Carbon monoxide

Health-based recommended occupational exposure limit
To: the state secretary for Participation and Integration
Nr. 2024/12, The Hague, September 3, 2024

Health Council of the Netherlands

contents

samenvatting

Op verzoek van het ministerie van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad een gezondheidskundige advieswaarde afgeleid voor de beroepsmatige blootstelling aan koolmonoxide.
Dit advies is tot stand gekomen in de commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS). Op www.gezondheidsraad.nl staat informatie over de taken van deze vaste commissie van de Gezondheidsraad. De samenstelling van de commissie is te vinden op de laatste pagina van dit advies.

Blootstelling aan koolmonoxide

Koolmonoxide komt in het menselijk lichaam voor als gevolg van normale endogene fysiologische processen en exogene blootstelling. Die exogene of externe blootstelling aan koolmonoxide kan afkomstig zijn van verschillende bronnen. Voor de beroepsbevolking zijn met name menselijke activiteiten waarbij koolmonoxide vrijkomt relevant.
Deze omvatten de onvolledige verbranding van fossiele brandstoffen, hout, en andere producten in de werkomgeving. De beroepsbevolking kan ook worden blootgesteld aan intentioneel geproduceerd koolmonoxide, een belangrijk industrieel gas dat gebruikt wordt om andere chemische stoffen te maken. Koolmonoxide wordt ook gebruikt voor de productie van anorganisch materiaal, organische stoffen en polymeren. Tot slot wordt koolmonoxide in diverse andere industriële processen gebruikt (waaronder het kalibreren van analyse-instrumenten, metaalbehandeling en de productie van farmaca).

Nadelige gezondheidseffecten

In de mens heeft endogeen geproduceerd koolmonoxide een belangrijke fysiologische signaalfunctie. Blootstelling aan extern geproduceerd koolmonoxide kan echter leiden tot verschillende nadelige gezondheidseffecten. Hierbij gaat het om acute effecten en werkingsmechanismen na hoge blootstelling, maar ook om effecten veroorzaakt door langdurige lage blootstelling. Acute hoge blootstelling leidt tot zuurstoftekort. De werkingsmechanismen die bijdragen aan toxiciteit na langdurige lage blootstelling aan koolmonoxide zijn nog grotendeels onduidelijk. De voornaamste (nadelige) gezondheidseffecten ten gevolge van langdurige lage blootstelling betreffen effecten op hart en vaten (angina pectoris, veranderingen in ST-geleiding, verminderde inspanningstolerantie en een toename van ischemische hartziekten), neurologische effecten (effecten op visuele en auditieve zintuigen) en effecten op de ontwikkeling van het nageslacht.

Gezondheidskundige advieswaarde

Voor schadelijke stoffen waaraan mensen tijdens hun werk kunnen worden blootgesteld, gaat de commissie GBBS na of er uit wetenschappelijk onderzoek een gezondheidskundige advieswaarde is af te leiden op basis van een veilige ondergrens van blootstelling aan de stof. Hiermee wordt een blootstellingsniveau bedoeld waarbij geen nadelige gezondheidseffecten te verwachten zijn. Op basis van de gezondheidskundige advieswaarde van de commissie kan de staatssecretaris een grenswaarde voor beroepsmatige blootstelling vaststellen.

Geraadpleegde onderzoeken

Over de nadelige gezondheidseffecten na blootstelling aan koolmonoxide is een grote hoeveelheid wetenschappelijk onderzoek beschikbaar. De commissie heeft zich daarom voor haar evaluatie gebaseerd op rapporten die eerder door andere expertgroepen zijn gepubliceerd. Aanvullend is er gezocht naar literatuur die meer recentelijk is gepubliceerd. De commissie is van mening dat effecten op het hart- en vaatstelsel, neurologische effecten en effecten op de ontwikkeling van het nageslacht het meest relevant zijn na blootstelling aan lage concentraties koolmonoxide. De commissie concludeert op basis van de beschikbare wetenschappelijke gegevens dat de beschreven effecten op het hart- en vaatstelsel het meest geschikt zijn om een gezondheidskundige advieswaarde af te leiden, omdat hiervoor kwantitatieve meta-analyses beschikbaar zijn bij lage concentraties koolmonoxide in de lucht.

Advies aan de staatssecretaris

Voor de beroepsmatige blootstelling aan koolmonoxide komt de commissie tot een gezondheidskundige advieswaarde van 7,5 milligram (mg) per kubieke meter (m^3) lucht (6,4 ppm *(parts per million)*), als een gemiddelde concentratie over een achturige werkdag.
De advieswaarde van 7.5 mg/m^3 (6.4 ppm) is drie keer lager dan de huidig geldende limiet van 23 mg/m^3 (20 ppm).

Aangezien de commissie geen bruikbare wetenschappelijke gegevens heeft gevonden om een advieswaarde voor kortdurende blootstelling vast te stellen, kan de commissie geen *STEL* (*Short Term Exposure Limit*) of plafondwaarde adviseren.

executive summary

At the request of the ministry of Social Affairs and Employment, the Health Council recommends health-based occupational exposure limits. This report contains an evaluation of the health hazard and recommendation for carbon monoxide. The evaluation was performed by the Dutch Expert Committee on Occupational Safety (DECOS), a permanent committee of the Health Council. Additional information on the task of the committee can be found at www.healthcouncil.nl. The members of the committee are listed on the last page of the advisory report.

Exposure to carbon monoxide

Carbon monoxide is present in the human body as a result of endogenous physiological processes, but also as a result of exogenous exposure. For exposure to carbon monoxide in the working environment, anthropogenic sources are of particular relevance. These include the incomplete combustion of fossil fuels, wood and other products. People can also be exposed exogenously to intentionally produced carbon monoxide, which is an important industrial gas used in the production of certain chemical intermediates. It is also a reducing agent in the production of inorganic materials, organic chemicals and polymers. Furthermore, various other uses at industrial sites (including calibration of analysis equipment, metal treatment and pharmaceutical production) can lead to exposure to carbon monoxide.

Adverse health effects

While carbon monoxide produced in the human body has an important physiological signalling function, external exposure to carbon monoxide can result in a variety of adverse effects. These can be acute effects and modes of action after high exposure, but also long-term effects caused by low levels of carbon monoxide. Acute high exposure leads to hypoxia, but non-hypoxic modes of action have also been identified. The mechanisms of toxicity after low exposure remain unclear. Regarding low exposure levels, the main effects consist of cardiovascular effects (angina pectoris, ST-segment changes, decreased maximum exercise tolerance and increased symptoms of ischaemic heart disease), neurological effects (visual and auditory sensory effects) and various effects on foetal development and offspring.

Health-based recommended occupational exposure limit

For hazardous substances to which people can be occupationally exposed, the committee determines whether a concentration can be derived at which no adverse health effects are expected. This health-

based recommended occupational exposure limit (HBR-OEL) is the basis for the state secretary to set a legally binding occupational exposure limit.

Consulted research

For the adverse effects of carbon monoxide, a vast amount of data is available. The committee has therefore used reports published previously by expert groups. Furthermore, a literature search was performed to include the most recent literature in this evaluation. The committee considers cardiovascular effects, neurological effects and (neuro)-developmental effects to be most relevant after exposure to low levels of carbon monoxide. The committee concludes that the studies that reported cardiovascular effects are most suitable for deriving a health-based occupational exposure limit, since quantitative meta-analyses are available concerning low carbon monoxide concentrations in air.

Recommendation to the state secretary

For occupational exposure to carbon monoxide, the committee recommends a health-based occupational exposure limit for carbon monoxide of 7.5 mg per m^3 air (6.4 ppm – parts per million), which represents a mean concentration during an 8-hour working day.

The advised limit of 7.5 mg/m^3 (6.4 ppm) is three times lower than the current applied limit of 23 mg/m^3 (20 ppm).

As the committee has not identified literature suitable for derivation of a recommended OEL for short term exposure, the committee cannot recommend a STEL (Short Term Exposure Limit) or ceiling value.

01 scope

1.1 Background

At the request of the ministry of Social Affairs and Employment, the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, performs scientific evaluations on the toxicity of substances that are used in the workplace. The purpose of the evaluation is to derive a health-based recommended occupational exposure limit (HBR-OEL) for carbon monoxide, expressed as concentration in the air, the provided literature allows the derivation of such a value. The letter of the request was not specified to carbon monoxide, but concerns a general letter of request that can be found on the website of the Health Council.

In 2019, the Health Council of the Netherlands published an advisory report on health risks due to low concentrations of carbon monoxide to the general population.[1] This advisory report contains an evaluation of the health hazard and derivation of a HBR-OEL for carbon monoxide.

1.2 Committee and procedure

The present document contains an evaluation by the DECOS, hereafter referred to as the committee. The members of the committee, including the consulted experts, are listed on the last page of this report.

In December 2023, the president of the Health Council released a draft of the report for public review. The committee has taken the comments received into account in preparing the final version of the advisory report. The received comments, and the replies by the committee, can be found on the website of the Health Council.

