occurs in a large number of situations and is nearly always concomitant with other exposures (mixed exposure). Workers exposed to vehicle exhausts, construction workers, firefighters and cooks are at increased risk for CO exposure. Industrial processes producing CO directly or as a by-product, including steel production, nickel refining, coke ovens, carbon black production and petroleum refining have also been associated with CO exposure (96).

CO exposure levels in different occupational situations in Norway and Finland are listed in Tables 3 and 4, respectively.

CO emissions from logs, and in particular from wood pellets, have been reported in Sweden and Finland as causes of accidents (5, 81, 216-218). During the transport and storage, the auto-oxidation of unsaturated lipids and other organic compounds gives rise to high CO concentrations which, in combination with significantly decreased oxygen levels, may be life-threatening or lethal in confined spaces like the hatches in ships and warehouses (217).

The distribution of biomonitoring data on COHb concentrations in 585 blood samples from workers, measured at the Finnish Institute of Occupational Health during 2000–2010, are presented in Table 5. Most of the samples were from workers exposed to CO, and some were also exposed to methylene chloride. One hundred and thirty four of the 585 workers showed COHb concentrations above the Finnish reference value of 5% (206). These high concentrations were mainly observed among different types of foundry workers.

Table 3. Carbon monoxide (CO) levels measured at various workplaces in Norway 2000–2009. About 15% of the measurements were obtained by personal monitoring in the breathing zone and the remaining 85% by stationary monitoring (EXPO data base [a]).

Occupational field	Number of measurements	CO max (ppm)	CO mean (ppm)
Defence activities (incl. submarines)	20	1 189	273
Manufacture of carbides	859	NA	124
Scheduled air transport	7	NA	44
Casting of iron	15	375	43
Other preventive health care	6	175	30
Stuff, tunnel, construction site	5	892	19
Manufacture of electrical equipment	4	NA	17
Manufacture of coke oven products	12	NA	14
Wholesale of mining, construction and civil engineering machinery	10	NA	11
Operation of gravel and sand pits	5	NA	11
Construction	107	210	10
Maintenance and repair of motor vehicles	9	37	6
Construction of motorways, roads, airfields and sport facilities	83	650	5
Installation of electrical wiring and fittings	9	38	4
Manufacture of veneer sheets, plywood, laminboard, particle board	8	682	3
Manufacture of other non-metallic mineral products n.e.c.	30	NA	3
Production of primary aluminium	9	63	2
Aluminium production	4	NA	2
Mining of non-ferrous metal ores, except uranium and thorium ores	7	160	< 2
Toll bar stations	15	20	< 2
Manufacture of industrial gases	5	9	< 2
Manufacture of paper and paperboard	4	3	< 2

[a] Description of data base in Rajan *et al* (174).
NA: not available.

There are some welding operations where CO exposure should be considered, although welding in general is not associated with CO formation. Blood COHb concentrations reaching 20% have been demonstrated after metal active gas (MAG) welding with shielding-gas containing carbon dioxide (47). The CO concentration in the breathing zone may reach 100 ppm during arc-air gouging with a carbon-graphite electrode (189). Acetylene gas welding or cutting is generally not related to hazardous CO-exposure. Some serious CO intoxications have, however, been reported during acetylene gas welding of pipes, when acetylene gas has degraded to CO in an atmosphere with oxygen depletion (10).

Table 4. Finnish occupational carbon monoxide (CO) air concentration ranges according to exposure situations, measured 2004–2007. Data obtained by personal monitoring in the breathing zone (18% of the measurements), fixed sampling at the working site (60%) and room air samples (22%) (188).

Occupational field	Number of measurements				
	Total	≤ 3 ppm	3–15 ppm	15–30 ppm	> 30 ppm
Metal ore mining	11	5	6		
Production of wood products (except furniture)	36	8	10	4	14
Production of paper and paper products	64	61	3		
Production of coke, oil products and nuclear fuel	2	1	1		
Production of rubber and plastic products	3		3		
Production of non-metallic mineral products	12	10	2		
Refining of metals	61	6	28	14	13
Production of metal products (except machines)	52	34	14	2	2
Production of machines	33	17	15	1	
Production of cars and trailers	9	6	3		
Production of other vehicles	4	4			
Recycling of waste	4	2	2		
Electricity-, gas- and heating service work	11	9	2		
Building/construction work	9	7	2		
Vehicle repairing, selling and service, fuel retail trade	3		3		
Official and defence sector	45	37	6		2
Control of the environment	9	9			
Work in the recreational, cultural and sports sector	4		1	1	2
Total	372	216	101	22	33
%	100	58	27	6	9

Table 5. Carboxyhaemoglobin (COHb) concentrations (%) measured in 585 blood samples from workers in 2000–2010 (unpublished data from the Finnish Institute of Occupational Health, 2011). The effects of cigarette smoking cannot be excluded.

Type of work	Mean (%)	Median (%)	95th percentile (%)	Maximum (%)	Number of samples	
					COHb > 5% [a]	Total
Foundry	5.2	5.0	9.6	16.9	121	245
Car inspection	1.7	1.5	3.5	8.8	1	83
Laboratory work	1.8	1.7	4.2	5.5	1	62
Vehicle repairing, service and selling	1.7	1.3	4.8	6.2	3	59
Production and maintenance of plastic products	2.3	2.0	5.4	6.9	3	49
Waste treatment, recycling	2.8	2.2	8.0	8.5	3	26
Production of chemicals	0.7	0.6	1.7	2.2	0	20
Production of metal products	2.5	1.8	5.4	7.6	2	19
Heating, use of smoke oven	2.6	2.7	3.9	4.5	0	12
Chimney sweeping	2.5	1.9	4.4	4.6	0	10

[a] Finnish reference value: 5% COHb (206).

7. Toxicokinetics

7.1 Absorption, distribution, metabolism and excretion

7.1.1 Uptake

The pulmonary uptake of CO is affected not only by the ambient CO concentration but also by physical (mass transfer, diffusion) as well as physiological factors (mainly alveolar ventilation and cardiac output) and environmental conditions. Dead space volume, gas mixing and homogeneity, and ventilation/perfusion matching are additional factors that affect the rate of CO uptake (96).

Inhaled CO diffuses from the alveolar gas phase to the red blood cells. To reach and bind to haemoglobin, CO has to pass across the alveoli-capillary membranes, diffuse in the plasma, pass across the erythrocyte cell membrane and diffuse in the cytosol to bind to haemoglobin. In the other cells, CO can bind to other haeme-containing molecules like myoglobin and cytochromes (229).

There are no reports indicating any significant uptake of CO via the oral or dermal route. Schoenfisch *et al* studied the COHb formation after a 5-second exposure of the oronasal cavity of four monkeys with 400 ppm CO. This exposure increased the COHb to < 3.5% (mean change in COHb < 0.5%) whereas comparative exposures of the lungs elevated COHb to almost 60% (194). This indicated that CO diffusion across the oronasal mucosa has a very small effect on the overall COHb concentration.

Factors modifying CO uptake are discussed in Section 7.4.

7.1.2 Distribution

7.1.2.1 Respiratory tract

Although generally all CO is taken up via the respiratory tract, there is not any detectable storage in these organs. A study with human volunteers inhaling CO indicated that CO was only taken up from the alveolar region of the lungs. Thus, a slight inhalation, leaving the gas just in the mouth and large airways, did not have any effects on blood levels (79). Similar results were also obtained in monkeys when cigarette smoke was passed either into the oronasal cavities only, or directly into the lungs (194). Post-mortem samples of humans exposed to CO showed a significant correlation between COHb levels and lung tissue CO concentrations. In patients who had died from CO poisoning (n = 7), the mean lung tissue CO concentration, expressed as % of blood CO concentration, was 52%. The corresponding value for non-exposed controls (patients that died for other reasons) was 34% (248).

7.1.2.2 Heart and skeletal muscles

Myoglobin (Mb) is a haemoprotein that binds oxygen in muscle tissues and facilitates its diffusion from the muscle sarcoplasm to the mitochondria. Small changes in tissue partial oxygen pressure (pO_2) can thus allow the release of a large amount of O_2 from oxymyoglobin (O_2Mb), in order to maintain a stable pO_2 in the mitochondria. CO binds reversibly to Mb with an affinity constant approximately 8 times lower than for haemoglobin (80, 190). Notable is that the

dissociation constant is approximately 630 times lower for carboxymyoglobin (COMb) than O_2Mb, making it possible for CO to be retained and stored in muscle tissue (73). In addition, the binding of CO to Mb decreases the storage capacity of O_2 to Mb, which may have marked consequences on the supply of O_2 to tissues.

The transfer of CO into muscle tissue is generally larger in males, than in females, most likely due to differences in muscle mass and capillary density (29). CO levels of 15 and 31 pmol CO/100 g wet weight on average have been measured in human muscle and heart tissue, respectively, when the background levels of COHb were less than 2%. During CO asphyxiation with COHb levels over 50%, the tissue concentrations increased to 265 pmol CO/100 g wet weight for muscle, and to 527 pmol CO/100 g wet weight for heart muscle, the inter-individual differences being marked (248).

7.1.2.3 Other tissues

CO can bind to other haemoproteins (cytochrome P450, cytochrome c oxidase, catalase and some peroxidases) but the significance of such binding on the whole body (CO/O_2) toxicokinetics has not been established.

Recent studies on the transport kinetics of CO show that redistribution to the extravascular tissues continues long after exposure has ended (31). The tissue CO concentrations of humans, rats and mice under various exposure conditions were studied by Vreman *et al* (247, 248). In humans, the correlation between COHb levels and tissue CO concentrations was strongest for the spleen (tissue CO 48–67%, expressed as % of blood CO). The tissue concentrations of adipose and kidney remained low (< 20% of the blood CO) even in tissues from persons who died due to CO asphyxiation.

7.1.3 Elimination

The absorbed CO is eliminated from the body by exhalation and oxidative metabolism. Endogenous oxidative metabolism has been estimated to account for only a small fraction of the elimination, and exhalation of CO is thus the major route of elimination of absorbed CO. The exhalation is based on diffusion, which occurs due to the difference in partial pressure of CO in alveolar air and alveolar capillary blood. Also the release of CO from intracellular stores to blood occurs due to diffusion mechanisms, driven by CO binding to extravascular haemoproteins and blood haemoglobin (16).

Recent reports have indicated that the elimination of CO is biphasic, especially after short-term (< 1 hour) CO exposure (31, 198). The elimination can be characterised by a 2-compartment model with an initial rapid decrease, followed by a slower phase.

The elimination half-times in sheep exposed to 2% CO for 1–3 minutes (peak COHb 30–40%) were 5.7 ± 1.5 minutes for the first fast phase and 103 ± 20.5 minutes for the subsequent slow phase (198).

Bruce and Bruce used model simulations to interpolate between measured COHb levels in 15 human volunteers after exposure to CO, in order to calculate

COHb half-times. The mean half-time for washout ($t_{0–50}$) was 4.1 ± 0.7 hours (range 3.4–5.5) (31).

The fact that the COHb elimination half-time depends on the inspired O_2 concentration has also been shown by others. At sea level, atmospheric pressure, the average expected COHb half-time when breathing air was 4.8 hours, according to Landaw (117). Inhalation of normobaric 40% O_2 decreased the expected half-times to 75 minutes, and further to 21 minutes when inhaling 100% O_2. The report by Weaver *et al* showed a COHb half-time of 74 minutes (range 26–148 minutes) when breathing 100% O_2 (235).

Elimination of foetal CO is slower than maternal elimination, showing half-times of 7.5 hours and 4 hours for foetal and maternal COHb, respectively (87).

7.2 Endogenous formation of carbon monoxide

The COHb levels of non-smokers are typically below 2%. Approximately 0.4–0.7% stem from endogenous formation of CO. For comparison, the COHb levels may in worst cases reach 10% immediately after cigarette smoking (16). Approximately 0.4 ml CO/hour is formed endogenously by haemoglobin catabolism and 0.1 ml/hour by catabolism of other haemoproteins. CO formation by catabolism of other than haemoproteins is minimal (41). The first indications of endogenous CO formation were observed already in the end of the 19th century, and in the early 1950s it was demonstrated that decomposition of haemoglobin *in vivo* produced CO (43, 202, 203).

A significant increase in the endogenous CO formation can be observed among neonates (average 0.9 ± 0.3%) (246) and pregnant women (98, 138) as well as in the premenstrual phase of the menstrual cycle (52, 130) due to increased breakdown of red blood cells (96). CO formation during pregnancy is 2–5 times that of the production during the oestrogen phase of the menstrual cycle, and returns to pre-pregnancy levels within a few days following delivery (124). The formation of CO is also accelerated during certain pathological conditions, like anaemia, haematomas, thalassaemia, Gilbert's syndrome and other haematological diseases (96). The CO formation rates are 2–3 times higher in patients with haemolytic anaemia than in healthy individuals (42).

The degradation of haemoglobin is induced by haeme oxygenase (HO). The porphyrin ring of the haeme molecule is broken resulting in the formation of iron, CO and biliverdin, which is further broken down to bilirubin. The reaction is induced by HO, which is complexed with reduced nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome P450 reductase and biliverdin reductase (96).

There are two main isoforms of HO. HO-1 is an inducible isoform, which is present in high amounts in the spleen and other tissues participating in the erythrocyte degradation, including specialised reticuloendothelial cells of the liver and bone marrow. In most other tissues, the basal level of HO-1 is very low, but increases rapidly upon stimulation by different chemical and physical stimuli

like haeme and haeme derivatives, oxidative stress, hypoxia (including altitude-induced hypoxia), various metals, cytokines, and exogenous CO (reviewed in (1, 134, 186, 249)).

The isoform HO-2 is expressed constitutively in the brain and central nervous system, vasculatory system, liver, kidney and gut. The highest expression seems to occur in the testes. HO-2 may respond to developmental regulation by adrenal glucocorticoids in the brain, but the expression is not affected by environmental factors (reviewed in (186, 249)).

A third isoform, HO-3, has only been found in rat brain, liver and spleen (136). Gene characterisation, however, indicates that there are no functional HO-3 genes in rat (84).

Currently, numerous studies focus on the potential role of induction of HO-1 and endogenous CO as targets for pharmaceutical applications, utilising the signalling molecule properties of CO (reviewed in (1, 186, 249)).

7.3 Carboxyhaemoglobin formation

COHb (%) describes the percentage of the total CO binding capacity of haemoglobin. COHb (%) can be defined by the following formula:

$$COHb\ (\%) = [CO\ content/(Hb \times 1.389)] \times 100$$

where *CO content* is the CO concentration (ml/dl) in blood at standard temperature and pressure, *Hb* is the haemoglobin concentration (g/dl), and *1.389* is the stoichiometric combining capacity of CO for Hb (ml CO/g Hb) (96).

Different types of models for predicting COHb formation have been created. Empirical models may be used to estimate COHb formation as a function of concentration and duration of exogenous CO exposure (229).

Mechanistic models are commonly used for COHb prediction. The most common and well known model is the Coburn-Forster-Kane (CFK) equation (42):

$$V_B d[COHb]/dt = \dot{V}_{CO} - [COHb]P_cO_2/MB[O_2Hb] + P_ICO/B$$

where
$B = 1/D_LCO + P_L/\dot{V}_A$
V_B = blood volume (ml) (5 500 ml)
$[COHb]$ = CO volume/blood volume (ml/ml)
$\dot{V}_{CO}$ = endogenous CO production (ml/minute) (0.007 ml/min)
P_cO_2 = average partial pressure of oxygen in lung capillaries (mmHg) (100 mmHg)
M = Haldane affinity ratio (ratio: 218)
$[O_2Hb]$ = volume of oxygen/volume of blood (maximum is 0.2)
P_ICO = partial pressure of CO in inhaled air (mmHg)
D_LCO = pulmonary diffusing capacity for CO (ml/min/mmHg) (30 ml/min/mmHg)
P_L = pressure of dry gases in the lungs (mmHg) (713 mmHg)
$\dot{V}_A$ = alveolar ventilation rate (ml/min) (6 000 ml/min)

The values in parentheses indicated for the variables are standard values given by Peterson and Stewart (167). The binding affinity of CO for human adult Hb is about 218 times greater than that of O_2 (60, 182, 185). The Haldane coefficient (M = 210–250) in the Haldane equation presented in 1912 (58) is a measure of this relationship, and is used in the CFK model.

The CFK equation is linear when the oxyhaemoglobin (O_2Hb) concentration is constant (COHb concentration is low). The model gives a good approximation of the COHb concentration at a steady level of inhaled CO. However, the linearity of the relationship also assumes equilibration of COHb concentrations between venous and arterial blood and gases in the lung, as well as between blood and extravascular tissues. Various modifications of the CFK model have been created to take into account physiological aspects in a more accurate way (24, 204, 205). Modifications for COHb prediction in rats have also been made (22).

As the CFK model does not account for extravascular storage sites of CO, a multicompartment model was created by Bruce *et al* (29-31). This model consists of separate compartments for lung, arterial blood, venous blood, muscle tissue and non-muscle tissue. Compared to the CFK model, the Bruce *et al* model predicts COHb levels better when the inhaled CO levels are rapidly changing. It also gives better predictions of the CO washout time course compared to the CFK model.

The affinity of human foetal Hb for CO is higher than that of adult Hb. Modelling maternal and foetal COHb concentrations with a modified CFK model indicates that foetal COHb can be up to 10% higher than the maternal levels. After treatment with 100% O_2, the foetal COHb levels are not reduced as fast as the mother's COHb levels (53, 87).

A competitive situation is related to the binding of CO and O_2 to Hb. The greater the number of haeme sites bound to CO is, the greater is the affinity of the remaining free haeme sites for O_2. CO binding to Hb also results in changes in the normal O_2Hb dissociation curve, causing tissues to have difficulties in obtaining O_2 from the blood (the so called Haldane effect) (6, 185).

7.4 Factors modifying carbon monoxide uptake and carboxyhaemoglobin formation

Altitude

At high altitudes, physiological changes occur to compensate the decreased barometric pressure. This can result in hypobaric hypoxia, causing humans to hyperventilate, which then results in reduced arterial blood carbon dioxide, and increased blood pressure and cardiac output. The compensatory mechanisms also include redistribution of blood from blood vessels to extravascular compartments and from skin to organs. As a general outcome, increased CO uptake and COHb formation as well as CO elimination can be observed (229).

In a study with human volunteers breathing ambient air, the COHb levels measured at an altitude of 3 500 meters were significantly higher than at sea level (0.95 versus 0.79%). The result was similar for both men and women. Breathing

9 ppm CO at rest at an altitude of 3 500 meters increased the COHb from the basal level of 0.95% at this altitude to 2.0% (137). On the contrary, the COHb levels measured in healthy volunteers after exposure to 150 ppm CO combined with exercise at an altitude of 3 000 meters were comparable to or even lower than the levels observed after the same exposure at sea level (90).

Exercise

During exercise, the respiratory exchange ratio and cardiac output are increased, red blood cell reserves are mobilised from the spleen and the diffusing capacity of CO increases. When the gas exchange efficiency increases, the CO uptake is promoted. As a consequence, the rates of CO uptake and COHb formation are proportional to the intensity of exercise (229).

Kinker *et al* studied the CO inhalation kinetics in six male volunteers by exposing them to about 500 ppm CO while changing from rest to increased workload levels corresponding to 40%, 60% and 80% of the maximal oxygen uptake (V_{O2max}). Oxygen uptake (V_{O2}), CO uptake (V_{CO}) and diffusing capacity for CO (DL_{CO}) were measured. DL_{CO} increased more steeply than V_{CO} with increased workload and V_{CO} rose more steeply than V_{O2}. Furthermore, the increase in DL_{CO} plateaued at about 60–80% V_{O2max}. The faster kinetics of CO compared to oxygen was interpreted by the authors as a consequence of increased recruitment of alveolar-capillary surface areas with increased exercise up to about 60% V_{O2max}, where after no further recruitment occurs (105).

Gender

Male subjects generally have higher COHb concentrations than females and the COHb half-time is longer in healthy men than in women of the same age. However, the difference in half-time between male and female subjects is usually < 6% (101). Women are showing variations in the COHb levels through the menstrual cycle, and during pregnancy the endogenous COHb production is increased (52). No differences in COHb levels between males and females were observed at high altitude (137).

Age

Age has been shown to have a greater effect on the half-time of COHb than does the gender (101). The CO uptake and elimination rates decrease with age. It has been established that the diffusing capacity for CO decreases with increasing age. In middle-aged women, the decline in CO-diffusing capacity with age is lower than in men, but at older ages, the rates are similar (146). The steady state transfer capacity of the lung for CO has been shown to be about 35 ml/min/kPa/m^2 in old persons (76 subjects, average age 82 years), which is approximately 50% of the capacity observed in younger persons (76, 229).

8. Biological monitoring

CO exposure is usually estimated by measuring COHb in blood, which can be considered as a reliable biomarker. CO in exhaled breath can also be used as an estimate of CO exposure. The relation between CO exposure and COHb is affected if exposure to dihalomethanes occurs, and therefore it is important to check the possibility for such co-exposure.

8.1 Carboxyhaemoglobin levels in blood

The COHb levels of non-smokers are typically < 2%. Approximately 0.4–0.7% is formed through endogenous production of CO (16).

During exogenous exposure to CO, the COHb levels increase based on the duration time and CO concentrations (see Figure 1).

Non-occupational factors affecting and modifying the basal COHb levels are for example:

- smoking (COHb may be up to 10% directly after smoking)
- metabolism of dihalomethanes (see below)
- environmental CO exposure
- altitude, exercise, gender, age (see Section 7.4)

Metabolism of dihalomethanes to CO

Dihalomethanes, including dichloromethane (methylene chloride) are industrial chemicals known to be metabolised to CO via a cytochrome P450 dependent pathway, both in humans and experimental animals. The metabolism results in elevated levels of COHb in the blood and increased levels of CO in expired air. In addition to CO, carbon dioxide and chlorine (or iodine or bromine) are also formed (95). Exposure of healthy volunteers to methylene chloride alone at 180 and 350 mg/m^3, levels which are within the range of occupational exposure limits for most countries, for 7.5 hours resulted in COHb levels of 1.9 and 3.4%, respectively (55).

Other sources causing CO formation

Other sources of CO production are for example the HO catalysis of products of auto-oxidation of phenols, photo-oxidation of organic compounds and lipid peroxidation of different cell membrane lipids (96).

8.2 Carbon monoxide levels in expired air

The partial pressure of CO in arterial blood is in equilibrium with the partial pressure of CO in the alveolar gas. COHb levels can be estimated by measuring CO in breath and by using the CFK relationship (Section 7.3).

As the CFK relationship is based upon attainment of an equilibrium, the results are always estimates (96).

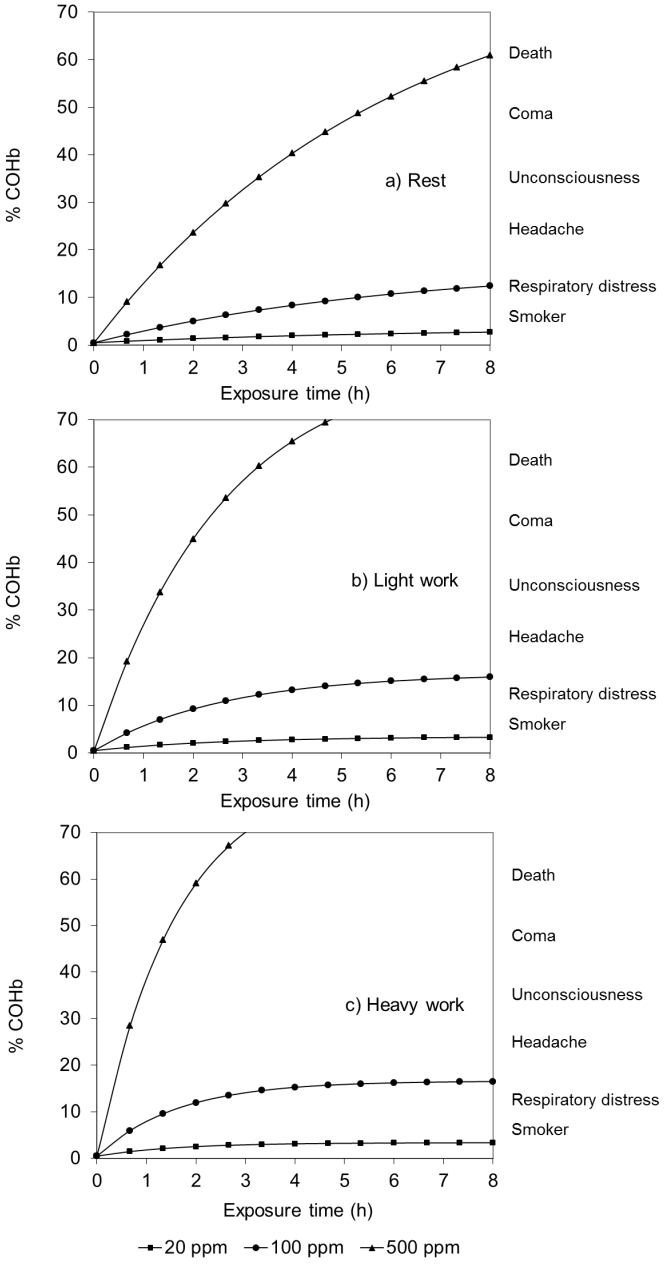

Figure 1. COHb levels for different CO exposure concentration-time combinations based on the CFK equation, taking into consideration the workload; a) at rest, b) at light workload, and c) at heavy workload. Modified from NRC 2010 and Peterson and Stewart 1975 (151, 168).

9. Mechanisms of toxicity

Binding of CO to haemoglobin and replacing oxyhaemoglobin with COHb has for decades been considered as the main mechanism behind CO toxicity. Studies during later years do, however, provide evidence that CO poisoning is a combined effect of COHb formation, direct cellular effects, and increased nitric oxide activity. Even long after the COHb levels have decreased to a normal level, the cellular energy metabolism is inhibited. This may explain the observations that measured COHb levels do not correlate with the severity of clinical effects (28, 103, 169, 170). The proposed mechanisms behind CO toxicity are presented in Figure 2.

The best known of the pathways behind CO toxicity is the haemoglobin binding, resulting in hypoxia or ischaemia. Other suggested pathways are the direct cellular toxic effects and the increased nitric oxide formation. Direct cellular toxicity is caused by CO binding to other haeme-containing proteins, like cytochromes, myoglobin and guanylyl cyclase. The clinical outcomes of such protein binding include arrhythmias and cardiac dysfunction, direct skeletal muscle toxicity and loss of consciousness. Nitric oxide activity is thought to cause loss of consciousness and is also important for oxidative damage, which can culminate in increased brain lipid peroxidation, and a clinical syndrome with delayed neurologic sequelae.

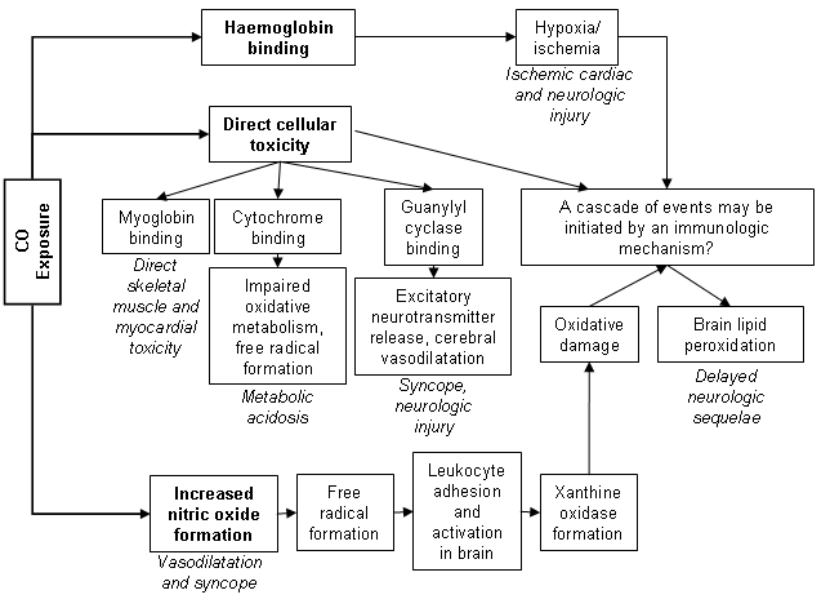

Figure 2. Proposed mechanisms for CO toxicity; a) Haemoglobin binding, b) Direct cellular toxicity, and c) Increased nitric oxide formation, and their biological and clinical effects. Modified from Kao and Nanagas 2006 (103).

Increased brain lipid peroxidation may also be an outcome of the combined effects of induced nitric oxide levels, hypoxia/ischaemia and direct cellular toxicity. It has been speculated that this cascade of events may require initiation by an immunological mechanism, but this has not been confirmed (reviewed in (103)).

The pathophysiological changes seen in relation to CO poisoning are often similar to those observed with post-ischaemic reperfusion injuries. The same type of pathology occurs also in the brain when hypoxia, followed by intervals of ischaemia, is created under circumstances other than CO exposure. The formation of oxygen radicals during reperfusion has thus been implicated as the major component of post-ischaemic brain injury caused by CO (112, 153, 232). Rat studies showing CO-induced brain lipid peroxidation after, but not during, CO exposure support this theory (221).

Endogenously produced CO (see Section 7.2) acts as a signalling substance in the neuronal system. The functions of endogenous CO involve the regulation of neurotransmitters and neuropeptide release, and it is thought to have an important role for neuronal activities like odour adaptation, learning and memory (249).

9.1 Haemoglobin binding

The major toxic effect of CO is hypoxia, which is caused by COHb formation resulting in impaired oxygen carrying capacity of the blood. CO can also cause injury by causing ischaemia due to impaired tissue perfusion. Both human and animal studies indicate that myocardial depression, peripheral vasodilatation and ventricular dysrhythmia, causing hypotension, may contribute to the generation of neurologic injury (reviewed in (158, 234)).

The most clear-cut mechanism by which CO toxicity occurs is the competitive binding of CO to the haemoglobin haeme groups (for details, see Section 7.1.1). When CO is bound at one of the four haeme sites of the haemoglobin molecule, its tetrameric structure undergoes a conformational change, resulting in an increased affinity of the remaining haeme groups for oxygen. The oxygen-haemoglobin dissociation curve is shifted to the left and the final result is a haemoglobin molecule which releases oxygen poorly at the tissue level. The decreased oxygen delivery is sensed centrally, stimulating ventilator efforts and increasing minute ventilation. The latter will increase uptake of CO and raise COHb levels. In addition, exhalation of carbon dioxide increases, resulting in respiratory alkalosis and further shifting of the oxygen-haemoglobin dissociation curve to the left. The clinical outcome of COHb formation may be hypoxia or ischaemia, resulting in ischaemic cardiac and neurological injuries (78, 96, 155, 183, 234).

Oxygen has been used as the main treatment for CO poisoning since the 1860s. In order to inhibit an induction of tissue hypoxia, the supplementation with 100% of normobaric oxygen is a critical step. The duration of the oxygen treatment is dependent of the COHb levels. If arrhythmia, ischaemia or haemodynamic instability occurs despite the therapy with 100% oxygen, treatment with hyperbaric oxygen (pressure >1.4 atm) should be considered. Hyperbaric oxygen treatment

increases the partial pressure of oxygen in the blood and the rate of displacement of CO from haemoglobin (242).