1.3 Data

The methodology the committee generally applies for its evaluations is described in the document *Guidance for recommending classifications and health-based occupational exposure limits*.[2] For the evaluation of carbon monoxide, the committee decided to deviate from this guidance. Given the complex toxicity profile of carbon monoxide (i.e. several potential health effects that may occur at low exposure levels) and the large amount of available data, the committee has decided to use assessment reports previously published by other scientific organisations as a starting point, and only address underlying literature when needed. These reports were assessed for the quality of systematic approaches and considered for evidence that could support an 8-h time-weighted average (TWA) exposure limit, a 15-min STEL (Short Term Exposure Limit), or a ceiling value.

Reports assessed are, in chronological order, the *Collection for Occupational Health and Safety* of the German Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) on carbon monoxide (1981)[3], the recommendation from the Scientific Expert Group on

Occupational Exposure Limits (SEG-OEL)[a] for carbon monoxide (1995)[4], the World Health Organisation (WHO) guidelines for indoor air quality (2010)[5], The toxicological profile for carbon monoxide by the Agency for Toxic Substances and Disease Registry (ATSDR) and the criteria documentation on carbon monoxide by the Nordic Expert Group (NEG) (2012)[6,7], scientific basis for Swedish occupational standards on carbon monoxide by the Swedish criteria group (2017)[8], and the WHO guidelines for outdoor air quality (2021)[9]. In addition to the evaluation of these reports, a search was performed between 2012 and until March 2023 for recent literature (See Annex B 'Search strategies').

The 2019 report by the Health Council[1] was not further considered by the committee. This report refers to a limit value of 9 ppm for the general population, set by the WHO in 1999, but does not provide substantiated information on the derivation of a limit value. The committee notes that the referred WHO limit value has since been updated by the WHO in an evaluation of 2021[9], which is addressed separately in the current report.

1.4 Quality assessment

The inclusion and exclusion criteria for scientific studies applied for the above mentioned reports (see Section 1.3 'Data') were assessed by the committee using the methodology described in its *Guidance for recommending classifications and health-based occupational exposure limits*.[2] In short, this methodology states that evidence regarding all possible adverse effects (local and systemic effects; acute, short-, mid- and long-term effects) is taken into account. For deriving a HBR-OEL, the committee prefers data derived from studies with humans (i.e. epidemiological data). The data used should be applicable to the working population (age ~18-67), which is assumed to be healthy with no underlying morbidities. If possible, sensitive groups (e.g. pregnant women and their unborn children) within the working population are considered in deriving the HBR-OEL.

[a] Predecessor of the Scientific Committee on Occupational Exposure Limits (SCOEL) of the European Commission, established in 1995.

02
identity, guidelines and exposure monitoring

2.1 Identity and physicochemical properties

Carbon monoxide is an odourless, tasteless and colourless gas. The gas has a density close to that of air and is mainly formed during incomplete burning of carbon.[6,7]

Physical and chemical properties of carbon monoxide are presented in Table 1.

Table 1 Physical and chemical properties of carbon monoxide.[10,11]

CAS number	630-08-0
EC/EINECS number	211-128-3
REACH Reg. Nr.	01-2119480165-39
Synonyms	carbonic oxide; carbon monoxide; carbon monooxide; carbon oxide; CO;
Molecular weight	28.01 g/mol
Molecular formula	CO
Physical state	Gas
Solubility	23 ml/L in water at 20°C
Structure	$O^+ \equiv C^-$
Relative density	0,97 at 20°C
Vapour pressure	3498.7 kPa at -140.3°C
Log P octanol/water	n.a.
Melting point	-205 °C
Boiling point	-191.5 °C
Flash point	n.a. (flammable gas)
Conversion factor 20°C and 101,3 kPa	1 ppm = 1.165 mg/m^3 1 mg/m^3 = 0.859 ppm

2.2 Exposure monitoring

2.2.1 Environmental exposure monitoring

Analytical approaches for carbon monoxide detection in air usually involve non-dispersive infrared detection (NDIR) and may include gas filter correlation techniques.[7,12] These approaches can detect carbon monoxide levels down to 0.05 mg/m^3 (0.04 ppm). Analysing samples using gas chromatography with flame ionisation detection could lower the detection limit of the analysis to 0.02 mg/m^3 (0.02 ppm).

2.2.2 Biological exposure monitoring

Exposure to carbon monoxide can be indirectly measured as carboxy-haemoglobin (COHb) levels in blood and as carbon monoxide levels in exhaled air, which reflects carbon monoxide levels in blood.

The correlation between the ambient carbon monoxide concentrations and these indirect measures in blood and exhaled air have been considered problematic because of the endogenous carbon monoxide production and potential confounders like smoking behaviour and activity levels of subjects at the time of measurement.[7]

Blood carboxyhaemoglobin measurement

A variety of methods are available to measure COHb in blood.

The majority use blood samples collected via skin puncture and direct-reading spectrophotometers. The detection limits of the currently available blood oxygen (oxi-) meters are below COHb concentrations of unexposed

persons.[7] More recently developed methods are fingertip pulse oximeters, which allow for a non-invasive measurement of arterial COHb. These measurements are based on near-infrared and long-wavelength emission of visible light diffusing through the tissue. The results from pulse-oximetry correlate well with blood COHb results obtained by traditional blood carbon monoxide-oximetry, albeit with a slight over-estimation. Lastly, analysis of the carbon monoxide gas released from blood when COHb dissociates using gas chromatography is the most sensitive technique with a limit of detection of 0.005% COHb (as a percentage of total haemoglobin).

Carbon monoxide measurement in exhaled air

Carbon monoxide in exhaled air can be measured with portable analysers that are based on e.g. electrochemical detection, infrared spectrometry, gas chromatography and tuneable diode laser spectrometry. Limits of detection are low, even below 1.2 µg/m^3 (1 ppb).[7]

Estimation of air carbon monoxide concentration based on COHb

Using these COHb levels, the concentration of carbon monoxide can be estimated using the Coburn-Foster-Kane (CFK) equation.[12,13] This equation was developed to calculate COHb levels upon endogenous carbon monoxide production and describes major physiological variables. It is also used for the calculation of COHb levels in blood after carbon monoxide inhalation.[12] Vice versa, this model can be used to estimate air exposure levels based on COHb measurements. The model is considered valuable when levels of carbon monoxide exposure in subjects are unknown; however, it also has limitations as baseline COHb levels between individuals vary substantially due to intrinsic or extrinsic factors that interfere with the COHb levels. This variation may result in a misprediction of the actual carbon monoxide exposure from the source of interest. Besides interindividual variations in baseline COHb, the half-life of COHb also seems to differ between individuals (see Chapter 6 Kinetics).[12] Additionally, it will take time to perform COHb measurements after subjects were exposed to carbon monoxide which could result in an underestimation of the peak exposure. All in all, these factors may affect the prediction of the actual carbon monoxide exposure based on COHb levels measured in blood.

The use of COHb as a biomarker for environmental carbon monoxide exposure was reviewed by Veronesi et al. (2017).[14] Only 7 out of 19 studies that were included showed a correlation between COHb and carbon monoxide exposure in non-smoking healthy subjects and the assessment of confounding factors was often incomplete according to the authors. A similar conclusion was reached in a study in which COHb levels were compared with symptoms collected with a standardized questionnaire from 1,323 carbon monoxide-poisoned patients by Hampson et al. (2012).[15] These authors concluded that a correlation between COHb and most common symptoms (chest pain, confusion,

dizziness, fatigue, headache, loss of consciousness, nausea/vomiting, shortness of breath) could not be made.[15]

The most prominent effect caused by the formation of COHb is hypoxia. However, carbon monoxide exposure can also have (adverse) human health effects with other mechanisms of action (see Chapter 7 Mechanisms of toxicity) for which COHb formation appears to be an unreliable parameter to predict the adverse effects.

Overall, COHb measurements can be predictive of CO exposure but are influenced by interindividual variability and by differences in time and are not well correlated with subsequent adversities. The committee concludes that COHb measurements can be supportive for hazard assessment, but are not suitable to the committee's objective of deriving an occupational exposure limit due to the interindividual variation in COHb levels. Therefore, only literature on carbon monoxide concentrations in air is considered for derivation of a HBR-OEL.

03 sources

3.1 Endogenous carbon monoxide formation

Carbon monoxide is produced endogenously and has various physiological functions. Most importantly, it mediates signalling processes in the brain, liver, and endothelium.[16] Carbon monoxide is produced by the human body itself through haem oxygenases (HO) which reside in practically every cell and platelet and catalyse oxidative cleavage of haem (haemoglobin catabolism) to biliverdin, ferrous iron and carbon monoxide. The formation of carbon monoxide from haemoglobin catabolism occurs around a rate of 0.4 mL/hour and from other haemoproteins this rate is 0.1 mL/hour.[12] This results in a background COHb saturation of 0.4-0.7% in resting healthy subjects.