9.2 Direct cellular toxicity and protein binding

CO binds to many haeme-containing proteins other than haemoglobin (37, 86). Cytochrome binding may result in impaired oxidative metabolism and formation of free radicals. Inactivation of mitochondrial enzymes and impaired electron transport from oxygen radicals may also be responsible for the impaired cellular respiration (225, 251, 252).

Binding of CO to myoglobin causes reduced oxygen availability in the heart, which can cause arrhythmias and cardiac dysfunction. CO binding to myoglobin may also result in direct skeletal muscle toxicity leading to rhabdomyolysis, or indirect muscle toxicity due to local ischaemia (49, 68, 177, 190).

9.3 Increased nitric oxide formation

CO-induced elevation of nitric oxide (NO) has been documented *in vivo* in both lung and brain of experimental animals, as well as in different *in vitro* studies (bovine lung endothelial cells, human and rat platelets). The elevation of NO appears to be caused by competition between CO and NO for intracellular haemoprotein binding sites, and not on an increase in enzymatic production of NO (222, 224, 226).

Cerebral vasodilatation, associated with temporal loss of consciousness and increased NO levels, has been observed in animals exposed to CO. It has thus been speculated that syncope may be related to NO-mediated low blood flow and cerebral vessel relaxation (97, 103, 201).

The role of CO-induced NO in the events culminating in oxidative damage of the brain, and possibly also the clinical syndrome delayed neurologic sequelae, is presented in Figure 2. NO can affect the adherence of neutrophils to the endothelium resulting in oxidative damage, lipid peroxidation and delayed neurologic sequelae (97, 221, 223, 225, 251).

9.4 Other mechanisms

CO is known to be a messenger molecule, affecting mechanisms like activation of cyclic guanosine monophosphate (cGMP), direct activation of calcium dependent potassium channels, and acting as a signalling molecule in modulating mitogen-activated protein kinases (MAPKs) (18).

10. Effects in animals and *in vitro* studies

10.1 Irritation and sensitisation

No animal studies on irritation or sensitisation caused by CO have been located.

10.2 Effects of single exposure

A number of lethality studies on acute inhalation of CO have been published. Table 6 summarises lethal concentrations at single inhalation exposure to CO. A clear inverse relation is seen between exposure duration and lethal concentration in both rats and mice.

The chemical company DuPont (E.I. du Pont de Nemours and Co) determined the LC_{50} values for male rats by exposure to CO for 5, 15, 30 and 60 minutes (Table 6). The exposures were carried out by head-only or in exposure chambers. The COHb levels were 50–60% for the rats which died after the treatment (151).

In the study by Rose *et al*, LC_{50} values were determined for rats, mice and guinea pigs exposed to CO for 4 hours (Table 6). The COHb levels for animals that had died were 50–80% and 57–90% for rats and guinea pigs, respectively. The COHb levels of mice were not reported (184).

Table 6. Lethal concentrations, expressed as LC_{50}, observed in animals after single inhalation exposure to carbon monoxide (CO).

LC_{50} value (ppm)	Exposure duration (min)	Species	Reference
14 200	5	Rat	Darmer *et al* 1972 in (151)
10 151	5	Rat	DuPont 1981 in (151)
8 636	15	Rat	Hartzell *et al* 1985 (82)
5 664	15	Rat	DuPont 1981 in (151)
5 607	30	Rat	Herpol *et al* 1976 in (151)
5 500	30	Rat	Kimmerle 1974 in (151)
5 207	30	Rat	Hartzell *et al* 1985 (82)
4 710	30	Rat	DuPont 1981 in (151)
4 070	30	Rat	Haskell laboratories 1978 in (151)
4 670	60	Rat	Kimmerle 1974 in (151)
3 954	60	Rat	DuPont 1981 in (151)
1 807	240	Rat	Rose *et al* 1970 (184)
10 127	15	Mouse	Kishitani and Nakamura 1979 in (151)
3 570	30	Mouse	Hilado *et al* 1978 (85)
8 000	30	Mouse	Hilado *et al* 1978 (85)
2 444	240	Mouse	Rose *et al* 1970 (184)
5 718	240	Guinea pig	Rose *et al* 1970 (184)

DuPont: E.I. du Pont de Nemours and Co., LC_{50}: lethal concentration for 50% of the animals at single inhalation exposure.

The study design and outcome of a number of single exposure studies (exposure time up to 24 hours) are compiled in Table 7.

Low-dose studies have demonstrated pulmonary vascular effects already after single exposure to 50–100 ppm CO in rats. Thom *et al* showed that 1 hour of exposure to 50 ppm CO (COHb not reported) resulted in increased rat lung capillary leakage. Furthermore, elevated nitrotyrosine concentrations in aorta and lung homogenates and increased nitric oxide levels in the lungs were detected, indicating an induction of pulmonary vascular stress (222, 224). In a study by Ghio *et al* signs of direct cellular effects were observed, as 24-hour exposure of rats to 50 ppm CO (COHb 6.9%) resulted in markedly increased levels of lavagable iron and decreased concentrations of non-haeme iron in the lungs, indicating an active removal of cellular iron. Similar results were also obtained *in vitro* in cultured normal human bronchial epithelium (BEAS-2) cells. The authors stated that the loss of non-haeme iron after CO reduced cellular oxidative stress (72).

Haemodynamic alterations, occurring as compensatory mechanisms for CO-induced hypoxia, were observed in rats at higher exposures (150–250 ppm). The observations included increased heart rate, cardiac output, coronary perfusion pressure and contractility, and decreased tissue oxygen tension (61, 102, 238). Reduction of the threshold for ventricular fibrillation was observed both in dogs (COHb 6.4%) and monkeys (COHb 9.3%) with induced myocardial injury, but also in healthy animals, after exposure to 100 ppm CO for 2 or 6 hours, respectively (13, 14, 49).

10.3 Effects of short-term exposure (up to 90 days)

Animal studies examining the effects of repeated short-term exposure (up to 90 days) are summarised in Table 8. The main parameters studied are the haematological, pulmonary and cardiovascular effects.

Many of the older studies focus on haematological effects, occurring as compensatory mechanisms due to the hypoxia induced by CO. These effects include increased blood volume, haemoglobin, haematocrit, erythrocyte count and erythrocyte volume, and have been observed for example in rats at $\geq$ 7.5% COHb and in monkeys at $\geq$ 10% COHb (50, 100, 156, 157).

Exposure of rats to 50 ppm CO for up to 21 days under hypobaric condition resulted in increased pulmonary vascular resistance and increased number of small muscular vessels. No such effects were seen when the exposure was carried out under normobaric condition (36).

Alterations in cardiac rhythm have been followed in a number of studies, also involving animals with induced myocardial ischaemia. Right ventricle ischaemia and dysfunction were observed in rats with pulmonary hypertension after exposure to 50 ppm CO (COHb 4.1%) for 1 week (71). Continuous exposure of healthy dogs to 50 or 100 ppm CO for 6 weeks caused significant histopathological changes in the brain. Both doses also caused alterations in the cardiac rhythm, heart dilation, and small histological alterations, like fatty degeneration of the

heart muscle (172). DeBias *et al* exposed two groups of dogs, healthy ones and dogs with induced myocardial infarction, to 100 ppm, 23 hours/day for 14 weeks (COHb 14%). Neither group showed any signs of abnormalities in electrocardiograms, serum enzymes or haematological parameters (51). Exposure of monkeys (100 ppm, 23 hours/day, 12 or 24 weeks; COHb 12%), on the other hand, resulted in significant cardiac effects. Electrocardiograms showed higher P-wave amplitudes in both infarcted and non-infarcted monkeys, and higher incidence of T-wave inversion in infarcted monkeys (50).

In some reports it has been suggested that CO might induce changes in lipid metabolism, resulting in atherosclerosis, or that atherosclerosis could be promoted by CO-induced oxidative stress, causing injuries of the vascular epithelium (229). In the evaluation by US EPA it was concluded that there is conflicting evidence, but that based on the weight-of-evidence there are no strong indications that CO exposure would result in atherosclerosis (229).

10.4 Mutagenicity and genotoxicity

No genotoxicity studies performed according to standard protocols were retrieved. The genotoxic potential of CO was tested in pregnant ICR mice. One group of animals was given a single exposure of 0, 1 500, 2 500 or 3 500 ppm CO for 10 minutes during gestation day 5, 11 or 16. The other groups were repeatedly exposed to 0 or 500 ppm CO for 1 hour/day on gestation days 0–6, 7–13 or 14–20. The incidence of micronuclei and sister chromatid exchanges in bone marrow cells from animals in the first group showed a dose-dependent increase in both maternal and foetal cell samples. These effects were also observed in both maternal and foetal samples from the repeatedly exposed group (500 ppm) (115) (see also Table 9). Some concern can be raised regarding the validity of the report, e.g. timing between exposure and cell harvesting and timing between labelling of the cells for the sister chromatid exchange assay and cell sampling.

No other valid studies were found.

10.5 Effects of long-term exposure and carcinogenicity

No carcinogenicity studies were retrieved. Sørhaug *et al* exposed 51 female rats to 200 ppm CO for 72 weeks (Table 8). The mean COHb concentration was 14.7%. No changes in morphology of the lungs, but significantly increased left and right ventricle weights, were reported (220).

Table 7. Effects in animals after single inhalation exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean blood COHb (%)	Species	No. and sex of CO exposed animals	Effects	Reference
35	1 h	–	Rat	19 males with myo-cardial infarction	Reduced ventricular beat frequency and decreased supraventricular ectopic beats. No effects on heart rate.	(239, 240)
50	24 h	6.9	Rat	Not given	Elevated iron levels, mild neutrophil accumulation, increased lactate dehydrogenase in lung lavage. Decreased non-haeme iron concentrations in the lungs.	(72)
50	1 h	–	Rat	5–8 males/group	Lung capillary leakage increased. Elevated nitro-tyrosine concentration in aorta. Nitric oxide synthase levels not affected.	(222, 224)
80	20 min	3.3 (at the end of the total experiment [a])	Rat, anaesthetised	33 in total, sex not specified	No effect on brain tissue oxygen tension. Decreased tissue oxygen tension in the biceps brachii muscle.	(238)
100	1 h	–	Rat	Males, total number not given, numbers used for different assays varies	Lung capillary leakage increased. Elevated nitro-tyrosine concentrations in aorta and lung homogenates, and increased nitric oxide levels in the lungs indicating induction of pulmonary vascular stress. Nitric oxide synthase levels not affected.	(222, 224)
100	2 h	6.4	Dog	10 healthy and 11 with myocardial injury. Sex not specified	Reduced ventricular fibrillation threshold in both groups.	(13, 14)
100	6 h	9.3	Monkey	5 healthy and 5 with myocardial infarction. Sex not specified	Reduced ventricular fibrillation threshold in both groups.	(49)
150	0.5–2 h	7.5	Rat, anaesthetised	6 males	Increased heart rate, cardiac output, cardiac index, time derivative of maximal force and stroke volume. Decreased mean arterial pressure, total peripheral resistance and left ventricular systolic pressure.	(102)

Table 7. Effects in animals after single inhalation exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean blood COHb (%)	Species	No. and sex of CO exposed animals	Effects	Reference
160	20 min	3.3 (at the end of the total experiment[a])	Rat, anaesthetised	33 in total, sex not specified	Decreased tissue oxygen tension in the cerebral cortex of the brain and in the biceps brachii muscle.	(238)
250	1.5 h	11	Rat	12 males/group	Decreased cardiac cGMP/cAMP ratio (indicating vascular relaxation abnormality). Increased coronary perfusion pressure and contractility.	(61)
1 500	30 min	23	Dog, anaesthetised	10, sex not specified	Increased coronary flow and heart rate. Decreased myocardial oxygen consumption.	(2)
1 500	1 h	–	Cat	5, sex not specified	Slightly decreased ventilation.	(70)
1 500	1.5 h	–	Rat	8–22 females/group	Altered blood glucose, unconsciousness, cerebral oedema, central nervous system damage and hypothermia.	(56, 159, 165)
2 700	1.5 h	–	Rat	9–10 females/group	Hypothermia, hypotension and bradychardia. Mortality rate 44%. Mortality rates were 50% in the group kept in +4 °C for 4 h after the exposure and 22% in the group kept on a heating pad.	(215)
5 000	5 sequential exposures within 40–50 min	4.9 and 17.0 (after 1st and 5th exposure, respectively)	Dog, anaesthetised	11, sex not specified	Increased myocardial ischaemia 1 h after coronary artery ligation (already at 4.9% COHb).	(19)
5 000	90 min	20	Dog, anaesthetised	No. of exposed animals unclear, males	Enhanced sensitivity to digitalis-induced ventricular tachycardia. No effect on sensitivity to epinephrine- or digitalis induced ventricular fibrillation.	(104)
8 000	15–45 min	63	Rabbit	5, sex not specified	Decreased mean blood pressure and arterial pH after 30 min. Induction of oedema of capillary endothelium and alveolar epithelium, suggesting increased alveolar-epithelial permeability. The heart rate was not affected.	(67)

Table 7. Effects in animals after single inhalation exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean blood COHb (%)	Species	No. and sex of CO exposed animals	Effects	Reference
10 000	3 + 3 min	21 (after 3 min), 28 (after 3 + 3 min)	Rabbit, anaesthetised	No. of exposed animals unclear, both sexes	Increased regional blood flow to the myocardium. Decreased mean blood pressure.	(110)
10 000 then 1 000	15–20 min (total)	61–67 (range)	Dog, anaesthetised	7, sex not specified	Cardiac output and stroke volume increased. Mean arterial pressure and total peripheral resistance decreased.	(219)
28 400	4 min	> 60	Rat, anaesthetised	15 males	Increased total pulmonary resistance.	(212)
28 400	4 min	> 60	Guinea pig, anaesthetised	15 males	Increased total pulmonary resistance.	(212)

[a] 2 × 20 min at 160 ppm and 2 × 20 min at 80 ppm in random order, with 30 min break between exposures.
cAMP: cyclic adenosine monophosphate, cGMP: cyclic guanosine monophosphate, CO: carbon monoxide, COHb: carboxyhaemoglobin.

Table 8. Effects in animals after repeated inhalation exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean blood COHb (%)	Species	No. and sex of animals	Effects	Reference
50	10 weeks continuously	–	Rat	9/group, both sexes	Increased cardiac dilation and decreased left ventricular function in rats with cardiac hypertrophy but not in healthy rats.	(139)
50	3 weeks	–	Rat	8/group, sex not specified	Vascular remodelling and increased pulmonary vascular resistance in rats with hypobaric hypoxia. No effect at normobaric conditions.	(36)
50	1 week	4.1	Rat	8–10 males/group	Right ventricle ischaemia and dysfunction in rats with pulmonary hypertension (hypobaric hypoxia treatment) but not in normal rats.	(71)
50	Intermittently or continuously for 6 weeks	2.6–12 (range)	Dog	4–8/group, sex not specified	Significant changes in brain and heart morphology. Abnormal electrocardiograms. Same effects seen at 100 ppm.	(172)
51	90 days continuously	5.3	Monkey	9 males	Haematocrit and haemoglobin not affected.	(100)
51	90 days continuously	5.1	Rat	15/group, sex not specified	Haematocrit and haemoglobin not affected.	(100)
96	90 days continuously	10.3	Monkey	9 males	Increased haematocrit. Haemoglobin not affected.	(100)
96	90 days continuously	7.5	Rat	15/group, sex not specified	Increased haemoglobin and haematocrit. Same effects seen at 200 ppm.	(100)
96	90 days continuously	4.9	Guinea pig	15/group, sex not specified	Haematocrit and haemoglobin not affected.	(100)
100	23 h/day for 14 weeks	14	Dog	12 males/group	No effects on serum enzymes, electrocardiograms or haematological parameters in normal animals or in animals with induced myocardial infarction.	(51)
100	23 h/day for 12 or 24 weeks	12.4	Monkey	7/group, sex not specified	Increased haematocrit, haemoglobin and red blood cell numbers in monkeys with induced myocardial infarction and in non-infarcted monkeys after 12 weeks of CO exposure. Electrocardiograms showed higher P-wave amplitudes in both infarcted and non-infarcted animals, and higher incidence of T-wave inversion in infarcted animals.	(50)

Table 8. Effects in animals after repeated inhalation exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean blood COHb (%)	Species	No. and sex of animals	Effects	Reference
100	46 days	9.3	Rat	12 males	Increased haemoglobin concentration. Heart weight and body weight not affected.	(156, 157)
100	1 week	12	Rat	10 females/group	Increased myocardial endothelin-1 expression, increased right and left ventricular weight. Same effects observed when the exposure was followed by 1 week of exposure at 200 ppm.	(123)
100–300	4 h/day, 5 days/week for 7 months; 0.5% cholesterol added to diet	23	Monkey	10–12 females/ group	Coronary atherosclerosis aggravated, but not aortic atherosclerosis.	(237)
150	6 h/day, 5 days/week for 52 weeks; 0.5–2% cholesterol added to diet	10	Pigeon	20 females/group	Increased incidence and severity of coronary atherosclerosis, compared to non-CO-exposed birds, in groups given 0.5% or 1% dietary cholesterol + CO, but not in the group given 2% cholesterol + CO. Similar results obtained at 300 ppm CO (1% cholesterol); increase in coronary atherosclerosis dose-dependent.	(227)
160	4 h/day for 1–16 days	–	Mini-pig	11 in CO-group, sex not specified	Adhesion of platelets to arterial endothelium (in some cases already seen after a single exposure), platelet aggregation, increased haematocrit and blood viscosity. Same effects observed at 185 ppm.	(135)
180	2 weeks	16–18 (range)	Rabbit	4 males	Ultrastructural changes in the aorta (oedema, irregular cellular structure).	(108)
200	30 days	15.8	Rat	7 males	Increased haemoglobin concentration and heart weight. Body weight not affected.	(156, 157)
200	90 days continuously	20	Monkey	9 males	Increased haemoglobin concentration and haematocrit.	(100)
200	90 days continuously	9.4	Guinea pig	15/group, sex not specified	Increased haemoglobin concentration and haematocrit.	(100)

Table 8. Effects in animals after repeated inhalation exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean blood COHb (%)	Species	No. and sex of animals	Effects	Reference
200	72 weeks	14.7	Rat	51 females	Induction of ventricular hypertrophy. No changes in lung morphology or signs of atherosclerosis.	(220)
250–1 300	250 ppm for 17 days followed by 500 ppm 13–14 days, 750 ppm 10 days, 1 300 ppm 10 days	–	Rat	6–9 males/group	Increased haematocrit, red blood cell volume and blood volume at 250 ppm and above. Plasma volume was not affected at any concentrations. Gross lung weight increased at 750 and 1 300 ppm.	(163)
400	6 weeks	35	Rat	7 males/group	Increased haemoglobin, haematocrit and relative heart weight. Myocardial lactate dehydrogenase M subunits elevated.	(213)
500	20–42 days	41.1	Rat	7 males	Increased haemoglobin concentration, heart weight and body weight.	(156, 157)
500	38–47 days	–	Rat	11 males/group	Increased haematocrit, weight of right and left ventricles, ratio of the sum of right and left ventricles to body weight, left ventricular apex-to-base length and left ventricular outside diameter.	(166)

CO: carbon monoxide, COHb: carboxyhaemoglobin.

10.6 Reproductive and developmental effects

A large number of studies on the developmental effects of exposure during the gestational or early postnatal period have been published (Table 9).

Exposure of rabbits to 90 ppm CO throughout gestation resulted in decreased birth weights and increased neonatal mortality (15). Decreased birth weights were also observed among rats exposed to CO concentrations of 100–150 ppm or higher during the gestational period (62, 129, 173). The pups of rats exposed to 75–300 ppm CO throughout the gestation and until postnatal day 10, showed dose-dependently decreased body weights at 10 days of age (211).

Adverse effects of CO on the development of the central nervous system have been observed in many studies. Impairment of aerial righting was observed at postnatal day 1 in mice pups exposed to 65 ppm or 125 ppm CO during pregnancy. Impairment of the righting reflex and negative geotaxis were observed in the pups of the 125 ppm-group on postnatal days 1 and 10, respectively (199). Delays in the development of negative geotaxis and homing behaviour were seen in rat pups of dams exposed throughout the gestation to 150 ppm CO (63). Exposure to 150 ppm CO throughout gestation resulted also in impairment of acquisition and retention of a learned active avoidance task in male rat pups at postnatal days 30–31 (133). De Salvia *et al* showed impairment of acquisition of a two-way active avoidance task in 90-day-old rats and impairment of acquisition and reacquisition of a two-way active avoidance task in 18-month-old rats after exposure of the mothers to 150 ppm CO throughout gestation. No effects were seen in a lower dose group (75 ppm) (48).

In a study on the developing peripheral auditory system of rats exposed to CO on postnatal days 8–22, swollen nerve terminals innervating the inner hair cells were observed at 25 ppm. No morphological differences were observed in the inner and outer hair cells of the organ of Corti. No effects were seen at 12 ppm (125). When studying the expression of neuroglobin and cytochrome c in the cochlea of the developing rat, Lopez *et al* observed a decrease in neuroglobin immunoreactivity and mRNA in the spiral ligament cells and spiral ganglia neurons but not in supporting cells after prenatal only or pre- and postnatal exposure to 25 ppm CO. Cytochrome c immunoreactivity decreased in the spiral ligament, spiral ganglia neurons and also in supporting cells. No significant changes were observed in rats exposed postnatally only (128). In a study on oxidative stress in the cerebellum of the developing rat, three study groups were included: prenatal only, prenatal and postnatal, and postnatal only exposure of rats to 25 ppm CO. Evidence for oxidative stress was seen in all groups, as indicated by increased expression of superoxide dismutase-1 and -2, and HO-1 in the cerebellar cortex and by an increase in inducible nitric oxide synthase and nitrotyrosine in blood vessels and Purkinje cells. The most marked effects were observed after prenatal or pre- and postnatal exposure (127). The same parameters related to oxidative stress were investigated in the cochlea of rats exposed to 25 ppm CO prenatally or pre- and postnatally. Superoxide dismutase-1 and HO-1 immunoreactivity increased in the stria vascularis and blood vessels in pups exposed pre-

and postnatally, but not in those exposed only during pregnancy. Inducible nitric oxide synthase and nitrotyrosine immunoreactivity increased in blood vessels of the cochlea of rats in both exposure groups. Vacuolisation of the afferent terminals at the basal portion of the cochlea was observed in both exposure groups (126). The same research group also investigated the effects of 25 ppm CO on the expression of neuroglobin and cytoglobin, which are potentially protective against hypoxia and oxidative stress. The mRNAs of neuroglobin and cytoglobin in the cerebellum were not affected in any of the exposed groups (prenatal only, pre- and postnatal, and postnatal only), but the cytoglobin protein levels were significantly increased in each of the exposed groups. This indicates that cytoglobin may play a role in protecting cerebellar cells from hypoxia-related oxidative stress (20). Few animals were used and the clinical relevance of the changes in protein levels is unclear.

The same research group also studied the effects of mild CO exposure on auditory function. Exposure of newborn rats to 12, 25, 50 or 100 ppm on postnatal days 6–22 resulted in an attenuation of the amplitude of action potential of the 8th cranial nerve. At the age of 73 days, the effect was not completely reversed in the 50 ppm group (not examined in the other groups). The authors stated that this reduction could affect the processing of auditory input, and could be a link to a mild form of the disorder auditory neuropathy, if exposed to CO during childhood. The otoacoustic emission amplitude was reduced at 50 ppm, but not at 25 ppm (not examined at 12 ppm). Auditory brainstem conduction times did not differ from those of the control animals in any of the study groups (208).

Exposure of rat pups to 12.5, 25, and 50 ppm CO, using the same protocol as in the study above (208) caused a significant decrease in the number of cells expressing a basal level of c-Fos in the central nucleus of the inferior colliculus. The expression of c-Fos was not attenuated in the other subregions of the inferior colliculus. At 75–77 days of age (55 days after the ending of the exposures), the c-Fos expression was still significantly lower than in the control animals. The authors concluded that this indicates a persistent effect. c-Fos belongs to the immediate early gene family of transcription factors. Its expression is increased by sound stimulation, and it is considered as a good marker for neuronal activation in the auditory system. However, the persistent decrease in basal c-Fos activity from CO exposure may not necessarily indicate that the central nucleus of the inferior colliculus is the location of the deficit (236).

CO also affects the development of the peripheral nervous system of the offspring of exposed dams. Significantly reduced myelin sheath thickness of sciatic nerve fibres was observed in rats after exposure to 75 ppm or 150 ppm CO during gestation days 0–20. No changes in axon diameters or motor activity were observed (33). Another study, with the same exposure pattern (75 and 150 ppm on gestation days 0–20), showed effects on ion channel development, as indicated by significantly slowed inactivation kinetics of transient sodium current in sciatic nerves isolated on postnatal day 40. A negative shift in sodium equilibration potential was observed both on postnatal days 40 and 270 (35).

Decreased haemoglobin and haematocrit values were observed in rats after exposure to 200–250 ppm CO throughout the gestation (160, 173). Gestational exposure (60–157 ppm) resulted also in a dose-related increase in absolute and relative heart weight of newborn rat pups (162, 173).

10.7 Combined exposures

The auditory effects of CO have recently been reviewed (99). In rat inhalation studies, CO alone did not affect the auditory function in adults at concentrations up to 1 500 ppm (no observed adverse effect level, NOAEL). However, it can potentiate the effects of noise even when noise levels alone would not cause a change in hearing. In combination with excessive noise (100 dB at 13.6 kHz OBN), the experimental NOAEL was 300 ppm and the lowest observed adverse effect level (LOAEL) 500 ppm. The calculated lower bounds for benchmark doses of CO that produced either an increase in auditory threshold equivalent to 10% of the effect of noise alone (100 dB at 13.6 kHz OBN) or produced a 5-dB potentiation of noise-induced hearing loss were 194 and 320 ppm (LOAELs), respectively (38, 64, 99).

Dihalomethanes are known to be metabolised via a cytochrome P450 dependent pathway to CO and to induce the CO levels, and an additive effect on blood COHb concentration by simultaneous exposure to CO and dichloromethane has been observed (95, 114).

Animal studies with combined exposure to CO and hydrogen cyanide indicate a synergistic effect (141, 149, 171). Dodds *et al* observed a synergistic effect for neurologic index and blood glucose concentration in rats exposed to CO and hydrogen cyanide. No synergistic relationship was observed with respect to haematocrit, blood pressure, body temperature or lactate concentration (56).

CO has been shown to inhibit the oxidation of acetonitrile to cyanide in rats (66, 69).

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
12	Newborns exposed continuously on PDs 8–22	–	Rat	–	Not specified	No effects on components of the inner ear observed.	(125)
12	Artificially reared newborns exposed continuously on PDs 6–22	–	Rat	–	7 litters, 10 pups/litter for the whole study, sex not specified	A consistent attenuation of the amplitude of the action potential of the 8th cranial nerve at PD 22. No effects on body weight or on auditory brainstem conduction times.	(208)
12.5	Artificially reared newborns exposed continuously on PDs 6–22	–	Rat	–	Not specified	Significantly decreased number of cells expressing a basal level of c-Fos in the central nucleus of the inferior colliculus; same effect in rats examined at 27 or 75–77 days of age. No effect on c-Fos expression in other regions of the inferior colliculus. Same effects seen at 25 and 50 ppm.	(236)
25	Newborns exposed continuously on PDs 8–22	–	Rat	–	Not specified	Effects on components of the inner ear; nerve terminals innervating the hair cells swollen. No morphological effects on the inner and outer hair cells of the Corti.	(125)
25	Artificially reared newborns exposed continuously on PDs 6–22	–	Rat	–	7 litters, 10 pups/litter for the whole study, sex not specified	A consistent attenuation of the amplitude of the action potential of the 8th cranial nerve at PD 22. No effects on body weight, otoacoustic emissions or on auditory brainstem conduction times.	(208)
25	10–18 h/day on GDs 5–20, GDs 5–20 + PDs 5–20, or PDs 5–20	–	Rat	Not reported	3 pups/exposure group, sex not specified	Neuroglobin and cytochrome c decreased in the spiral ganglia neurons and in the spiral ligament after prenatal only or pre- and postnatal exposure.	(128)

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
25	10–18 h/day on GDs 5–20, GDs 5–20 + PDs 5–20, or PDs 5–20	–	Rat	Not reported	Not specified	Superoxide dismutase-1, and -2, and haeme oxygenase-1 immunoreactivity increased in the cerebellar cortex. Inducible nitric oxide synthase and nitrotyrosine immunoreactivity increased in blood vessels and Purkinje cells. Effects were seen in all exposure groups.	(127)
25	10–18 h/day on GDs 5–20, or GDs 5–20 + PDs 5–20	–	Rat	Not reported	Not specified. 3 pups/ exposure group for some parameters.	Superoxide dismutase-1 and haeme oxygenase-1 immunoreactivity increased in the stria vascularis and blood vessels in pups exposed pre- and postnatally. Inducible nitric oxide synthase and nitrotyrosine immunoreactivity increased in blood vessels of the cochlea of rats in both exposure groups. Vacuolisation of the afferent terminals at the basal portion of the cochlea in both exposure groups at PD 20.	(126)
25	12 h/day on GDs 5–20, GDs 5–20 + PDs 5–20, or PDs 5–20	–	Rat	Not reported	3 pups/exposure group, sex not specified	Cytoglobin protein levels increased in the cerebellum in all exposure groups. No effects on neuroglobin or cytoglobin mRNA expression.	(20)
50	Artificially reared newborns exposed continuously on PDs 6–22	–	Rat	–	7 litters, 10 pups/litter for the whole study, sex not specified	A consistent attenuation of the amplitude of the action potential of the 8th cranial nerve at PD 22. Otoacoustic emission amplitudes reduced. No effects on body weight or on auditory brainstem conduction times.	(208)
60	GDs 0–20	–	Rat	Not reported	12–13 litters (males and females), no. of pups/ litter not specified	Increased foetal haematocrit. Increased absolute and relative heart weight.	(173)
65	GDs 7–18	–	Mouse	Not reported	14 litters/group (males and females), no. of pups not specified	Impairment of aerial righting. The righting reflex and geotaxis were not affected.	(199)

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
65	24 h/day on GDs 7–18	–	Mouse	Not reported	17 litters/group (males and females), no. of pups not specified	No effects on embryo lethality; live litter size or mean foetal weight.	(200)
75	24 h/day on GDs 0–20	–	Rat	Not reported	6 male pups/litter, no. of litters not specified	Effects on ion channel development: increase in time constant of sodium current inactivation (on PD 40) and negative shift of equilibrium potential (on PD 40 and 270) in myelinated nerve fibres; depression of the rate of myelin formation. Same effects observed at 150 ppm.	(35)
75	24 h/day continuously throughout gestation	–	Rat	24	8 litters, 6 male pups/litter	No significant effect on locomotor activity or on acquisition of an active avoidance task.	(54)
75	24 h/day on GDs 0–20	7.4	Rat	Not reported	16–18 male pups/group	Reduced myelin sheath thickness of sciatic nerve fibres. No changes in axon diameters or motor activity. Similar results obtained at 150 ppm.	(33)
75	24 h/day on GDs 0–20	7.3	Rat	Not reported	10 male pups/group	Lowered exploratory activity (alterations in habituation and working memory). No effects on spontaneous motor activity. Similar results obtained at 150 ppm.	(74)
75	Throughout gestation	11.5	Rat	24	11–15 litters/dose, 8 pups/litter	Decrease in norepinephrine and serotonin concentration in the pons/medulla at PD 21, but not at PD 42; increase in norepinephrine concentration in the neocortex at PD 42, but not at PD 21. Similar (dose-dependent) effects at 150 and 300 ppm.	(210)
75	From GD 0 to PD 10	11.5	Rat	Not reported	10 litters, no. and sex of pups not specified	Dose-dependent decrease in body weights. See also 150 ppm.	(211)