Endogenous carbon monoxide levels are elevated in neonates, and in women that are pregnant or in the premenstrual phase of the menstrual cycle. The breakdown of red blood cells in the premenstrual phase is responsible for the observed increase in carbon monoxide levels.[7] Pregnant women have increased carbon monoxide levels due to the foetus also producing carbon monoxide, in conjunction with an increase in maternal red blood cell production, which results in changes in haemoglobin metabolism.[6]

Carbon monoxide levels are also elevated during pathological conditions that increase the catabolism of haemoglobin. Also, other haemoproteins can increase the endogenous production of carbon monoxide, like Gilbert's syndrome and haemolysis.[6]

Lastly, while non-smokers on average have COHb levels of less than 2% of total Hb, COHb levels of smokers can rise up to 10% directly after smoking.[7]

3.2 Environmental sources

Various natural carbon monoxide sources exist. Carbon monoxide can originate from volcanic activity and fires.[7] Environmental oxidation of methane and non-methane hydrocarbon also results in the formation of carbon monoxide.[17] Finally, plants and oceans produce carbon monoxide. It is estimated that approximately 33% of the carbon monoxide in the atmosphere originates from environmental sources.[5,12] A typical concentration in the atmosphere is around 0.1 mg/m^3 (100 ppb); especially clean air can have concentrations as low as 0.06 mg/m^3 (50 ppb).[a]

3.3 Anthropogenic sources

3.3.1 Production

Carbon monoxide is a product of incomplete combustion of coal, fossil fuels, wood and other products. The oxidation of methane and non-

[a] https://scied.ucar.edu/learning-zone/air-quality/carbon-monoxide (accessed June, 2023)

methane hydrocarbons, resulting in the formation of carbon monoxide, is partly derived from anthropogenic sources (and partly from natural sources).[12] Anthropogenic sources for the emission of carbon monoxide can be categorised into four main categories: fuel combustion, industrial processes, on-road vehicles and non-road vehicles and engines.[18] Examples of fuel combustors are power plants (coal-, gas- or oil-fired) and residential heaters. Industrial processes include the production of metals and chemicals and refining of petroleum.

By burning any product that contains a large amount of carbon, two primary products are produced: carbon monoxide and carbon dioxide. The conditions during combustion determine which of the two is predominantly produced. Carbon dioxide is mainly formed when there is sufficient oxygen, while under low oxygen conditions the formation of carbon monoxide predominates.

3.3.2 Intentional use

Carbon monoxide is an important industrial gas which can be used to produce chemical intermediates. It is also used as a reducing agent when producing inorganic materials and is used in the production of organic chemicals like acetic acid and formic acid.[7]

Uses at industrial sites are diverse, including polymer production, calibration of analysis equipment, metal treatment, pharmaceutical production, and laboratory activities.[10]

04
exposure levels

4.1 General population

As carbon monoxide is present in the atmosphere the general population is widely exposed to carbon monoxide, albeit at different concentrations depending on the local conditions, personal habits and occupational settings.

Indoor concentrations of carbon monoxide are usually low, apart from accidents or peak exposures resulting from the above-described incomplete combustion processes (see Chapter 3). Indoor concentrations have been summarised by the WHO and in Europe varied between 0.2 and 33 mg/m^3 carbon monoxide (0.17 and 28.3 ppm), with the highest concentrations measured in indoor ice rinks, service stations, bars and restaurants. Lowest concentrations were measured in homes.[5] Accidental or peak exposures are reported up to 182 mg/m^3 (156 ppm) in homes with defective stoves, boilers or other equipment that involves combustion of gas but also concentrations up to 550 mg/m^3 (472 ppm) in a camping tent with a kerosene cooking stove have been reported.[5]

Only a few studies have reported on the exposure of the general Dutch population to carbon monoxide. These data were summarised in a report on carbon monoxide of the Health Council.[1] In one study, the concentration of carbon monoxide was measured in 74 kitchens. The average concentration over a week was 0.5 mg/m^3 (0.4 ppm) with a maximum concentration of 6.0 mg/m^3 (5.2 ppm). In another study, carbon monoxide concentrations in seven homes (duration of measurements unknown) varied between 23 and 208 mg/m^3 (20 and 178 ppm).[1] In a study including 1,028 homes with a gas appliance, the carbon monoxide concentrations in rooms were below the limit of detection of 1.1 mg/m^3 (0.9 ppm) in 84% of the houses. The highest carbon monoxide concentrations reported ranged between 58 and 87 mg/m^3 (50-75 ppm)), which were observed in only 0,3% of the houses. Finally, in living rooms of 85 homes, the reported average concentration of carbon monoxide was 0 mg/m^3 and the highest peak concentration was 17.5 mg/m^3 (15 ppm).

4.2 Working population

Occupational carbon monoxide exposures are usually higher than exposure through ambient air and commonly involve co-exposure to other substances. In a 10-year survey of carbon monoxide-related incidents in the United States, 27.7% of 3,414 cases of carbon monoxide-injured people were work related. Most injuries were related to heating, (inadequate) ventilation and air conditioning systems, followed by exposure to emissions from forklifts and power machinery.[19]

People with occupations involving manufacturing of carbides (and to a lesser extent manufacturing of electrical equipment and coke oven products), airplane cabin personnel, iron casting and construction and mining are at risk of increased carbon monoxide exposure (Table 2).[7]

Table 2 Occupational carbon monoxide levels measured at various workplaces in Norway 2000–2009 (taken from the NEG, 2012 (p6)).[7]

Occupational field	Number of measurements	CO max in mg/m³ (ppm)	CO mean in mg/m³ (ppm)
Defence activities (incl. submarines)	23	1,385 (1,189)	318 (273)
Manufacture of carbides	1,001	NA	144 (124)
Scheduled air transport	8	NA	51 (44)
Casting of iron	17	438 (375)	50 (43)
Other preventive health care	7	204 (175)	35 (30)
Stuff, tunnel, construction site	6	1,039 (892)	22 (19)
Manufacture of electrical equipment	5	NA	20 (17)
Manufacture of coke oven products	14	NA	16 (14)
Wholesale of mining, construction and civil engineering machinery	12	NA	13 (11)
Operation of gravel and sand pits	6	NA	13 (11)
Construction	125	245 (210)	12 (10)
Maintenance and repair of motor vehicles	10	43 (37)	7 (6)
Construction of motorways, roads, airfields and sport facilities	97	757 (650)	6 (5)
Installation of electrical wiring and fittings	10	44 (38)	5 (4)
Manufacture of veneer sheets, plywood, laminboard, particle board	9	795 (682)	3 (3)
Manufacture of other non-metallic mineral products n.e.c.	34	NA	3 (3)
Production of primary aluminium	10	73 (63)	2 (2)
Aluminium production	5	NA	2 (2)
Mining of non-ferrous metal ores, except uranium and thorium ores	8	186 (160)	<2 (2)
Toll bar stations	17	23 (20)	<2 (2)
Manufacture of industrial gases	6	10 (9)	<2 (2)
Manufacture of paper and paperboard	5	3 (3)	<2 (2)

N.A. = not available

05 current OELs, classification and labelling

5.1 Occupational Exposure Limits

Occupational exposure limits for carbon monoxide in some European countries and the United States are presented in Table 3.

In The Netherlands, the current occupational exposure limits are in accordance with the limits set by the EU: 23 mg/m^3 8-hour TWA; 117 mg/m^3 15 minutes TWA.[20]

Table 3 Occupational exposure limits (in mg/m^3 (ppm)) as 8-hour time-weighted average (TWA), 15-minute TWA and a ceiling value for carbon monoxide in various countries. Source: GESTIS substance database from IFA.[21]

Country – organisation	TWA 8 hours	TWA 15 minutes	Ceiling
The Netherlands	23 (20)	117 (100)	
European Commission (2017, indicative OEL)	23 (20)	117 (100)	-
Denmark	23 (20)	46 (40)	-
Finland	23 (20)	87 (75)	-
Germany (AGS and DFG)	35 (30)	70 (60)	-
Norway	23 (20)	117 (100)	
Sweden	23 (20)	70 (60)	
UK	23 (20)	117 (100)	
US - NIOSH	40 (35)	-	229 (200)[a]
US - OSHA	55 (50)	-	-

a NIOSH defines an Immediately Dangerous to Life or Health (IDLH) value of 1200 ppm for Carbon monoxide. CDC - Immediately Dangerous to Life or Health Concentrations (IDLH): Carbon monoxide - NIOSH Publications and Products https://www.cdc.gov/niosh/idlh/630080.html

5.2 Classification on the carcinogenic properties

Carbon monoxide has not been classified for carcinogenic properties.

5.3 Classification on the reproduction toxic properties

Carbon monoxide has been classified for reproduction toxicity in Category 1A (a 'known human reproductive toxicant') and labelled with H360D (may damage the unborn child) according to a harmonised classification in Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation).[10,22]

5.4 Biological limit values

In the United States, the American Conference of Governmental Industrial Hygienists (ACGIH) recommends a Biological Exposure Indices (BEI) of 3.5% COHb, sampled at the end of a working shift. In Germany, the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (*MAK Kommission*) has derived a Biological Tolerance Value (*Biologische Arbeitsstoff-Toleranzwerte BAT*) of 5% COHb, at the end of the working shift for non-smokers.[23] No legally binding biological limit values currently exist.

06 kinetics

The absorption, distribution, metabolism and excretion of carbon monoxide has been studied in both animals and humans. A short summary is provided below.