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
75	24 h/day throughout gestation	15 (estimated)	Rat	Not reported	6 pups/litter (males and females)	No effects on acquisition of a two-way active avoidance task in 90-day-old rats; acquisition and reacquisition of a two-way active avoidance task in 18-month-old rats.	(48)
90	Continuously through-out gestation	9–10 (range)	Rabbit	14	81 (males and females)	Decreased birth weights and increased neonatal mortality.	(15)
100	GDs 1–16, or 4–12	11.7	Rat	13–16/ group	11–16 litters/group (males and females), 11–12 pups/litter	Placental and foetal weights not affected in either of the groups.	(129)
100	GDs 18–22	11.7	Rat	11	14–16 litters/group (males and females), 11–12 pups/litter	Increased placental weight. Foetal weight not affected.	(129)
100	GDs 1–22, or 10–22	11.7	Rat	14–16/ group	14–16 litters/group (males and females), 11–12 pups/litter	Increased placental weight and decreased foetal weights in both groups.	(129)
125	GDs 7–18	–	Mouse	Not reported	14 litters/group (males and females) no. of pups not specified	Impairment of the righting reflex on PD 1 and negative geotaxis on PD 10; impairment of aerial righting.	(199)
125	24 h/day on GDs 7–18	–	Mouse	Not reported	17 litters/group (males and females), no. of pups not specified	Increase in embryolethality and dose-dependent decrease in live litter size.	(200)
125	GDs 0–20	–	Rat	Not reported	10 litters (males and females), no. of pups/ litter not specified	Decreased body weight and increased absolute and relative heart weight. Haemoglobin and haematocrit not affected.	(173)
150	24 h/day on GDs 0–20	16.0	Rat	Not reported	6 male pups/group	Increased sphingosine concentration in the sciatic nerve. No changes in motor activity.	(34)

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
150	24 h/day throughout gestation	–	Rat	Not reported	6 male pups/group	Delayed action potential duration in ventricular myocytes.	(192)
150	24 h/day on GDs 0–20	14.4	Rat	Not reported	5–9 male pups/group	Decreased hippocampal neuronal nitric oxide synthase and haeme oxygenase-2 activities.	(231)
150	24 h/day on GDs 0–20	14.4	Rat	Not reported	6 male pups/litter, total no. unclear	Impairment of long-term potentiation expression (de-creased potentiation of evoked field excitatory potentials in response to tetanisation) in hippo-campal slices of 15–30-day-old males. Presynaptic potentials not affected, indicating normal basal synaptic excitability and calcium influx.	(140)
150	Continuously throughout gestation	15–17 (range)	Rat	Not reported	18 litters, 4–15 pups/ litter (males and females)	Delays in the development of negative geotaxis and homing behaviour.	(63)
150	Continuously throughout gestation	15	Rat	37	12 litters, 44 pups totally (males and females)	Increased wet heart weights and slight decrease in body weights.	(65)
150	Continuously throughout gestation	15.6	Rat	16	10 males	Impairment of acquisition and retention of a learned active avoidance task at PDs 30–31.	(132, 133)
150	24 h/day continuously throughout gestation	15	Rat	24	8 litters, 6 male pups/ litter	No significant effect on locomotor activity. Impairment of acquisition of an active avoidance task.	(54)
150	24 h/day throughout gestation	15	Rat	Not reported	26 litters, 8 pups/litter (males and females)	Reduced open-field activity levels, birth weight and total brain protein at birth. Decreased body weight gain.	(63)
150	Chronic, prenatal	18.5	Rat	25	7 litters, 8 pups/litter (males and females)	Decreased cerebellar weight at PD 21.	(210)
150	Chronic, prenatal	–	Rat	Not reported	7 litters, 8 pups/litter (males and females)	Decreased cerebellar weight, increased norepinephrine level at PDs 14–42.	(209)

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
150	24 h/day throughout gestation	15 (estimated)	Rat	Not reported	6 pups/litter (males and females)	Impairment of acquisition of a two-way active avoidance task in 90-day-old rats; impairment of acquisition and reacquisition of a two-way active avoidance task in 18-month-old rats.	(48)
150	From GD 0 to PD 10	18.5	Rat	Not reported	10–11 litters	Dose-dependent decrease in body weights, decreased cerebellar weights and total GABA levels on both PDs 10 and 21, reduction in total GABA uptake. Same effects observed at 300 ppm.	(211)
150	48–96 h between GDs 108 and 110	15	Swine	3	13	Number of stillbirths not affected. Same result at 200 ppm.	(57)
157	Last 17 days of gestation	22 (foetal)	Rat	24	24/group/8–49 foetuses/ neonates/group	Decreased foetal red blood cell count and birth weight. Elevated absolute and relative heart weight and placental weight. Number of foetuses/litter was unaffected. Same effects at 166 and 200 ppm.	(162)
180	Continuously throughout gestation	16–18 (range)	Rabbit	17	123 (males and females)	Decreased birth weight and increase in foetal mortality. Increased frequency of malformations.	(15)
200	7 h/day on GDs 8.5, 9.5 and 10.5	–	Mouse	Not reported	24–70 pups/exposure day/concentration (males and females)	Congenital spinal deformities (wedge, hemi, fused and missing vertebrae, and fused ribs) observed among pups of mothers exposed at GD 9.5. The incidence increased dose-dependently after exposure at 400 and 600 ppm. GD 9.5 was the most sensitive time of gestation.	(122)
200	24 h/day on GDs 7–21	–	Rat	Not reported	18–23 pups/group	Increase in right ventricular weight; increase in left ventricular weight.	(39)

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
200	Continuously throughout gestation	28	Rat	Not reported	10–22 pups/group, sex not specified	Decreased litter sizes and birth weights. Cardiomegaly, decrease in haemoglobin, haematocrit and red blood cells. Relative heart weight elevated in newborns but not at adult age.	(160)
200+ 500	Continuously throughout gestation (200 ppm) + neonatally until the age of 29 days (500 ppm)	28	Rat	Not reported	10–22 pups/group, sex not specified	Cardiomegaly, decrease in haemoglobin, haematocrit and red blood cells. Relative heart weight elevated in young adult rats (29 days) but not at adult age (105 days).	(160)
200	From GD 109 until birth	14.7	Pig	6	Totally 123 piglets (200 + 250 ppm), (males and females)	Impairment of open field activity 48 h after birth.	(142, 143)
250	From GD 109 until birth	16.8	Pig	6	Totally 123 piglets (200 + 250 ppm), (males and females)	Impairment of negative geotaxis behaviour and open field activity 24 h after birth and impairment of open field activity 48 h after birth.	(142, 143)
250	24 h/day on GDs 7–18	–	Mouse	Not reported	17 litters/group (males and females), no. of pups not specified	Increase in embryolethality; dose-dependent decrease in live litter size and mean foetal weights (also seen at 500 ppm).	(200)
250	GDs 0–20	–	Rat	Not reported	10–22 litters (males and females), no. of pups/ litter not specified	Increased absolute and relative heart weight and relative body weight. Decreased haemoglobin and haematocrit. Same effects observed at 500 ppm.	(173)
250	48–96 h between GDs 108 and 110	24	Swine	5	15	Increased number of stillbirths. The effect increased dose-dependently at 300, 350 and 400 ppm.	(57)

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
250	7 or 24 h/day on GDs 6–15	10–11 (range)	Mouse	20 for 7 h/day; 18 for 24 h/day	7 h/day: 20 litters (71–231 foetuses) 24 h/day: 17 litters (69–209 foetuses)	No teratogenicity. Minor skeletal variants. Increased body weight in the 7-h/day group, and decreased body weight in the 24-h/day group. Increase in resorptions in 7-h/day group.	(195)
250	7 or 24 h/day on GDs 6–15	13–15	Rabbit	9/group	7 h/day: 9 litters (27–81 foetuses) 24 h/day: 9 litters (19–58 foetuses)	No teratogenicity. Increased body weight in the 7-h/day group.	(195)
300	Chronic, prenatal	26.8	Rat	24	7 litters, 8 pups/litter (males and females)	Decreased cerebellar weight at PD 21 and PD 42.	(210)
500	Newborns, continuous, 30 days	–	Rat	–	4–7 pups/group, sex not specified	Increased number and size of arteries and veins in heart.	(164)
500	Newborns, continuous, 32 days	38–42	Rat	–	Approx. 60 pups in the CO-group	Increased right ventricle weight, relative right ventricle weight, and relative heart weight. Hydroxyproline concentration unaffected, indicating no increase in collagen content.	(161)
500	Newborns, continuous, 32 days	–	Rat	–	No. of pups unclear, sex not specified	Increased relative ventricular weight, indicating severe cardiomegaly. Increased length to width ratio of myocytes. Nearly complete regression of cardiomegaly after ending exposure, but myocyte hypertrophy still significant at an age of 200 days.	(40)
500	Birth through PD 33	40	Rat	–	No. of pups unclear (males and females)	Increased absolute and relative ventricular weight after exposure and during follow-up (up to 339 days of age). Increased heart rate, blood pressure not affected. Body weights of male neonates depressed, returned to normal after 290 days.	(166)

Table 9. Reproductive and developmental effects in animals after exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration	Mean maternal COHb (%)	Species	No. of exposed dams	No. and sex of animals in offspring	Effects in offspring	Reference
500	Neonates exposed 24 h/day on PDs 1–32	–	Rat	–	10 females/group	When studied at adulthood, the *in vitro* coronary flow increased in the hearts, chronic adaptations in the myocardium occurred.	(27)
500	1 h/day on GDs 0–6, 7–13 or 14–20	–	Mouse	50	No. of pups unclear (males and females)	Increased incidence of micronucleated polychromatic erythrocytes and sister chromatid exchanges. No statistically significant difference in the incidences between the exposure groups.	(115)
1 500	10 min/day on GDs 5, 11 and 16	–	Mouse	64	No. of pups unclear (males and females)	Increased incidence of micronucleated polychromatic erythrocytes and sister chromatid exchanges. Results increased dose-dependently at 2 500 and 3 500 ppm. See also Section 10.4.	(115)

CO: carbon monoxide, COHb: carboxyhaemoglobin, GABA: gamma-aminobutyric acid, GD: gestation day, PD: postnatal day.

11. Observations in man

11.1 Irritation and sensitisation

No studies or reports on skin, eye or respiratory irritation in humans have been found. Based on its chemical and physical properties and the lack of reports, CO is not likely to be irritating at relevant exposure levels.

No studies or reports on dermal sensitisation have been found. Based on its chemical and physical properties, CO is not likely to be a skin sensitiser.

11.2 Effects of single and short-term exposure

11.2.1 Acute poisoning

CO intoxication resulting in COHb levels of 50–60% is often lethal. However, much lower concentrations of CO may cause lethality in susceptible subgroups, primarily persons with coronary artery disease and foetuses. Patients with severe coronary artery disease may die, due to coronary events, if their COHb levels are around 20% (96, 151).

The acute symptoms depend on the CO concentration and the exposure duration. Exposure to low CO levels may result in subtle changes in time discrimination, visual vigilance and choice response. The symptoms observed after exposure to high concentrations of CO include severe headache, dizziness, nausea, vomiting, mental confusion, visual disturbances, reddening of the skin, compartment syndrome (increased pressure within muscles, leading to decreased blood flow and lack of oxygen), fatigue, hypotension and coma (59). The main symptoms occurring at different COHb levels are summarised in Table 10. The effects observed in healthy individuals are grouped separately from the effects in risk groups. The main susceptible subgroups for non-lethal CO effects are patients with coronary artery disease and children.

Acute poisoning cases have been reported in relation to CO exposure in closed rooms, like wood pellet storages and the hatches in ships and warehouses (5, 81, 216-218).

11.2.2 Effects in children

Retrospective data is available from some case studies on children accidentally exposed to CO.

A total of 564 persons, of whom 504 children, were exposed to CO in an elementary school due to a CO leak. One third of the children (n = 177) (mean age 8.7 years) were examined at one hospital and their mean COHb level was shown to be 7.0%. Of these 177 children, 139 reported headache, 69 nausea, 30 dizziness, 19 dyspnoea, 13 vomiting, 11 abdominal pain and 9 drowsiness. The authors concluded that there was a correlation between the COHb concentrations and total number of symptoms reported (109).

Table 10. Acute effects related to CO exposure in healthy adults and susceptible subpopulations at different COHb levels. Taken from IPCS 1999 and NRC 2010 (96, 151).

COHb%	Effects
Background concentrations	
ca 1	Physiological background concentration.
3–8	Background concentration in smokers.
Effects observed in healthy adults	
10	Shortness of breath on vigorous exercise, dilation of cutaneous blood vessels, possible tightness across the forehead.
20	Shortness of breath on moderate exercise, occasional headache.
30	Headache, irritability, disturbed judgement, possible dizziness, dimness of vision.
40–50	Headache, confusion, collapse, fainting on exertion.
60–70	Unconsciousness, intermittent convulsion, respiratory failure. Death if exposure is long continued.
80	Rapidly fatal.
Effects observed in susceptible subpopulations	
2	Reduced time to onset of angina and signs of myocardial ischaemia after physical exercise in persons with coronary artery disease.
5–6	Increase in cardiac arrhythmias in persons with coronary artery disease.
7	Headache and nausea in children.
13	Cognitive development deficits in children.
15	Myocardial infarction in persons with coronary artery disease.
25	Syncopes in children.
25	Stillbirths.

CO: carbon monoxide, COHb: carboxyhaemoglobin.

In a study analysing 16 children with CO poisoning (mean age 7.0 years, COHb > 15%) the following symptoms were reported: nausea (16/16 patients), vomiting (12/16), headache (13/14), lethargy (11/16), visual problems (3/14), at least one syncopal episode (9/16) (45).

More examples on case studies on children are presented in NRC 2010 and White 2000 (151, 241).

The observations in human studies are supported by a large number of animal studies indicating developmental effects at relatively low doses. In conclusion, children can be regarded as being more sensitive towards the hazardous effects caused by CO.

11.2.3 Cardiovascular and circulatory effects

Studies on the cardiovascular effects of CO in adults are summarised in Table 11. The reports include controlled exposure studies in healthy persons and in patients with diagnosed cardiovascular disease, as well as one study of a group exposed occupationally.

The clinical studies carried out with healthy subjects were mainly focusing on exercise performance after acute CO exposure. Davies and Smith exposed healthy volunteers to CO for 8 days continuously in indoor air in a closed exposure room. Smoking was not allowed during the experiment, or three days before it began.

The electrocardiograms of 3 of 15 subjects exposed at 15 ppm CO (COHb 2.4%) showed P-wave deviations and the same effect was observed in 6 of 15 subjects exposed at 50 ppm CO (COHb 7.1%). The smoking status of the subjects was not reported (46). In the evaluation by ATSDR it was concluded that the interpretation of these effects is limited due to lack of statistical analyses and data on confounding factors (e.g. smoking) (16). Unspecific P-wave changes are quite common and may, for example, occur as a result of stress. The clinical relevance of these changes is not clear, therefore the effects observed in the study by Davies and Smith (46) cannot be considered as adverse effects.

Horvath *et al* exposed 4 healthy male volunteers to 75 or 100 ppm CO in an environmental exposure chamber resulting in COHb levels of 3.4% and 4.3%, respectively. After exposure, the volunteers participated in an exercise challenge test. The CO exposure caused decreased lung ventilation at maximum performance at both exposure levels and decreased maximal aerobic capacity (V_{O2max}) at 4.3% COHb only. No signs of abnormalities in electrocardiograms were observed (91). No explanation for the decreased lung ventilation was given. The COHb of 4.3% is taken as the LOAEL.

Adir *et al* exposed 15 healthy male volunteers to a high concentration of CO for 4 minutes resulting in COHb levels of 5.1%. In the exercise test following the exposure, decreased exercise duration and maximal effort were observed. No arrhythmias, ST-segment changes or changes in myocardial perfusion were detected (4). Similarly, Kizakevich *et al* reported that CO exposure of 16 healthy male volunteers resulting in COHb levels of 5.0%, did not induce any exercise-induced ST-segment changes or other signs of cardiac arrhythmias, which have commonly been observed among coronary artery disease patients exposed to CO (107). In the evaluation by US EPA (229) it was concluded that in the controlled studies with healthy volunteers, the reported reductions in maximal exercise duration and performance were small, and thus likely to affect only competing athletes.

The controlled exposure studies on patients with exertional angina clearly indicate an induction of symptoms, as measured by evaluating the effects on several different parameters. The lowest COHb level at which significant symptoms occurred was 2.4%. At this concentration, Allred *et al* observed decreased time to onset of angina symptoms, time to onset of ischaemic ST-segment changes (indicative of myocardial ischaemia) and mean duration of exercise (7, 8). A number of other studies on patients indicate similar results at COHb levels between 2.9 and 5.9% (3, 9, 12, 111). However, Sheps *et al* did not observe any change in time to onset of angina, ST-segment depression, heart rate, blood pressure or exercise duration in patients exposed to CO (COHb 4.1%) compared to the same subjects' responses to air exposure (196).

Significantly increased number of ventricular arrhythmias and increased heart rate during exercise were observed in exercise challenge tests with angina patients (COHb 5.9%) (197). In contrast, another study did not show any effects on frequency of arrhythmias in patients after CO exposure resulting in 5.8% COHb (88).

Table 11. Acute cardiovascular effects in humans after controlled exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration and conditions	Mean COHb (%)	No. of subjects and gender	Effects	Reference
Healthy adults					
15	8 days, continuous exposure	2.4	15 healthy young adults	Marked ST-segment depression in 1 subject. P-wave changes in 3 of 15 subjects.	(46)
50	As above	7.1	15 healthy young adults	No marked ST-segment depression. P-wave changes in 6 of 15 subjects.	(46)
75	3 test days, exposure duration not reported; exercise challenge test	3.4	4 men (3 non-smokers)	Decreased lung ventilation at maximum performance. Maximal aerobic capacity (V_{O2max}) and ECG not affected.	(91)
100	As above	4.3	4 men (3 non-smokers)	Decreased lung ventilation at maximum performance and decreased maximal aerobic capacity (V_{O2max}). ECG not affected.	(91)
–	4 min; exercise challenge test	5.1	15 young adult males (non-smokers)	No arrhythmias, ST-segment changes or changes in myocardial perfusion during treadmill exercise at maximal capacity. Decreased duration of the post-exposure exercise by 10%. Maximal effort significantly decreased.	(4)
500	30 min	8.5	6 men (non-smokers)	Significant increases in retinal and choroidal blood flow and retinal vessel diameter. Same effects observed after 60 min exposure.	(176)
1 000	30 min, followed by 100 ppm for 30 min	8.3	8 men, 2 women (non-smokers)	No effects on forearm blood flow, blood pressure, heart rate, minute ventilation, muscle sympathetic nerve activity.	(83)
1 000	4–6 min, followed by continued exposure (27–100 ppm) to maintain COHb levels; exercise challenge test	5, 10, 15 and 20	16 men (non-smokers)	No ST-segment changes or effects on cardiac rhythm during upper or lower body exercise (studied only in 5% COHb group). Heart rate increased at COHb > 5%, and cardiac output and cardiac contractility increased at COHb > 10%.	(107)
1 200	CO inhalation 20 times/day, every 45 min, 7 days	6	12 men (smokers)	No effects on serum levels of C-reactive protein (CRP), plasma platelet factor 4, heart rate, blood pressure or catecholamine release.	(250)
3 000	6 min	6.2	12 men (non-smokers)	Decreased muscle fatigue resistance and electrically evoked stimulation. Leg strength not affected.	(144)

Table 11. Acute cardiovascular effects in humans after controlled exposure to carbon monoxide (CO).

CO level (ppm)	Exposure duration and conditions	Mean COHb (%)	No. of subjects and gender	Effects	Reference
Subjects with coronary heart disease[a]					
50	4 h; exercise challenge test	2.9	19 men (5 smokers, 5 non-smokers) with diagnosed CAD	Decreased time to onset of angina symptoms. Duration of angina symptoms not affected.	(9)
53 (mean)	Breathing freeway air for 90 min; exercise challenge test	5.1	10 men with cardiovascular disease	Decreased exercise performance until angina. Decreased systolic blood pressure, heart rate, and systolic blood pressure × heart rate at angina.	(12)
100	4 h; exercise challenge test	4.5	19 men (5 smokers, 5 non-smokers) with diagnosed CAD	Decreased time to onset of angina symptoms. Increased duration of angina symptoms.	(9)
100	1 h; exercise challenge test	3.0	24 men (non-smokers) with diagnosed CAD	Decreased time to onset of angina, time to onset of ischaemic ST-segment changes, duration of angina symptoms and oxygen uptake at angina. No effects on systolic blood pressure and heart rate.	(111)
100	1 h; exercise challenge test	4.0	7 men, 3 women (non-smokers) with diagnosed CAD	No effects on frequency of ventricular arrhythmia. Same results at 200 ppm (COHb 5.8%).	(88)
100	1 h; exercise challenge test	4.1	30 patients with CAD, sex not specified (non-smokers)	No change in time to onset of angina, ST-segment depression, heart rate, blood pressure or mean duration of exercise.	(196)
100	1 h; exercise challenge test	4.0	36 men, 5 women (non-smokers) with diagnosed CAD	No effect on number of ventricular arrhythmias during exercise or on blood pressure, heart rate or mean duration of exercise.	(197)
100–200	1 h; exercise challenge test	5.9	22 men, 8 women (non-smokers) with diagnosed CAD	Decreased mean duration of exercise, time to onset of angina symptoms and left ventricular ejection fraction. Time to onset of ischaemic ST-segment changes and systolic blood pressure not affected.	(3)
117 (mean)	1 h; exercise challenge test	2.4	63 men (non-smokers) with stable angina	Decreased time to onset of angina symptoms, time to onset of ischaemic ST-segment changes and mean duration of exercise. Heart rate-systolic blood pressure double product not affected. Similar, dose-dependent, results at exposure to 253 ppm CO (mean) (COHb 4.7%).	(7, 8)
200	1 h; exercise challenge test	5.9	36 men, 5 women (non-smokers) with diagnosed CAD	Significant increase in number of ventricular arrhythmias and heart rate during exercise. Blood pressure or exercise duration unaffected.	(197)

[a] The majority of the patients having a history of myocardial infarction or > 70% occlusion of one or more of the coronary arteries.

CAD: coronary artery disease, CO: carbon monoxide, COHb: carboxyhaemoglobin, CRP: C-reactive protein, ECG: electrocardiogram.

11.2.4 Central nervous system and behavioural effects

Central nervous system effects occur commonly in acute CO poisoning cases (COHb > 20%), and have unambiguously been demonstrated in humans (see Section 11.2.1). The central nervous system effects after exposure to lower concentrations are less known, and available study results are inconsistent.

Studies of central nervous system effects of controlled CO exposure have mostly been carried out with healthy volunteers, mainly at COHb concentrations of 5–20%, and the study results include observations on decreases in visual and auditory vigilance and visual tracking (229). Benignus performed extensive meta-analyses of the available CO-behavioural literature and concluded that 18–25% COHb would be required to produce a 10% decrement in behaviour (21). Furthermore, Benignus concluded that the studies focusing on CO induced effects on behaviour suffer from some technical problems, as single-blind and non-blind experiments tend to show a much higher rate of significant effects than do double-blind studies (21). The same authors concluded in another literature review that COHb should not be expected to produce behavioural effects at concentrations lower than 20% (175).

Benignus and Coleman estimated using a whole-body human physiological model that the brain aerobic metabolism remains unaffected at COHb levels < 25% in healthy subjects. A similar simulation of the situation in subjects with stenosis showed that the brain aerobic metabolism, which might affect behaviour, was impaired immediately as COHb increased above the baseline. No threshold level could thus be identified for these types of patients (23).

The effect on visual luminance and contrast detection was studied by a battery of visual tests in healthy male volunteers exposed to CO. At a COHb level of 15.8–19.8%, no effects on the studied parameters were observed (92).

In the study by Aronow *et al*, 20 men with diagnosed cardiovascular disease were exposed to 100 ppm CO resulting in 3.9% COHb (mean) and to compressed air under the same exposure conditions on another day (double-blind, randomised, crossover study). After the exposure, the effect of CO was evaluated by carrying out a set of performance tests, including seven measures of higher mental processes, the critical flicker fusion test, and one measure of reaction time. The results showed impairment in the visualisation test performance ($P < 0.001$). In that test, the ability to visualise the contemplated outcome of objects manipulated in space was followed. Perceptual speed, flexibility of closure, number facility, digit symbol, time perception, flicker fusion, or reaction time tests did not indicate any effects of CO (11).

It can be concluded that relatively high doses of CO may cause central nervous system and behavioural effects. The majority of the studies are also focusing on CO poisoning or exposure to high concentrations of CO. Due to lack of valid reports on studied performed at low CO concentrations it is not possible to establish a dose-response relationship or to identify a reliable NOAEL for central nervous system effects caused by CO.

11.3 Effects of long-term exposure

Chronic CO poisoning is generally characterised by headache, dizziness and tiredness. CO poisoning was commonly occurring during the World War II, due to the use of wood as fuel for generator vehicles. These cases are uncommon nowadays, although some case reports have been found. Tvedt and Kjuus reported on a crane driver at a smelting works, who developed permanent symptoms after 20 years of exposure. Long-lasting symptoms have also been observed in residents exposed to CO due to a faulty oil fired central heating system (228).

Electrocardiographic changes among indoor barbeque workers occupationally exposed to CO (mean work duration 15.6 years) were investigated by Sari *et al*. The average COHb level among the exposed was 6.5%, whereas the corresponding value in the control group was 2.2%. Several electrocardiographic parameters differed between the groups with increased values for maximum P-wave duration, P-wave dispersion, maximum QT interval, QT dispersion and corrected QT dispersion in the exposed group. Significant correlations were found between COHb and P-wave dispersion, maximum QT interval, QT- and corrected QT dispersion (191). However, no exposure measurements other than COHb were carried out in this study, and therefore it cannot be ruled out that the electrocardiographic disturbances were caused by other environmental pollutants.

Many studies focusing on air quality and pollution have also evaluated the presence of asthma among study subjects. Positive associations between long-term exposures to CO and asthma or asthma symptoms were observed in population studies among 6–16-year-old children in Taiwan and Germany (77, 89, 94, 233). Hirsch *et al* concluded that the increased prevalence of cough and bronchitis was related to exposure to traffic-related air pollutants (i.e. NO_2, CO and benzene) (89). Hwang *et al* conducted a co-pollutant analysis and concluded that long-term exposure to traffic related air pollutants (NO_x, CO and O_3) increased the risk of asthma in children, and that the risk of asthma was not related to the levels of PM_{10} (particulate matter with aerodynamic diameter up to 10 μm) and SO_2 (94). However, there is a strong correlation between NO_x and NO_2 and CO, making it difficult to separate the effects attributed to each pollutant. The other reports either did not interpret the association between long-term exposure to CO and adolescent asthma (233) or concluded that it is unlikely that CO directly affects the respiratory system (77).

The effects of long-term exposure to air pollutants and the prevalence of allergic rhinitis were studied among school children in Taiwan. An association between CO, but also NO_x, exposure and allergic rhinitis was observed (93, 120).

11.4 Combined exposure

The principal mechanism underlying the hypoxic effects of CO is the binding to haemoglobin and myoglobin and concomitant displacement of O_2 (see also Chapter 7) (30, 31, 247, 248). Decreased levels of O_2 facilitates CO binding, whereas increased O_2 concentration in inspired air reverses the binding, thereby increasing the elimination rate of CO.

Methylene chloride and other dihalomethanes are metabolised to CO in the body (see Section 8.1). Therefore, combined exposure to dihalomethanes and CO results in COHb levels which are higher than could be expected based on the CO exposure alone (95).

Acute human CO poisoning has been associated with hearing loss, despite lack of excessive noise exposure. However, most field studies lack noise exposure estimates. It is therefore not clear if noise exposure is a prerequisite for the auditory effects seen following long-term occupational exposure to CO. In a study analysing 6 812 audiograms, exposure to CO and noise levels below 90 dBA had no effect on hearing thresholds, whereas workers who were exposed to CO and noise levels above 90 dBA displayed significantly poorer hearing thresholds at high frequencies (CO levels not given) (conference proceedings cited in (99)). In a small subset (two subjects), the adjusted ORs for audiometric hearing loss were significant for exposures in the 16 to 35 ppm range in combination with noise exposure (reviewed by (99)).

There is no direct information available on CO interactions with drugs, but some studies provide data on the effects of combined exposure to CO and alcohol. In the report by IPCS, it was concluded that there is some evidence that CO toxicity may be enhanced by drug use, and also that the toxicity of other drugs may be altered after exposure to CO (96). Enhanced CO induced central nervous system toxicity has been reported at concomitant intake of barbiturates, amphetamine, chlorpromazine, nicotine, diazepam and morphine. Drugs used to treat patients with coronary artery disease might also affect the susceptibility to CO (229).

Rockwell and Weir investigated interactive effects of CO and alcohol on actual driving and driving-related performances in young non-smoking college students. Combined exposure (resulting in COHb levels of 0, 2, 8 and 12% and blood alcohol levels of 0.5‰) caused perceptual narrowing and decreased eye movement. The effects of CO and alcohol were often additive. At the 12% COHb level, a supra-additive interaction between CO and alcohol was observed, indicating effects many times higher than would have been expected by summarising the effects caused by CO and alcohol separately (96, 181).

11.5 Genotoxic effects

Only one study focusing on the potential of CO to induce genotoxic effects has been found.

Oztürk *et al* studied the frequency of sister chromatide exchanges among non-smoking persons visiting the emergency room due to acute CO intoxication, caused by dysfunctioning coal or wood stoves. A significant increase in the mean frequency of sister chromatide exchanges was observed among the CO-exposed group as compared to the healthy non-smoking controls. No dose-response correlation was seen between COHb level and frequency of sister chromatide exchanges (154).

11.6 Carcinogenic effects

No data on carcinogenic effects of CO have been found.

11.7 Reproductive and developmental effects

11.7.1 Effects on fertility

No data have been found related to fertility effects of CO.

11.7.2 Developmental effects

CO is transferred to the foetus via the placenta, and foetal haemoglobin has higher affinity for CO than maternal haemoglobin. Therefore, it is not possible to assess the severity of foetal intoxication based on the state of the mother. The rate of COHb formation and dissociation differs between the mother and the foetus, resulting in a delay in foetal CO elimination and a prolonged exposure (16, 96).