6.1 Absorption

The pulmonary absorption of carbon monoxide is affected by numerous physiological factors, like alveolar ventilation and cardiac output.[7]
For instance, exercise increases cardiac output and respiratory exchange ratio, resulting in increased carbon monoxide uptake and increased COHb formation. Sex and age also influence COHb formation. Males usually have higher COHb concentrations than females and the half-life of COHb is longer in males. Older people have a slower uptake and excretion of carbon monoxide than younger people.[7]

Environmental conditions, like carbon monoxide concentration in air and altitude, also affect carbon monoxide uptake.[12] At a high altitude, humans can hyperventilate due to physiological changes, resulting in reduced arterial blood carbon dioxide concentration and increased cardiac output and blood pressure. This results in an increased absorption of carbon monoxide in blood, increased formation of COHb, and increased excretion of carbon monoxide.[6]

The rate of carbon monoxide absorption also depends on the rate of COHb formation. The formation rate and the concentration of COHb in blood depends on multiple processes, including dead space volume in the lungs, ventilation/perfusion ratio and alveolo-capillary membrane diffusion.[17]

Oral and dermal absorption of carbon monoxide has not been extensively studied but appears to be minimal. Absorption of carbon monoxide into the blood via nasal and oral cavities has been shown to be negligible in cynomolgus monkeys (mean change in COHb <0.5%).[7]

6.2 Distribution

Inhaled carbon monoxide passes the capillary membranes of the alveoli, diffuses into the plasma, passes the erythrocyte cell membrane and diffuses into the cytosol to bind to haemoglobin, for which it has a higher affinity (approximately 230 times) than oxygen.[6]

In the other cells such as heart and muscle cells, carbon monoxide can bind to haem-containing molecules like myoglobin and cytochromes.[7] Myoglobin binds oxygen and serves as the local tissue storage of oxygen.[17] The affinity constant of carbon monoxide for myoglobin is lower than for haemoglobin and the dissociation velocity constant of carbon monoxide for myoglobin is much lower than for oxygen (approximately 630 times), resulting in storage of carbon monoxide in muscle.[7,17] It has been suggested that differential binding of carbon monoxide to haemoglobin and myoglobin provides different layers of buffering and protection

against possible inhibition of cellular respiration by carbon monoxide.[16] Intracellularly, carbon monoxide binds to other haemoproteins, including cytochrome P450, cytochrome c oxidase, some peroxidases, and catalase.

Correlations between COHb levels and tissue carbon monoxide concentrations were strongest for the spleen, which had 48-67% carbon monoxide (expressed as % of blood carbon monoxide). Concentrations of carbon monoxide in adipose and kidney tissue were low (<20%).[7]

6.3 Metabolism

Carbon monoxide is metabolically generated from endogenous and exogenous precursors. The major endogenous source of carbon monoxide production is the oxidative metabolism of haem by the enzyme haem oxygenase. Less than 10 percent of endogenously produced carbon monoxide is oxidised to carbon dioxide, mainly by cytochrome c oxidase.[6] The majority of carbon monoxide leaves the body unchanged through exhalation after diffusion from alveolar capillary blood to alveolar air.

6.4 Excretion

Carbon monoxide can be excreted from the body through exhalation or by the previously described oxidative metabolism (see 6.3), although the latter is estimated to minimally contribute carbon monoxide elimination.[6] The excretion of carbon monoxide follows a biphasic model, with an initial rapid decrease and a subsequent slower elimination phase.[7]
The elimination half-life ($t_{1/2}$) of COHb depends on the concentration of oxygen inhaled. When the $t_{1/2}$ was calculated in a single human subject immediately after smoking a cigarette, it was almost 5 hours at sea level and atmospheric pressure but decreased to 75 minutes at 40% normobaric (1 atmosphere pressure) oxygen and to 21 minutes at 100% oxygen. Another study showed a COHb half-life of 74 minutes in 93 carbon monoxide -poisoned patients (carbon monoxide from various sources) at 100% oxygen.[7] The discrepancy between these studies may be due to the differences in sample size, differences in study set-up (experimental vs clinical) and differences in times of COHb sampling (initial elimination vs slower elimination). Also, considerable differences have been reported in COHb $t_{1/2}$.[24] Foetal carbon monoxide is eliminated more slowly than maternal carbon monoxide, as shown by half-lives for COHb (7.5 hours for foetal COHb versus 4 hours for maternal COHb).[7]

07 mechanisms of toxicity

In general, hypoxia is seen as the major toxic effect of carbon monoxide exposure. More recently, however, additional non-hypoxic effects have been identified.

7.1 Hypoxic mechanisms of toxicity

On a molecular level, when carbon monoxide binds to one of the four haem groups, this results in an increased affinity of the other haem groups for oxygen. This affinity becomes even higher upon binding of carbon monoxide to the remaining haem groups. As a consequence, this process makes the dissociation of oxygen into the tissues more difficult.[6]

The decrease in oxygen delivery to tissues will result in increased breathing, which in turn will increase uptake of carbon monoxide and further increases COHb formation particularly at high inhaled CO concentrations. The clinical outcome of COHb formation is ischaemia and hypoxia, which can result in severe damage of the heart (myocardial infarction), the brain (stroke), and other tissues.[7]

Exposure during pregnancy can also affect foetal development. Carbon monoxide in the maternal system can distribute to foetal tissues and COHb concentrations have been shown to be 10-15% higher in foetal blood than in maternal blood. Foetal haemoglobin has an approximately two times higher binding affinity for carbon monoxide than maternal haemoglobin. The higher binding affinity combined with small diffusion gradients for carbon monoxide between maternal and foetal blood result in slower kinetics of COHb in foetal blood.[6] Results from laboratory animal studies suggest that acute exposure to lower levels of carbon monoxide, leading to =<10% COHb has little effect on the developing foetus until possibly later in gestation, when the embryo is much larger and more dependent on transport of oxygen by red blood cells.[25] In addition, results from studies of foetal outcome following mild to moderate accidental carbon monoxide poisoning in pregnancy suggest that hypoxemia associated with measured COHb saturations of up to 18% (or even higher estimated levels) does not impair the growth potential of the foetus when pregnancy continues normally.[25]

7.2 Non-hypoxic mechanisms of toxicity

The binding of carbon monoxide to other haemoproteins, like cytochromes and myoglobin, has been linked to various non-hypoxic mechanisms of toxicity. Endogenously formed carbon monoxide is a signalling molecule involved in regulation of various physiological processes. Increasing carbon monoxide levels from an exogenous source can interfere with components involved in these processes, including brain and muscle oxygen storage and utilisation (myoglobin, neuroglobin), nitric oxide cell signalling pathway (e.g. nitric oxide synthase, guanylyl cyclase), prostaglandin cell signalling pathway (cyclooxygenase, prostaglandin H synthase), and energy metabolism and mitochondrial respiration (e.g. cytochrome c oxidase, cytochrome c, NADPH oxidase).[6,26]

7.3 Molecular events

No specific adverse outcome pathways have been described up to date. Table 4 shows a list of carbon monoxide-mediated effects that may play a role in hypoxic and non-hypoxic effects observed after carbon monoxide exposure. Although the involvement of carbon monoxide to the various listed processes is known and has been reviewed in existing literature,[25-30] the precise mechanisms are not always clear.

Table 4 Overview of molecular events and adverse effects of carbon monoxide (drafted based on the evaluated reports of other organisations and additional literature[26,27,29])

Molecular initiating event	Key event	Adverse outcome
Binding of CO to haemoglobin	Impaired oxygen transport and delivery to organs	Damage to heart, brain and other tissues
Binding of CO to the haem containing soluble guanylate cyclase (sGC)	Activation of the enzyme and production of the second messenger cyclic guanosine monophosphate (cGMP) Pathway of cGMP / p38 MAPK leading to p21 upregulation, which regulates cell cycle progression	To protect for excitotoxicity and ischaemic insults in neurons. Smooth muscle cell proliferation inhibition, platelet aggregation, neurotransmission, vasodilation Cellular proliferation
Binding of CO to haem groups of cytochrome A, A3 and cytochrome C oxidase in mitochondria	Inhibition of mitochondrial metabolism and subsequent cellular respiratory dysfunction. Reduction in ATP production and superoxide generation. Excess NO production generating peroxynitrite	Impaired mitochondrial function Damage to cells and tissues, such as ischemic and anoxic brain injury, leading to cognitive deficits in survivors.
Binding of CO to the haem group of cytochrome P450	P450 inactivation	Reduced oxidation of synthetic and organic compounds resulting in reduced breakdown
Binding of CO to the haem group of nitric oxide synthase (NOS)	NOS dependent NO production	NO dependent mobilisation of endothelial progenitor cells affecting vessel integrity
Binding of CO to cytochrome in NADPH oxidases (NOX)	Inhibition NOX mediated ROS activation	ROS generation initiates death and survival pathways
Binding of CO to haem in calcium-dependent potassium channels	Regulation of channel activity	Disruption of ion-channels
Binding of CO to haem in myoglobin (carboxymyoglobin)	Impaired oxygen delivery to the heart	Cardiac dysfunction
CO displaces NO from platelet surface haemoproteins	Displaced NO reacts with oxygen free radicals producing peroxynitrite Platelet activation and aggregation with neutrophils	Inhibition mitochondrial function Inflammation which can result in oxidative stress and neurological damage or apoptosis

08 health effects: previous reports and recent literature

8.1 Previous reports from other expert groups

As noted in Section 1.3 Data, the committee deviated from its guidance document and based its hazard assessment of carbon monoxide on reports published previously by other expert groups. In this section, the most relevant aspects of these reports for derivation of a health-based recommended OEL (occupational studies, critical effects, and the derivation of guidance values) are summarised. For its evaluation of these reports, the committee has considered the methodology applied by the expert groups.