High doses of CO may result in preterm birth, developmental disorders, reduced foetal growth or even foetal death (16, 96). Epidemiological data also show some evidence that exposure to CO via ambient air pollution during early pregnancy may be associated with an increased risk of preterm birth or with reduced birth weight. However, the interpretation of epidemiological studies is often complicated due to lack of specific exposure level data during particular periods of gestation. There is usually a clear correlation between ambient CO concentrations and other air quality variables that may affect developmental outcomes which should also be considered. Therefore, based on the available epidemiological data, it is not possible to make any conclusions on dose-response relationships, or to define any safe levels of exposure (16, 87, 96, 124).

In the assessment by US EPA, a large number of epidemiological studies of birth outcomes and developmental effects in relation to ambient CO exposure among the general population were reviewed. It was concluded that there is some evidence that ambient CO exposure during the first trimester is associated with preterm birth. A relationship between reduced foetal growth and CO levels was also suggested. However, there was an inconsistency concerning the results on the correlation between CO and the parameters “low birth weight”; “intrauterine growth restriction”; and “small for gestational age” obtained in the different studies (230).

Some of the most extensive retrospective cohort studies were conducted in California by Ritz *et al* (178-180, 245). The mean air CO concentrations ranged from 0.75 to 2.4 ppm. The cohorts included 97 000 births in 1989–1993 and 106 000 births in 1994–2000. In the study by Ritz and Yu published 1999, exposure to > 5.5 ppm CO (3-month average) in the outdoor air during the last trimester was associated with a significantly increased risk of low birth weight (odds ratio 1.22, 95% confidence interval (CI) 1.03–1.44). The relative risks of preterm birth, low birth weight and congenital anomalies were estimated after adjustment for other risk factors and ambient air concentrations of NO_2, O_3, and PM_{10}. The relative risk of preterm birth was estimated to be 1.12 (95% CI 1.04–

1.21) per 3 ppm increase in CO during the last 6 weeks of pregnancy (180). In the follow-up, a relative risk of 1.10 (95% CI 1.03–1.08) per ppm increase in air CO during the last 6 weeks of pregnancy was obtained when no adjustment was made for PM_{10}. No significant association was seen, however, when the results were adjusted for PM_{10} (relative risk 0.98; 95% CI 0.83–1.18) (245). When considering the correlation between CO and low birth weight, and including NO_2, O_3, and PM_{10} in the model, an elevated risk was observed in the first study, covering 126 000 births (179), but not in a follow-up (245).

Sixty case reports related to CO exposure, pregnancy, and teratogenicity were evaluated by Norman and Halton. Among the 60 cases, there was only one description of an acute occupational CO exposure affecting pregnancy (32). CO exposure was not related to occupational situations in any of the other cases. In the studied cases, there was a direct relationship between foetal effects, maternal COHb and maternal toxicity. Norman and Halton concluded that, although no such cases have been reported, there is a risk of occupationally related developmental toxicity of CO, as exposure to CO is very likely at certain working places (148).

In a prospective study, data on the foetal outcome following accidental CO poisoning during pregnancy were collected and followed. The main conclusion was that no indications of adverse effects could be observed among the babies of the mothers (n = 31) with mild signs of CO poisoning (COHb range 0.8–18%). Among the mothers suffering from severe CO poisoning (COHb = 21–50%) during pregnancy (n = 5), two were giving birth to babies with no signs of developmental effects, whereas the babies of three of the mothers showed developmental delays during follow-up examinations (113).

12. Dose-effect and dose-response relationships

The main mechanism behind CO-induced toxicity has for long times been known as the binding of CO to haemoglobin, resulting in COHb formation and hypoxia. The relations between CO in air and the subsequent COHb levels are also well-known, and can be calculated using the CFK equation for rest or during exercise (42).

Endogenous CO formation leads to a background COHb concentration in blood of about 0.4–0.7%. Non-smokers typically have COHb levels up to 2% whereas smokers may have COHb levels up to 10% immediately after smoking (16).

Studies examining acute health effects of low CO levels have focused on organ systems particularly vulnerable to hypoxia, including the heart and the brain. Patients with coronary artery disease as well as the developing foetus appear especially sensitive to CO.

Human studies

The effects of single/short-term exposure to CO (summarised in Table 11) have been investigated in several controlled exposure studies in healthy volunteers

and patients with coronary artery disease. Generally, the CO exposures were designated to reach target blood COHb levels between 2 and 6% and cardiovascular function assessments were made during exercise challenge.

In controlled exposure studies of healthy volunteers, CO exposures producing COHb levels between 3.4 and 5.1% have been related to effects on exercise performance including decreased lung ventilation at maximum performance, decreased maximal aerobic capacity, decreased maximal effort and decreased exercise duration (4, 91). Exposure to CO (COHb levels up to 5.1%) was not observed to induce myocardial ischaemia or cardiac arrhythmias (4, 91, 107).

In a large controlled exposure study of patients with coronary artery disease, CO exposures resulting in COHb concentrations of 2.4% (lowest concentration evaluated) and 4.7% significantly reduced the time to onset of angina symptoms and of ST-segment changes during exercise in a dose-dependent manner (7, 8). Other studies on patients have also shown that CO exposure (COHb 2.9–5.9%) aggravated exercise-induced myocardial ischaemia including decreased time to onset of angina symptoms, decreased time to onset of ST-segment changes and increased duration of angina symptoms (3, 9, 111). In another study on patients, no change in time to onset of angina and of ST-segment changes were observed at a COHb of 4.1% (196). At a COHb level of 5.9%, but not at 4.0%, an increase in number of ventricular arrhythmias was reported (197). In contrast, no such effect was seen in another study on patients at same COHb level (5.8%) (88).

Behavioural effects, including decrease in visual and auditory vigilance and visual tracking, following controlled CO exposures resulting in COHb levels between 5 and 20% have been observed in healthy subjects. The findings have, however, not been consistent across studies and dose-response relationships have not been firmly established (229). In the only study conducted on patients with coronary artery disease, impaired performance in a visualisation test following controlled CO exposure resulting in a COHb level of 3.9% was observed. Other performance tests did not indicate any effects of CO at this level (11).

Effects in individuals suffering acute CO poisoning cover a wide range, depending on severity of exposure (Table 10). At COHb levels of 20%, the effects observed are mild, like shortness of breath during exercise or occasional headache. At higher levels (COHb $\geq$ 30%) symptoms include headache, dizziness, disturbed judgement, dimness of vision, confusion, unconsciousness, intermittent convulsion and respiratory failure. COHb levels of 50–60% are often lethal. For patients with coronary artery disease, COHb levels around 20% may be lethal. Children appear also to be particularly vulnerable to CO and experience headache and nausea already at COHb levels of 7%. At higher levels, cognitive development deficits (COHb 13%) and syncopes and stillbirths (COHb 25%) have been reported (96, 151).

In studies investigating health effects of occupational and environmental exposures to CO, the presence of other pollutant gases and particles hamper the interpretation. The utility of these types of studies for establishing dose-response relationships is therefore limited.

Animal studies

The findings in the animal studies (summarised in Tables 7 and 8) are consistent with those in humans, indicating effects on the cardiovascular and the central nervous systems.

Brief exposure to CO increased myocardial ischaemia (as indicated by ST-segment alteration) in coronary artery ligated dogs at a COHb level of 4.9% and increased further with increasing CO exposure (19). In another study, single CO exposure (COHb 6.4%) reduced the threshold for ventricular fibrillation in healthy dogs and in dogs with myocardial injury (13, 14). This effect was also seen in healthy and infarcted monkeys following single exposure to CO (COHb 9.3%). The cardiovascular disease made the animals more vulnerable to CO exposure, i.e. the voltage required to induce fibrillation was lowest in infarcted animals breathing CO (49).

Abnormal cardiograms were observed for dogs exposed to CO for 6 weeks (COHb 2.6–12%) and monkeys exposed for 24 weeks (COHb 12.4%) (50, 172). In contrast, no sign of such abnormalities was seen in a study on dogs exposed to CO for 14 weeks (COHb 14%) (51). Exposure to CO for 30 days (COHb 15.8%) or for 72 weeks (COHb 14.7%) induced cardiomegaly in rats (156, 157, 220). Haematological effects, occurring as compensatory mechanism due to hypoxia, including increases in haemoglobin and/or haematocrit following repeated exposure CO, were seen in rats at COHb ≥ 7.5% and in monkeys at COHb ≥ 10% (50, 100, 156, 157).

Gestational and early postnatal exposures to CO have been shown to cause adverse effects in e.g. the central and peripheral nervous system, in behaviour and the cardiovascular system (Table 9). Effects on the developing auditory system, i.e. a consistent attenuation of the amplitude of action potential of the 8^{th} cranial nerve, were observed in newborn rats exposed from 12 ppm (lowest dose tested, estimated to correspond a COHb level of 2%) up to 50 ppm on postnatal days 6–22 (208). Using the same protocol, decreased c-Fos immunoreactivity in the central inferior colliculus (marker for neuronal activation in the nervous system) was observed over all dose groups (12.5, 25 and 50 ppm) (236). Furthermore, CO exposure of newborn rats caused swelling of the nerve terminals innervating the inner hair cells of Corti at 25 ppm but not at 12 ppm (125) and decreased otoacoustic emission at 50–100 ppm but not at 25 ppm (208). Gestational exposure of rats to 75 ppm CO caused effects in offspring peripheral nervous system including reduced myelin sheath thickness of sciatic nerve fibres (33, 35).

Gestational exposures to CO have also been shown to impair multiple behaviour outcomes in offspring including aerial righting (65 ppm CO, mice), negative geotaxis (125 ppm, mice), homing behaviour (150 ppm, rats) and avoidance behaviour (150 ppm, rats) (48, 63, 65, 199).

Cardiovascular effects have also been observed in offspring of dams exposed during gestation from 60 ppm CO (i.e. cardiomegaly) (173) and higher (Table 9).

In addition, there are consistent data showing that gestational exposure to CO significantly decreased birth weight in a dose-related manner in rabbits (≥ 90 ppm CO) and rats (≥ 100 ppm CO) (15, 129, 173).

13. Previous evaluations by national and international bodies

The *Nordic Expert Group for Documentation of Occupational Exposure Limits* (previous name for NEG) concluded in 1980 that when setting an occupational exposure limit value, the effects of CO on the following organs and functions have to be considered: heart, arteries, central nervous system, foetus and maximal aerobic capacity (114).

In the *International Programme on Chemical Safety (IPCS)* report from 1999, the basis for the recommendations is that the COHb level should not exceed 2.5% even during moderate or light exercise. The values aim to protect the most sensitive groups, non-smokers with coronary artery disease from acute ischaemic heart attacks, and to protect foetuses of non-smoking pregnant women from hypoxic effects. In addition, the Task Group agreed that the COHb of workers exposed occupationally to CO should not exceed 5%. This recommendation was based on the assumption that workers are mainly healthy, physiologically resilient and under regular supervision. The guideline values for CO in ambient air given were: 87 ppm for 15 minutes, 52 ppm for 30 minutes, 26 ppm for 1 hour and 9 ppm for 8 hours (96).

The *World Health Organization (WHO)* guideline values from 2000 for outdoor air are 90 ppm for 15 minutes, 50 ppm for 30 minutes, 25 ppm for 1 hour, and 10 ppm for 8 hours. WHO based its recommendation on the same assumptions that were made by IPCS (96), meaning that the COHb should not exceed 2.5% in order to protect patients with coronary artery disease and foetuses from the health hazards caused by CO (243).

The updated WHO indoor air recommendations from 2010 are 90 ppm for 15 minutes and 30 ppm for 1 hour, assuming light exercise and that such exposure levels do not occur more than once per day. The recommended upper level for 8 hours is 9 ppm (arithmetic mean concentration, light to moderate exercise) and 6 ppm for 24 hours (arithmetic mean, assuming that the exposure occurs when a person is awake but not exercising). The exposure-related decrease in maximal exercise performance and increase in symptoms of ischaemic heart disease after CO exposure in persons with stable angina were identified as the critical effects. Based on these symptoms, it was concluded that the COHb should not be over 2%, and the corresponding CO levels were calculated accordingly (244).

The *US Environmental Protection Agency (US EPA)* published a document on air quality criteria for CO in 2000 (229). The document contains an extensive evalua-

tion and synthesis of the exposure and health hazard data relevant for reviewing national ambient air quality standards. It was concluded that young, healthy non-smokers are not at risk when exposed to CO at ambient concentrations resulting in COHb below 5%. Patients with exercise-induced angina were identified as a susceptible subgroup. US EPA's latest evaluation on health effects associated with ambient CO exposure were released 2010 (230). It was concluded that consistent and coherent evidence from epidemiologic and human clinical studies, along with biological plausibility provided by the role of CO in limiting O_2 availability, is sufficient to conclude that a causal relationship is likely to exist between relevant short-term exposures to CO and cardiovascular morbidity.

In the *National Research Council (NRC)* documentation published 2010 (151) Acute Exposure Guideline Levels (AEGLs) were proposed for CO as follows:

No AEGL-1 values (Airborne concentration causing "notable discomfort, irritation, or certain asymptomatic, nonsensory effects", which are transient and reversible, in the general population, including susceptible subgroups) were given as it was concluded that serious effects may occur among susceptible persons at concentrations which are not causing AEGL-1 effects in the general population.

The AEGL-2 values (Airborne concentration above which the general population, including susceptible individuals, could suffer from "irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape") given were: 10 minutes for 420 ppm, 30 minutes for 150 ppm, 1 hour for 83 ppm, 4 hours for 33 ppm and 8 hours for 27 ppm. The AEGL-2 values were based on observed cardiovascular effects in coronary artery disease patients, who were considered as the most susceptible subpopulation.

The AEGL-3 values (Airborne concentration above which life-threatening health effects or death might occur among the exposed general population, including susceptible subgroups) given were: 10 minutes for 1 700 ppm, 30 minutes for 600 ppm, 1 hour for 330 ppm, 4 hours for 150 ppm and 8 hours for 130 ppm. The starting points for the AEGL-3 values were analyses of poisoning cases, indicating that the threshold for lethality is 40% COHb.

In the *Agency for Toxic Substances and Disease Registry (ATSDR)* evaluation from 2012 no minimal risk levels (MRLs) were proposed. This decision was justified by the fact that the LOAELs observed in clinical and experimental animal studies (2.4% COHb and 12 ppm CO, respectively) are relatively low. Application of standard uncertainty factors to the LOAELs would thus result in CO concentrations within the range of ambient CO levels in the US. The decision not to propose any minimal risk levels was also justified by the fact that if there is a threshold for the toxic effects, it is likely to be very close to the endogenous production rate of CO. It was also concluded that an exposure level determined to be of minimal risk at sea level might not be applicable at higher altitudes with lower partial pressures of O_2 (16).

14. Evaluation of human health risks

14.1 Assessment of health risks

The effects seen in acute CO poisoning cover a wide range (Table 10) from mild symptoms, like shortness of breath during exercise or occasional headache at COHb 20% to more severe ones like headache, dizziness, disturbed judgement, dimness of vision, confusion, unconsciousness, intermittent convulsion and respiratory failure at COHb above 30%. COHb levels of 50–60% are often lethal. Even COHb levels of 20% may be lethal for patients with coronary artery disease. The foetus is at higher risk than the healthy adult because of higher CO haemoglobin affinity. Children appear also to be particularly vulnerable to CO and experience headache and nausea already at COHb levels of 7%. At higher levels, cognitive development deficits (COHb 13%) and syncopes and stillbirths (COHb 25%) have been reported (96, 151).

Exposure to low or moderate CO levels causes different kinds of symptoms, the major ones related to cardiovascular or central nervous system effects. These types of effects have been observed in both animal tests and controlled human exposure studies.