8.1.1 MAK Commission

The Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) is a scientific committee that advises the *Deutsche Forschungsgemeinschaft* and federal/state governments, parliaments and authorities in Germany with respect to exposure to hazardous substances and health, especially in the field of occupational safety. The MAK Commission evaluated carbon monoxide in 1981.

Methodology

The MAK Commission provides general information on its methodology on its website and its published list of MAK-values. No specific information was provided on the literature search and literature selection of its evaluation of carbon monoxide.

Occupational carbon monoxide exposure

With regard to adverse effects due to carbon monoxide exposure in the occupational setting, the MAK Commission stated that no symptoms were reported in larger occupationally exposed groups that worked for 8 hours daily at average CO concentrations up to 134 mg/m^3 (115 ppm) (COHb in non-smokers 4.0%, in smokers 7.6%).

The MAK Commission also identified persons with cardiac or vascular disease and pregnant women as high-risk groups. The MAK Commission concluded that adverse health effects for high-risk groups were to be at COHb levels >2-3%, whereas expected corresponding COHb levels in healthy individuals would be >4%. A COHb level of 4% was noted to correspond to an exposure level of 35 mg/m^3 (30 ppm), at the end of an 8-h shift under the usual working conditions.

Derivation of guidance values

The MAK Commission prepared an extensive evaluation of a wide variety of exposure conditions and defined (latent) cardiovascular disease as the critical effect for an 8-h TWA (Table 9). A short term exposure limit was not derived.

Until 1981, the MAK value for carbon monoxide was 58 mg/m^3 (50 ppm), which was based on the prevention of adverse effects in healthy persons. In 1981 the MAK value was lowered to 35 mg/m^3 (30 ppm) for a better

protection of high-risk groups, although a threshold for adverse effects in persons with latent cardiovascular disease could not be derived. The threshold value was based on data obtained from non-smokers and does not apply to pregnant women, as the MAK Commission states that adherence to this value does not completely exclude the possibility of damage to the developing embryo or foetus.[3]

8.1.2 SCOEL

The Scientific Committee on Occupational Exposure Limit Values (SCOEL) was a Committee of the European Commission which was established in 1995 and disestablished in 2018 to advise on occupational exposure limits for chemicals in the workplace. The ECHA/RAC took on this task in 2019. In 1995, the SCOEL published a report on carbon monoxide.

Methodology

The expert opinion of the SCOEL does not contain information on the methodology of the evaluation.

Effects after occupational carbon monoxide exposure

The SCOEL noted a report of two fatalities concerning the exacerbation of coronary artery disease by occupational carbon monoxide exposure.

Derivation of guidance values

The SCOEL designated effects on the brain, cardiovascular system and foetus as the critical effects of carbon monoxide. The SCOEL identified an 8-hour time-weighted average (TWA) of 23 mg/m^3 (20 ppm) (Table 9).[4] This value was based on changes in CNS activity and susceptibility to cardiovascular disease that started to increase when the concentration of COHb is in the region of 5%, indicating that the limit value should not produce a COHb concentration in excess of 4%. This correlates with 35 mg/m^3 (30 ppm) carbon monoxide in the workplace for average exposures of 8 hours and taking into account the preferred value, the recommended 8-hour TWA is 23 mg/m^3 (20 ppm).[4]

A 15-minute short-term exposure limit (STEL) of 117 mg/m^3 (100 ppm) was proposed to limit COHb accumulation (Table 9).

8.1.3 WHO report indoor air quality

The World Health Organization (WHO) presented guidelines for indoor air quality in 2010 for the protection of public health from health risks following exposure to commonly present pollutants in indoor air, including carbon monoxide.

Methodology

In the WHO report the search strategy for scientific papers is described. The WHO used the search terms ‘carbon monoxide’ and ‘health’ to search

for studies on acute and chronic health effects in PubMed and Web of Science. A special additional search for behavioural and neurological effects was performed in PubMed with the exclusion of (co-)smoking. Additionally, search terms were used to obtain physiological and mechanistic literature. The exact search terms used by the WHO were not stated in the report. The obtained articles and the references cited in these articles were assessed for relevance. It was not specified when the last literature search was executed, but this is assumed to be before 2010, which is the year in which the study was published.

The assessed literature by the WHO was limited to human carbon monoxide exposure in enclosed spaces (indoor air) and occasionally outdoor air exposure was considered as often outdoor air will become indoor air. High exposure levels that can be lethal and delayed effects were not examined. Animal studies were also not considered, except to explore the mode of action. The strength of evidence for a link between exposure and health outcome was classified using the approach developed by the Institute of Medicine committee.[31]

The main types of studies used in the WHO report are controlled human exposure studies. A general finding was that carbon monoxide exposure at ambient levels (expressed as 2-6% COHb) caused a decrease in the time to angina and ST-segment changes in individuals with cardiovascular disease. Multiple studies on laboratory carbon monoxide exposure of young healthy humans and stable angina patients decreased the duration of maximum exercise tests in a dose-related fashion. Based on these studies, the WHO defined a decrease in exercise tolerance and increase in symptoms of ischaemic heart disease (e.g. ST-segment changes) as the endpoints with the highest strength of evidence upon acute exposure (Table 5).

Table 5 Strength of evidence for several important health outcomes (taken from the WHO indoor air quality report).[5]

Strength of evidence	Health outcomes
Sufficient evidence of a causal relationship	Acute exposure-related reduction of exercise tolerance and increase in symptoms of ischaemic heart disease (e.g. ST-segment changes)
Sufficient evidence of a relationship	Chronic epidemiological studies of cardiovascular morbidity (heart attack, congestive heart failure, ischaemic heart disease) Associations between short-term exposure to carbon monoxide and hospital admissions or emergency department visits for respiratory complaints derived from chronic time-series studies
Limited or suggestive evidence of a relationship	Low birth weight, congenital defects and infant mortality Total mortality Increased risk of cardiovascular mortality and stroke Asthma, bronchiolitis, sinusitis, tuberculosis, pneumonia, etc. Neurological, neuropsychological and psychiatric deficits (human and animal studies) Effects on the developing auditory system Immunological impairment (animal studies)

Effects after occupational carbon monoxide exposure

In the WHO Guidelines for indoor air quality four occupational studies have been summarised.

In a study by Stern et al. (1988) that described New York City bridge and tunnel employees, it was concluded that tunnel workers had a 35% excess mortality risk compared with the New York City general population over the period 1952-1982.[32] The risk was only elevated in higher exposed workers. The 24-hour average tunnel carbon monoxide concentrations were reported to be approximately 58 mg/m^3 (50 ppm) in 1961 and 47 mg/m^3 (40 ppm) in 1968, with peak concentrations during periods of rush hour traffic in 1968 of 76-192 mg/m^3 (65-165 ppm).

The WHO also cites a study by Komatsu et al. (1958) which reports the effects of prolonged CO exposure in 733 workers at a steel-making facility (no further details provided; original publication is not available).[5] Workers were divided in groups with different estimated exposures, ranging from groups exposed to 12 mg/m^3 (10 ppm) (with a corresponding COHb-level of 1-5%) and 23 mg/m^3 (20 ppm) (1-5% COHb) to highly exposed groups (≥58 mg/m^3 (50 ppm); ≥10% COHb). The average frequency of mostly subjective health complaints (e.g. headache, poor hearing, chest pain, lassitude, fatigue and forgetfulness) was much higher in workers of the higher exposed groups. Also, incidences of objective health complaints (e.g. pallor, cardiac enlargement (cardiomegaly), coldness of the extremities and hyperactive patellar reflex, average vital capacity, back strength) were reported in groups exposed to ≥58 mg/m^3 (50 ppm).

Ely et al. (1995) described 30 people, most of whom developed ‘warehouse workers’ headache’ which are mostly acute types of headache, dizziness, weakness, nausea and chest pain.[33] These symptoms were considered chronic conditions due to prolonged complaints. Mean COHb levels in the workers most exposed to exhaust gases were 21.1%. In a two-year follow up after the exposure ended, several symptoms were noted (e.g. numbness in the extremities, restlessness, persistent headaches, irritability, confusion, difficulty in walking or moving the extremities, and memory loss).[33]

In another study (Sari et al. 2008) associations were found between chronic carbon monoxide exposure and P-wave and QT interval characteristics of the electrocardiogram in 48 healthy male indoor barbecue workers (with 6.48% COHb) and 51 age-matched healthy male controls (with 2.2% COHb).[34] Significant correlations were observed between COHb level and changes in P-wave duration, maximum QT height, QT duration and corrected QT duration.[34]

Derivation of guidance values

The WHO identified an exposure-related reduction of exercise tolerance and increase in symptoms of ischaemic heart disease (e.g. ST-segment changes) as critical outcome for setting its guideline value. In a weight of evidence approach considering both exercise experiments in healthy subjects and epidemiological studies that also included healthy subjects, the WHO recommended maintaining the previously recommended guideline of 10 mg/m^3 (9 ppm) for 8-h indoor exposure to carbon monoxide. For this value, the WHO takes into account light to moderate exercise and notes the relevance of this value for the occupational setting. The WHO suggests that this exposure, when applying the CFK equation, does not exceed exposure that corresponds to 2% COHb in a normal adult under resting conditions.