The clinical studies carried out with healthy subjects were mainly focusing on exercise performance after acute CO exposure (Table 11). In the study by Horvath *et al*, 4 healthy males were exposed to concentrations of 75 or 100 ppm CO in an environmental exposure chamber, resulting in COHb levels of 3.4% and 4.3%, respectively. After exposure, the volunteers participated in an exercise challenge test. The maximal aerobic capacity was decreased in the group exposed to the higher concentration. The LOAEL identified in this study was 4.3% COHb (91). In the study by Adir *et al*, 15 male volunteers were exposed to a high concentration of CO for 4 minutes, resulting in 5.1% COHb. In the exercise test following the exposure, the maximal effort and the duration of the exercise were significantly decreased. No arrhythmias, ST-segment changes or changes in myocardial perfusion were detected (4). In the evaluation by US EPA (229) it was concluded that in the controlled studies with healthy volunteers, the reported reductions in maximal exercise duration and performance were small, and thus likely to affect only competing athletes. In the study by Davies and Smith, healthy volunteers were exposed continuously to 15 or 50 ppm CO for 8 days. The electrocardiograms of 3 of 15 subjects exposed to 15 ppm CO (COHb 2.4%) showed P-wave deviations and the same effect was observed in 6 of 15 subjects exposed to 50 ppm CO (COHb 7.1%). Marked ST-segment depression was seen in one subject (heavy smoker) exposed at 15 ppm but in none of the subjects exposed at 50 ppm (46). P-wave changes are generally not considered as being specific markers of toxicity or as clinically relevant, and are therefore not considered as adverse effects. COHb 4.3% is identified as an overall LOAEL in healthy volunteers.

In other clinical studies, the effect of controlled CO exposure on various performance parameters were investigated in patients with diagnosed coronary artery disease (Table 11). In the studies by Allred *et al*, 63 men with stable angina were

exposed to a mean concentration of 117 ppm CO for 1 hour, resulting in COHb levels of 2.4%. The exposure resulted in decreased time to onset of angina symptoms and ischaemic ST-segment changes, and decreased mean duration of exercise in exercise tests. Similar, dose-dependent effects were also seen after exposure to a mean CO concentration of 253 ppm (COHb 4.7%) (7, 8) as well as in other studies on patients exposed to CO (COHb 2.9–5.9%) (3, 9, 111). Aronow *et al* reported impaired results in a visualisation test among angina patients after exposure to CO (COHb 3.9%, only dose tested) compared with the results of the same test persons without previous CO exposure (11). COHb 2.4% is identified as an overall LOAEL in patients with coronary artery disease.

The lowest CO exposure causing health effects in animals have been observed in studies evaluating effects of CO on the developing auditory system (Table 9). In the study by Stockard-Sullivan *et al*, exposure of rats to 12–50 ppm CO post-natally caused a consistent attenuation of the amplitude of the action potential of the 8th cranial nerve in all dose groups and decreased otoacoustic emission at 50 ppm (208). Using the same protocol, decreased c-Fos immunoreactivity in the central inferior colliculus (marker for neuronal activation in the nervous system) was observed in all dose groups (12.5, 25 and 50 ppm) (236). Exposure of new-born rats to 25 ppm CO, but not to 12 ppm, caused swelling of the nerve terminals innervating the inner hair cells of the organ of Corti. No morphological changes were observed on the inner and outer hair cells of the Corti (125). In other studies by the same group, exposure to 25 ppm CO was also up-regulating markers of oxidative stress (superoxide dismutase-1, HO-1, and inducible nitric oxide) in the cerebellum of rat pups exposed prenatally, pre- and postnatally, or postnatally. The effects were most significant if the exposure period included the prenatal period (days 5–20) (127). Superoxide dismutase-1 and HO-1 were also elevated in the stria vascularis and blood vessels of rat pups exposed to 25 ppm CO pre- and postnatally. Inducible nitric oxide synthase and nitrotyrosine immunoreactivity were increased in blood vessels of the cochlea both in the group exposed pre-natally and in that exposed pre- and postnatally. Afferent terminals innervating the inner hair cells were swollen in both exposure groups (126). Based on these studies, all performed by the same research group, 12 ppm is identified as an overall LOAEL in animals (NOAEL not identified).

No or limited data were found regarding genotoxicity, carcinogenicity, irritation and sensitisation.

Combined exposure to CO and dihalomethanes causes increased formation of COHb. Combined exposure to CO and noise may potentiate noise-induced hearing loss.

14.2 Groups at extra risk

In relation to CO exposure, the following sensitive risk groups have been identified:

- Subjects with coronary heart disease, as both human and animal data clearly indicate that these patients may get symptoms at lower CO exposure levels than healthy subjects (see Section 11.2.3).
- Pregnant women and their offspring, because CO is causing developmental toxicity (Sections 10.6 and 11.7.2).
- Children, who are known to be more sensitive towards the hazardous effects caused by CO than adults (Section 11.2.2).
- Smokers, as their basal COHb levels are significantly elevated (Section 8.1).
- Subjects performing heavy exercise, including those with heavy work load, as the rates of CO uptake and COHb formation are proportional to the intensity of exercise (Section 7.4).
- Subjects at low oxygen pressure, including high altitude, as those conditions may result in elevated CO uptake and COHb formation (Section 7.4).
- Subjects co-exposed to chemicals that are metabolised to CO in the body (e.g. dihalomethanes), resulting in increased COHb levels (Sections 8.1 and 11.4).
- Subjects co-exposed to asphyxiants such as hydrogen cyanide, as synergistic effects may occur (Section 10.7).
- Subjects co-exposed to noise, as CO may potentiate noise-induced hearing loss (Sections 10.7 and 11.4).

14.3 Scientific basis for an occupational exposure limit

When inhaled, CO binds rapidly to haemoglobin forming COHb. Upon continued exposure COHb builds up in a curvilinear fashion. COHb correlates better with the observed health effects than the concentration of CO in air or the product of CO concentration and exposure time. COHb is therefore regarded as a more accurate dose measure than the two latter ones.

Several adverse effects appear at approximately the same COHb level, therefore no single critical effect can be identified. The adverse effects of concern are impaired exercise performance in healthy volunteers, increased myocardial ischaemia in patients with coronary artery disease and persistent changes in the developing auditory system of the rat.

Decreased maximal aerobic performance at COHb 4.3% and decreased maximal effort and exercise duration at COHb 5.1% were observed in two independent controlled exposure studies on healthy volunteers. According to the CFK equation, a COHb level of 4.3% corresponds to a concentration of CO in air of 33 ppm and 26 ppm, assuming 8 hours of constant exposure at rest and heavy work, respectively.

Induced myocardial ischaemia, i.e. decreased time to onset of exercise induced angina symptoms and of ST-segment changes, were observed at COHb levels of 2.4% (LOAEL, corresponding to 17 ppm and 14 ppm at rest and heavy work, respectively) and 4.7% in a large controlled exposure study on patients with coronary

artery disease. Other studies on patients have also shown that CO exposure (COHb 2.9–5.9%) aggravated exercise-induced myocardial ischaemia.

Persistent changes in the developing auditory system of the rat, i.e. a consistent attenuation of the amplitude of action potential of the 8th cranial nerve, were observed in pups exposed to 12–50 ppm on postnatal days 6–22. Using the same protocol, decreased c-Fos immunoreactivity in the central inferior colliculus (marker for neuronal activation in the auditory system) was observed at 12.5–50 ppm. In addition, the nerve terminals innervating the inner hair cells of Corti were swollen and the otoacoustic emission decreased at 25 and 50 ppm, respectively. The LOAEL of 12 ppm corresponds to a COHb level in humans of 1.8% and 2.0% at rest and heavy work, respectively.

No NOAELs have been identified for the cardiovascular and developmental effects described above.

It should be noted that endogenous CO formation leads to a background COHb level of about 0.4–0.7%. Non-smokers typically have COHb levels up to 2% whereas smokers may have COHb levels up to 10% immediately after smoking.

15. Research needs

Although numerous studies on the health effects of CO have been published, further information would be needed in order to complete the data on the potential health hazards related to exposure levels relevant for occupational exposure. The following data gaps and research needs were identified:

- Exercise performance test at low CO exposure levels.
- Electrocardiographic alterations during controlled exposure and occupational exposure.
- Epidemiological studies on co-exposure to noise and CO and hearing impairment.

16. Summary

Stockmann-Juvala H. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 147. Carbon monoxide.* Arbete och Hälsa 2012;46(7):1-78.

Carbon monoxide (CO) is an odourless and colourless gas produced by incomplete burning of carbon-based fuels. CO is also a constituent of tobacco smoke. Exposure to CO is common in many occupational areas, including those associated with vehicle exhaust. CO is an important industrial gas used in the production of chemical intermediates. CO is formed endogenously and acts as a signalling substance in the neuronal system.

The main mechanism behind CO-induced toxicity is the binding of CO to haemoglobin in the blood, resulting in carboxyhaemoglobin (COHb) formation, reduced oxygen transport capacity of the blood and hypoxia. The relation between CO in air and COHb is well known and can be calculated using the Coburn-Forster-Kane (CFK) equation. Endogenous CO formation leads to a background COHb of 0.4–0.7%. Non-smokers typically have COHb levels up to 2% whereas smokers may have COHb levels up to 10% immediately after smoking.

The effects seen in acute CO poisoning cover a wide range, from mild symptoms, like shortness of breath during exercise or occasional headache at COHb 20%, to more severe ones like headache, dizziness, disturbed judgement, dimness of vision, confusion, unconsciousness, intermittent convulsion and respiratory failure at COHb above 30%. COHb levels of 50–60% are often lethal. Even COHb levels of 20% may be lethal for patients with coronary artery disease. The foetus is at higher risk than the healthy adult because of higher CO haemoglobin affinity.

From controlled human and animal exposure studies the adverse effects of concern are impaired exercise performance, i.e. decreased maximal aerobic capacity in healthy volunteers (lowest observed adverse effect level (LOAEL) COHb 4.3%), increased myocardial ischaemia in patients with coronary artery disease (LOAEL COHb 2.4%), and persistent changes in the developing auditory system of the rat (LOAEL 12 ppm, corresponding to COHb 1.8% and 2.0% assuming 8 hours constant exposure at rest and heavy work, respectively). It was not possible to identify any no observed adverse effect levels (NOAELs) in these studies.

No or limited data were found regarding genotoxicity, carcinogenicity, irritation and sensitisation.

Combined exposure to CO and dihalomethanes causes increased formation of COHb. Combined exposure to CO and noise may potentiate noise-induced hearing loss.

Keywords: auditory, carbon monoxide, carboxyhaemoglobin, cardiovascular, central nervous system, developmental, occupational exposure limit, review, risk assessment, toxicity.

17. Summary in Swedish

Stockmann-Juvala H. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 147. Carbon monoxide.* Arbete och Hälsa 2012;46(7):1-78.

Kolmonoxid (CO) är en luktfri och färglös gas som bildas vid ofullständig förbränning av kolbaserade bränslen. CO finns också i tobaksrök. Exponering för CO är vanligt inom många yrkesområden, bland annat de som förknippas med bilavgaser. CO är en viktig industriell gas som används vid framställning av kemiska intermediärer. CO bildas endogent och fungerar som en signalsubstans i nervsystemet.

Den huvudsakliga mekanismen för CO-inducerad toxicitet är bindning till hemoglobin i blodet, dvs bildning av karboxyhemoglobin (COHb), vilket resulterar i försämrad syretransport i blodet och hypoxi. Relationen mellan CO i luft och COHb är välkänd och kan beräknas med hjälp av Coburn-Forster-Kane (CFK) ekvationen. Endogen bildning av CO leder till bakgrundsnivåer mellan 0,4 och 0,7% COHb. Icke-rökare har vanligtvis COHb-nivåer upp till 2%, medan rökare kan ha nivåer upp till 10% omedelbart efter rökning.

Effekterna vid akut CO-förgiftning omfattar ett brett spektrum från milda symtom som andfåddhet och sporadisk huvudvärk vid 20% COHb, till mer allvarliga som huvudvärk, yrsel, försämrat omdöme, synstörningar (dimsyn), förvirring, medvetslöshet, kramper och andningssvikt vid 30% COHb. COHb-nivåer runt 50-60% är ofta dödliga. För patienter med kranskärlsjukdom kan även COHb nivåer runt 20% vara dödliga. Foster löper högre risk än friska vuxna på grund av att deras hemoglobin har högre affinitet till CO.

Kontrollerade exponeringsstudier visar att de viktigaste negativa hälsoeffekterna är försämrad fysisk prestation i form av nedsatt maximal syreupptagningsförmåga hos friska frivilliga (lägsta observerade effektnivå (LOAEL) 4,3% COHb) och ökad myokardiell ischemi (kärlkramp) hos patienter med kranskärlssjukdom (LOAEL 2,4% COHb). På råtta har bestående förändringar under den tidiga utvecklingen av hörselsystemet observerats vid 12 ppm (LOAEL), vilket motsvarar 1,8% och 2,0% COHb vid 8 timmars konstant exponering under vila respektive tungt arbete. I dessa studier kunde inga icke-effektnivåer (NOAEL) identifieras.

Det går inte att bedöma om CO har genotoxisk eller carcinogen potential eller om CO orsakar irritation och sensibilisering eftersom data saknas eller är begränsade.

Kombinerad exponering för CO och dihalometaner orsakar ökad bildning av COHb. Kombinerad exponering för CO och buller kan förvärra bullerinducerad hörselnedsättning.

Nyckelord: centrala nervsystemet, hygieniskt gränsvärde, hörsel, karboxyhemoglobin, kardiovaskulär, kolmonoxid, riskbedömning, toxicitet, utveckling, översikt.

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19. Data bases used in search of literature

In the search for literature the following data bases were used:
Chemical abstracts
Google Scholar
HSELINE
NIOSHTIC
PubMed
Toxline
Last search was performed in May 2012.

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Appendix 1. Occupational exposure limits

Occupational exposure limits for carbon monoxide (CO) in different countries.

Country	8-hour TWA		STEL		Reference
(organisation)	ppm	mg/m^3	ppm	mg/m^3	
Denmark	25	29	50	58	(1)
Finland	30	35	75	87	(2)
Norway	25	29	-	-	(3)
Sweden	35	40	100	120	(4)
The Netherlands	-	29	-	-	(5)
Germany (DFG)	30	35	60	70	(6)
United Kingdom	30	35	200	232	(7)
US (ACGIH)	25	-	-	-	(8)
US (NIOSH)	35	40	200 C	229 C	(9)
US (OSHA)	50	55	-	-	(9)
EU	-	-	-	-	(10-12)

C: ceiling value, STEL: Short-term exposure limit (15-min TWA), TWA: time-weighted average (8 hours or for NIOSH up to 10 hours).

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Appendix 2. Previous NEG criteria documents

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium and aluminium compounds	1992:45, 1993:1*, 2011;45(7)*D
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel exhaust	1993:34, 1993:35*
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4)*D
Enzymes, industrial	1994:28*, 1994:42

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isoflurane, sevoflurane and desflurane	2009;43(9)*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*
Lithium and lithium compounds	2002:16*
Manganese	1982:10
Mercury, inorganic	1985:20
Methacrylates	1983:21
Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
Nickel	1981:28, 1995:26*, 1995:27
Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Nitrous oxide	1982:20
Occupational exposure to chemicals and hearing impairment	2010;44(4)*
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
Paper dust	1989:30, 1989:37*
Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7
Phenol	1984:33
Phosphate triesters with flame retardant properties	2010;44(6)*
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polychlorinated biphenyls (PCBs)	2012;46(1)*
Polyethylene,	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27
Propylene glycol	1983:27
Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Sulphuric, hydrochloric, nitric and phosphoric acids	2009;43(7)*
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

* in English, remaining documents are in a Scandinavian language.
D = collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
N = collaboration with the US National Institute for Occupational Safety and Health (NIOSH).
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2011;45(4). The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Safety. 144. Endotoxins.

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