For 24-h exposures, the WHO states that this value should be below the 8-h guideline of 10 mg/m^3 (9 ppm) and should be possibly as low as 4.6-5.8 mg/m^3. Ultimately, a guideline of 7 mg/m^3 (6 ppm) is set by the WHO for 24-h indoor carbon monoxide exposure (for people 'Awake and alert but not exercising').

The carbon monoxide guidance values derived by WHO are depicted in Table 6.

Table 6 Indoor carbon monoxide guidance values from the WHO report on indoor air quality in 2010.

Averaging time	Concentration (mg/m^3)	Concentration (ppm)
15 minutes	100	86
1 hour	35	30
8 hours	10	9
24 hours	7	6

The WHO identified several high-risk groups, including the unborn and individuals with coronary artery disease, congestive heart failure or potential stroke.

8.1.4 ATSDR

The Agency for Toxic Substances and Disease Registry (ATSDR) published a toxicological profile for carbon monoxide in 2012.[6]

Methodology

The ATSDR assessed relevant peer-reviewed information and toxicologic testing, albeit indicating that its evaluation was 'not intended to be comprehensive'. Search terms used were not indicated. The most recently cited study was published in 2012.

Effects after occupational carbon monoxide exposure

No specific information on adverse effects after occupational exposure was included in the ATSDR report.

Derivation of guidance values

For its evaluation, the ATSDR focussed on studies that have potential relevance to understanding the lower end of the dose-response relationship, and noted that the heart and cardiovascular system and the brain and developing nervous system are particularly sensitive to carbon monoxide. Based on controlled human clinical studies, epidemiological studies, and various animal models, the ATSDR concluded that cardiovascular effects due to carbon monoxide exposure are associated with blood COHb levels ≥2.4%, and subjects with compromised cardiovascular function are most sensitive. The ATSDR summarised the lowest carbon monoxide exposure levels and COHb levels that were associated with health effects from selected studies (Table 3.1 p26 of the ATSDR report). The most critical effects reported in these studies which are relevant for HBR-OEL-derivation are increased risk of cardiovascular disease in the general population, at exposure levels in the range of 0.3-2.3 mg/m^3 (0.3-2 ppm).

The ATSDR did not propose Minimal Risk Levels (MRLs) for carbon monoxide. It noted the growing evidence for a role of endogenous carbon monoxide production in various important physiological processes. Any exogenous carbon monoxide levels that potentially cause adverse effects will be at or near endogenous carbon monoxide levels, according to the ATSDR. As no NOAELs were identified and as the assessed LOAELs were relatively low, minimal risk levels for the general population (which also includes sensitive groups) would be close to ambient carbon monoxide concentration ranges after applying uncertainty factors. Lastly, ATSDR concluded that minimal risk levels are dependent on the altitude as this affects particular modes of action that involve competition between carbon monoxide and O_2 for haem binding sites.[6]

8.1.5 Nordic Expert Group

The NEG is a collaboration of the Nordic European countries and produce ‘criteria documents’ that form a scientific basis for the regulatory authorities to set occupational exposure limits. The aim of the NEG is to assess dose-response and dose-effect relationships and to determine a critical effect. The NEG published a report on carbon monoxide in 2012.

Methodology

For each criteria document, one or several authors are appointed to evaluate all relevant published, peer-reviewed original literature found. The NEG evaluation builds partly on the reviews by the WHO/IPCS 1999, the US EPA 2000 superseded by NRC 2010, and ATSDR 2012.[6,12,17,35] In May 2012, additional databases (i.e. Chemical abstracts, Google Scholar, HSELINE, NIOSHTIC, PubMed and Toxline) were consulted. No further details on the used assessment methodology were provided by the NEG.

Effects after occupational carbon monoxide exposure

Two occupational studies were summarised by the NEG in the section Effects of long-term exposure, of which one is a chronic poisoning case study of a crane driver by Tvedt et al. (1997).[36] The other is a case study with indoor barbecue workers by Sari et al (2008)[34], which is summarised in section on the WHO indoor air report (2010) (see Section 8.1.3 'WHO report outdoor air quality').[5]

Derivation of guidance values

Derivation of guidance values is not a task of the NEG (Table 9). However, the NEG notes that studies examining acute effects due to low carbon monoxide exposure have focussed on organ systems that are particularly vulnerable to hypoxia, including the heart and the brain. Furthermore, patients with coronary artery disease and the developing foetus were identified as sensitive groups.

In its evaluation of the concentration-response relationship of single or short exposures to carbon monoxide, the NEG considered several cardio-vascular effects observed in studies with humans and animal studies.

The NEG concludes that no single critical effect exists for which a NOAEL was observed. The NEG identifies several groups at extra risk (e.g. people with coronary heart disease, pregnant women and their foetuses, children, and smokers).

For humans, the NEG derived LOAELs based on clinical exercise performance studies. An overall LOAEL of 4.3% COHb was derived for healthy individuals. This exposure was reported to correspond to 38 mg/m^3 (33 ppm) and 26 ppm (30 mg/m^3) carbon monoxide in air, for an 8-h period of rest and heavy work, respectively. For patients with coronary artery disease, the NEG derived LOAELs of 20 mg/m^3 (17 ppm) and 16 mg/m^3 (14 ppm), at rest and heavy work, respectively.

With respect to the findings in animals, the NEG notes a LOAEL of 14 mg/m^3 (12 ppm) for effects of carbon monoxide on the developing auditory system of newborn rats (assumed to correspond to COHb levels of 1.6% (at rest) and 2.0% (heavy work) in humans).

8.1.6 Swedish Criteria Group for Occupational Standards

Similar to the NEG, The Swedish Criteria Group for Occupational Standards (SCGOS) assesses the available data that could be used as a scientific basis for setting occupational exposure limits. In 2017, the SCGOS evaluated the available data on carbon monoxide to assess dose-effect and dose-response relationships and to address the critical effect of occupational exposure with the aim to generate a scientific basis for the Swedish Work Environment Authority to set occupational exposure limits.[8]

Methodology

Literature was searched in various databases (KemI-Riskline, PubMed, Toxline). Information was also drawn from existing criteria documents (NEG, WHO, EU, NIOSH, DECOS). The Swedish criteria document on carbon monoxide is based primarily on the evaluation of the NEG (2012), the WHO/IPCS (1999) and the ATSDR (2012). The Last PubMed search was performed in January 2016, but the search terms and criteria are not stated.

Effects after occupational carbon monoxide exposure

The SCGOS also mentioned the study of Sari et al. (2008)[34], summarised in the section on the WHO indoor air report (see Section 8.1.3).[5]

In addition, the SCGOS concluded that a few studies suggest that exposure to carbon monoxide may potentiate the development of hearing loss caused by noise (ototoxicity). Ototoxicity is not further considered by the committee as a basis for a guidance value for carbon monoxide.

Derivation of guidance values

The SCGOS assessed dose-effect and dose-response relationships but did not derive or propose guidance values for carbon monoxide (see Table 9). The SCGOS focussed on cardiovascular and neurodevelopmental effects in its evaluation of low exposure levels.

8.1.7 WHO report outdoor air quality

In 2021 the WHO updated its guidelines for a number of key pollutants, including carbon monoxide, to offer quantitative health-based recommendations for air quality management.[9] WHO Member States can use the guidelines for legislation and policy. These guidelines are applicable to both outdoor and indoor environments, although they do not cover occupational settings.

Methodology

The WHO has based its report on a systematic review and meta-analysis (see 'Derivation of guidance values' of this section). The WHO guideline development consists of several steps, including a systematic review of the relevant evidence and an assessment of the certainty level of the subsequent body of evidence that resulted from Integrated Science Assessments (ISAs), performed by the US EPA. An ISA results in a classification of the relation of the pollutant and the effect as being causal, likely causal, suggestive of a causal relationship, inadequate to infer a causal relationship or not likely to be a causal relationship. The methods used for these classifications can be further consulted in the ISA for Carbon Monoxide of the US EPA.[18] Thereafter, air quality guidelines were formulated. Throughout the process, the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach were followed. The evidence for causality for the relevant health effects as determined by the US EPA are summarised in Table 7.

Table 7 Causal determinations for health effects categories of carbon monoxide (US EPA; 2010)[18]

Outcome Category	Exposure period	Causality determination
Cardiovascular morbidity	Short-term	Likely to be a causal relationship
	Long-term	Inadequate to infer a causal relationship
Central nervous system effects	Short- and long-term	Suggestive of a causal relationship
Birth outcomes and Developmental effects	Long-term	Suggestive of a causal relationship
Respiratory morbidity	Short-term	Suggestive of a causal relationship
	Long-term	Inadequate to infer a causal relationship
Mortality	Short-term	Suggestive of a causal relationship
	Long-term	Not likely to be a causal relationship

Effects after occupational CO exposure

Since the WHO report *Outdoor air quality* is focussed on the general population, studies in occupational settings were not included.

Derivation of guidance values

The WHO has based its 24-h short-term guideline for outdoor air on a systematic review and meta-analysis of Lee et al. (2020).[37] Lee et al. build on the evidence of a systematic review of Mustafic et al. (2012)[38], who previously studied the association between exposure to air pollutants (including carbon monoxide) and myocardial infarction occurrence or mortality resulting from myocardial infarction.[38]

Lee et al. (2020) studied the association between short-term exposure to ambient carbon monoxide (up to a lag of seven days) and emergency department visits or hospital admissions and mortality due to myocardial infarction.[37] They updated the literature search by Mustafic et al. (2012)[38] until September 30, 2018, including 26 articles in their meta-analysis. Studies were assessed for risk of bias related to six domains: adjustment for critical confounders (seasonality, long-term trends, weekday, meteorological confounders), selection bias, bias for exposure assessment, bias for database selection, missing data, and incomplete or selective reporting. Lee et al. (2020) also performed analyses for several subgroups, by stratification for e.g. individual lag days, study design, low/moderate versus high risk of bias due to adjustment for confounding, publication year, study location, and median carbon monoxide concentration in air.[37] Subgroup analysis showed that the risk estimate was lower in studies at high risk of bias compared to those at low/moderate risk of bias. No statistically significant heterogeneity across subgroups was identified.

Assuming a loglinear relationship, a meta-RR of 1.052 (95% CI 1.017-1.089) for a standardised increment of 1 mg/m^3 (0.859 ppm) increase in carbon monoxide was calculated. Significant heterogeneity for the overall pooled estimate was observed and the WHO selected a lower RR of 1.019 (95% CI 1.011-1.027) based on studies with a median carbon monoxide level of more than 1.15 mg/m^3 (0.99 ppm) to set a guideline value for carbon monoxide. The WHO selected this lower RR of 1.019 as an effect estimate, as it would exclude obvious outliers, uses only one

outcome of myocardial infarction (instead of admissions and mortality combined), and is restricted to the actual measured concentration range.

Based on Lee et al. (2020)[37], the WHO recommended a 24-h guidance value of 4 mg/m^3 (3.4 ppm) (Table 9). This value corresponds to an expected excess in myocardial infarctions of 5.4% per mg/m^3 compared to a day with a carbon monoxide concentration of 1.15 mg/m^3 (0.99 ppm) (the guidance value of 4 mg/m^3 (3.4 ppm), minus the background level of 1.15 mg/m^3, multiplied with a risk increment of 1.9%). The WHO also recommended an interim target concentration of 7 mg/m^3 (6 ppm), proposed as an incremental step for reduction of air pollution for use in areas where pollution is high. The interim target concentration corresponds to an excess risk of 11.1% ((7-1.15) *1.9=11.1%).

8.2 Evaluation of recent literature

Since the previously published reports of expert committees did not include the most recent literature, the committee performed a literature search concerning the most critical endpoints identified previously. An additional search was done to retrieve recent occupational studies addressing the occupational situation. The studies that were considered relevant are summarized below.

8.2.1 Cardiovascular effects

As the WHO outdoor air report (which specifically addresses cardiovascular effects) included literature published until 2018, the committee conducted a search for the literature published since (see Annex B for search strategy). The retrieved references are summarised below, and in Table 8.

Davoodabadi et al. (2019) reported a case-crossover study and investigated the association between air pollutants including carbon monoxide and hospitalization of patients with myocardial infarction in 319 patients from Isfahan, Iran.[39] The data were analysed using an adjusted model with corrections for meteorological confounding factors. For the relationship of carbon monoxide and ST-elevation myocardial infarction, the Odds Ratios (OR) with 95% confidence intervals using the adjusted model were 2.86 (0.29-33.33) at 24 hours, 1.02 (0.85-1.23) at 48 hours, and 1.01 (0.90-1.12) at 1 week before hospitalization. For the relationship of carbon monoxide and non-STEMI (ST-segment Elevation Myocardial Infarction), the ORs were 1.50 (0.08-27.30) at 24 hours, 1.02 (0.77-1.36) at 48 hours, and 1.02 (0.77-1.36) at 1 week before hospitalization.

Pothirat et al. (2019) performed a time series study and investigated the association between air pollutants including carbon monoxide and hospitalised patients' and community dwellers' mortality and incidences of serious respiratory, cardiovascular and cerebrovascular disease events.[40]

Data of in total 4,685 emergency and hospitalization visits were studied from the Chiang Dao district (Chiang Mai, Thailand) between March 2016 and March 2017. ICD-10[a] registry records related to acute respiratory, acute cardiovascular, and acute cerebrovascular events were used to classify the disease outcomes. Data on deaths of hospitalized patients and community dwellers were collected from the Chiang Dao district. Associations between pollutants and deaths or diseases were determined using a linear model with Poisson distribution after correction for meteorological data. Separate models for deaths or disease outcomes were examined from lag day 0 (day of measurement of the pollutants) to lag day 7 prior to death or hospital visit. Mean daily carbon monoxide level was 1.1 mg/m^3 (Interquartile Range (IQR) 0.97-1.3 mg/m^3).

The statistically significant levels ($p<0.05$) that were observed with an increment of 0.01 mg/m^3 of carbon monoxide, were for community acquired pneumonia at lag days 0-3 (RR (95%CI) lag 0: 1.007 (1.001-1.014), lag 1: 1.008 (1.002-1.015), lag 2: 1.007 (1.001-1.014), lag 3: 1.007 (1.001-1.013)) and myocardial infarction at lag day 7 (RR (95%CI) 0.976 (0.960-0.993)).

Liu et al. (2020) investigated the association between short-term exposure of air pollutants including carbon monoxide and hospital visits for MI in a case-crossover study.[41] Data of 6,142 patients were included from Calgary from 2004 to 2012. A time-stratified approach was used to correct for confounders such as obesity, diabetes, smoking and socioeconomic status. It additionally adjusts for effects related to the day of the week and seasonal trends. Temporal relations for air pollutants and MI related hospital visits were assessed for same-day exposure, 1-day and 2-day lagged exposures and cumulative 3-day and 5-day average exposure estimates. A 24-hour median of 0.35 with interquartile range 0.27-0.47 for CO resulted in a statistically significant Odds Ratio (OR; 95% CI) of 1.10 (1.02-1.18) in the high NO_2 tertile on lag day 1. It is unclear which unit the authors used for the concentration levels.

Liu et al. (2021) studied the association of air pollutants including carbon monoxide and myocardial infarction mortality in a time-stratified case-crossover study.[42] 151,608 MI death cases from the Hubei province in China were examined from 2013 to 2018. The authors controlled for long-term trends, season, and day of the week. The daily mean pollutant exposures on the day of death (lag day 0) and 1 day prior to death (lag day 1) were assessed. Two-pollutant models were also conducted to evaluate the robustness of the results. A mean daily CO exposure of 1.14 mg/m^3 (0.99 ppm) was assessed. However, no consistent associations between CO and myocardial infarction mortality were determined.

Zhang et al. (2022) performed a retrospective cohort study and investigated the presence of an association between air pollution including

[a] International Statistical Classification of Diseases and Related Health Problems 10th Revision.

carbon monoxide and recurrent cardiovascular events of 1,641 discharged STEMI patients.[43] Data were collected from the Xuanwu Hospital, Capital Medical University (Beijing) from 2013 until the end of 2019. Daily average concentrations of air pollutants were collected, as well as daily meteorological data on temperature. The average exposure on the day of the recurrent event and on each of the previous 5 days was collected. For long-term exposure, the average exposure from the first day of study enrolment until the recurrent event was assessed. Next to each the Air Quality Index, which combines concentrations of air pollutants, increase of 10 units and each 10 µg/m^3 increase in PM2.5, PM10, SO_2, NO_2, and O_3, each 0.1 mg/m^3 (0.08 ppm) increase in carbon monoxide exposure were calculated for the risks on recurrent cardiovascular events.
The confounder-adjusted HR (95% CI) for CO were 1.18 (1.14-1.21) for short-term exposure and 1.46 (1.39-1.53) for long term exposure.
The long-term average carbon monoxide concentrations was determined to be 0.88 +/- 0.16 (sd) mg/m^3 (0.76 ppm).

Zhu et al. (2022) investigated the association between traffic-related air pollution including carbon monoxide and STEMI events in a retrospective case-crossover study.[44] 1,416 STEMI patients that had a primary percutaneous coronary artery (PPCI) intervention at the Peking University Third Hospital were included between October 2014 and January 2020. Generalized linear regression models were fitted to assess associations of GRACE scores, left ventricular ejection fraction (LVEF), and concentrations of cardiac troponin T (cTnT) with traffic related air pollution. The analysis of association between traffic-related air pollution and STEMI onset was time-stratified with corrections for confounders. Effects of IQR increases in air pollution concentrations were expressed as percentage changes with 95% CI. Pollutants' moving average (MA) concentrations up to 24 hours before STEMI onset or clinical examination were calculated. An average carbon monoxide concentration of 0.84 ppm (0.98 mg/m^3) was determined during the study period. IQR increases of carbon monoxide (0.54 ppm or 0.63 mg/m^3) resulted in around 10% change in STEMI risk of after 18 and 24 MA hours; around 20% changes in cTnT for 1, 4, 8, 12, 18, and 24 MA hours; and approximately -2% change in LVEF after 8 hours.

Table 8 Relevant literature on cardiovascular effects of carbon monoxide, published since 2018.

Reference	Study type	CO concentration	Time	CO effect/conclusion	Remark
Davoodabadi et al. 2019[39]	Case-crossover study of 319 patients with diagnosis of ST-elevation MI or non STEMI. Air pollutants PM10, PM2.5, NO_2, SO_2, CO and O_3 and climate indices (temperature, wind speed, humidity)	4.4 +/-2.3 (sd) µg/m^3 CO in air	24 hours, 48 hours, one week before admission	No statistically significant association between CO and increased risk of hospitalisation was observed	Relatively low sample size; No statistically significant effect
Pothirat et al. 2019[40]	Time series study (total visits 4,685) for association of PM10, PM2.5, SO_2, NO_2, CO, O_3 and daily mortality of hospitalized patients and community dwellers, and emergency and hospitalization visits for serious respiratory, cardiovascular and cerebrovascular diseases	(median) 1.1 mg/m^3 (IQ range) 0.97-1.3	Lag time zero was defined as the day of air pollutants measurement and examined sperate models for each lag from 0 to 7 days prior to the deaths or visits.	CO was associated with emergency visits for community acquired pneumonia.	No association with cardiovascular effects
Liu et al. 2020[41]	Case-crossover study for association of O_3, NO_2, SO_2, CO, PM10, PM2.5 and hospital visits for MI (total visits 6,142).	Regional estimates of hourly concentrations of 6 air pollutants. Mean daily exposure estimates were calculated *Units of concentrations not indicated*	Same-day exposure, 1, day and 2, day lagged exposures and cumulative 3-day and 5day average exposure estimates.	No strong temporal effects of air pollution on MI	Units of concentrations not indicated
Liu et al. 2021[42]	Case-crossover study for association of PM2.5, PM10, SO_2, NO_2, CO, O_3 and MI deaths (151,608 patients).	Collected daily 24-h average concentrations from 109 monitoring stations. Mean daily 1.14 +/-0.37 (sd) mg/m^3 CO	Exposure on the same day of death and 1 day prior (lag 1-day)	No consistent associations for CO and MI mortality	No association
Zhang et al. 2022[43]	Retrospective cohort study for association of PM2.5, PM10, SO_2, NO_2, CO, O_3 and recurrent cardiovascular events of discharged patients after ST-segment elevation MI (STEMI)	Short-term: 0.83 mg/m^3 +/-0.27 (sd) Long-term: 0.88 mg/m^3 +/-0.16 (sd)	Short-term: the average exposure on the event day and the previous five days. Long-term: the average air pollution exposure from the date of study enrolment to occurrence of endpoints (established in 2013 and followed until the end of 2019).	Both short-and long-term exposure to high levels of air pollutants other than ozone was associated with increased risks of recurrent cardiovascular events in STEMI survivors.	Concerns recurrent event and thus underlying disease

Reference	Study type	CO concentration	Time	CO effect/conclusion	Remark
Zhu et al. 2022[44]	Case-crossover study for association between traffic-related air pollution (black carbon, PM2.5-560), NO_x, NO_2, CO) and STEMI events (in total 1,416 patients, 1,094 included in analysis)	0.84 ppm +/-0.66 (sd) (or 0.98 mg/m^3)	Moving average concentrations of ambient air pollutants up to 24 hours before the hours of STEMI onset or clinical examination for each participant.	Hourly exposure to traffic-related particles (PM2.5, PNC5-560, BC) and gaseous pollutants (Nox, NO_2, CO) was associated with significantly increased STEMI risks. For CO this was approximately 10% changes in STEMI risk at prior 18-24 MA hours.	

8.2.2 Developmental toxicity

A general PubMed literature search was conducted using the terms ‘reproductive toxicity’ AND ‘carbon monoxide’ (see Annex B for search strategy). Only studies between 2012 (publication year of the reports of the NEG and the ATSDR) until March 2023 were included. After selection, only one animal study remained for evaluation.

Trentini et al. (2016) studied the effect of carbon monoxide on neuronal migration into the neocortex of newborn pups or adults exposed in utero to carbon monoxide from embryonic day 7 until birth.[45] Pregnant mice were exposed to 175 mg/m^3 (150 ppm) carbon monoxide and compared to controls, since 87 mg/m^3 (75 ppm) did not reach sufficiently high COHb levels and 583 mg/m^3 (500 ppm) induced clear maternal toxicity in a dose range finding study. Prenatal carbon monoxide at 175 mg/m^3 (150 ppm) resulted in a thinner cerebral wall at post-natal day 4. BrdU was injected during corticogenesis and showed altered distribution of early (E12) and late (E16) embryonic neocortical cells. Furthermore, adult mice exposed in utero demonstrated functional impairment in behavioural tests, specifically the pre-pulse inhibition test and the hot plate test.[45]

8.2.3 Neurotoxicity

Also, for neurotoxicological effects a general PubMed literature search was conducted, only studies between 2012 until March 2023 were included (see Annex B for search and selection strategy). After selection, two publications remained for evaluation.

Lukina et al. (2022) studied the associations between day to weeklong exposure to ambient carbon monoxide concentrations and emergency department (ED) visits for central nervous system diseases in Toronto, Canada, by means of a time-stratified case-crossover study.[46] 140,511 emergency department visits were included and contained individuals from newborn to over 60 years. Episodic and paroxysmal disorders were the major part (63.8%) of diagnosed nervous system diseases. 38.9% of these disorders were diagnosed as migraines. The analysis was stratified

by seasons, age and sex. Mean daily carbon monoxide concentration was 0.3 mg/m^3 (0.3 ppm). An increase of an interquartile range (IQR) of 0.12 mg/m^3 carbon monoxide (or 0.1 ppm) in air resulted in statistically significant RRs (95% CI) of 1.019 (1.004-1.033) on lag day 1, 1.024 (1.010-1.039) on lag day 6, and 1.022 (1.007-1.036) on lag day 7 for episodic and paroxysmal disorders in females.

Thilakaratne et al. (2020) studied the association between carbon monoxide and NO_2 exposure in ambient air and general and cause-specific ED visits related to mental health in California from 2005-2013.[47] Relevant mental health outcomes were assessed and included all mental disorders, depression, bipolar disorder, substance abuse, schizophrenia, homicide/inflicted injury and suicide/self-harm. Overall mean carbon monoxide concentrations were 0.45 mg/m^3 (0.39 ppm) (SD 0.27 ppm) with an IQR of 0.28 ppm. The day/days of exposure prior to ED-visit that were assessed were same-day (lag 0), previous day (lag 1), 2-day cumulative lags (lag 0-1), 4-day lags (lag 0-3), one week (lag 0-6), two weeks (lag 0-13), three weeks (lag 0-20), and one month (lag 0-30). In a full year analysis, an increase of 0.28 ppm of 2-day carbon monoxide was associated with an increase of 2.30% (95%CI: 1.28 to 3.32%) in risk and ED visit due to homicide/inflicted injury. This same increase in exposure over a one-week average was associated with a change in risk of -1.93% (95% CI: -3.74 to -0.08%) for an ED visit due to depression. Seasonal analysis showed a warm-season effect as a 2-day average carbon monoxide exposure with IQR increase of carbon monoxide was associated with an increase of 3.13% (1.43 to 4.84%) in homicide/inflicted injury risk compared to the cool season (0.45% risk; -0.60 to 1.50%). In the cool season, a decrease in risk of all mental disorder visits (-1.77%; CI -2.4% to -1.13%), depression (-2.26%; CI -3.9 to -0.60%), and suicide/self-harm (-3.36%; CI -5.56 to -1.12%) were determined.

8.2.4 Occupational studies

For effects caused by occupational exposures, a PubMed search (see Annex B) was conducted for the period 2012-March 2023. No suitable literature remained after selection.

8.2.5 Conclusions on recent literature

Six recent publications on carbon monoxide exposure and cardiovascular effects were retrieved. In two publications (Davoodabadi et al. (2019)and Liu et al (2021)) no consistent or statistically significant association between carbon monoxide and cardiovascular effects were reported.[39,42] Liu et al. (2020)observed no strong temporal effects of air pollution on myocardial infarctions and the unit of the carbon monoxide levels was unclear to the committee.[41] Zhang et al. (2022)investigated recurrent cardiovascular events of discharged patients, a population that is not representative.[43] Pothirat et al. (2019)reported an association between exposure to carbon monoxide and an increased risk of community acquired pneumonia, but not for cardiovascular effects.[40] Zhu et al. (2022)

expressed myocardial infarction outcome as % changes in ST-segment elevation myocardial infarction risk.[44]

From these additional studies, the committee considers the study by Zhu et al. (2022)[44] to be of particular interest, as it provides information on the exposure-risk relationship at lower exposure levels in addition to the previously identified systematic review and meta-analysis of Lee et al. (2020).[37] The data from Zhu et al. (2022)[44] are in line with the relative risks reported by the individual studies included in the systematic review and meta-analysis by Lee et al. (2020).[37]

Only one developmental toxicity study using animals has recently been published. No studies with humans were available. Trentine et al. (2016)[45] reported neuro-developmental effects in newborn mice after exposure in utero to 175 mg/m^3 (150 ppm) carbon monoxide. Exposure to 87 mg/m^3 (75 ppm) was suggested to be a general NOAEL for maternal toxicity, although no details were provided. The committee notes that these results are in line with results from other developmental toxicity studies (Annex A).

Two additional epidemiological studies on carbon monoxide and neurological effects were found (Lukina et al. (2022)[46] and Thilakaratne et al. (2020)[47]). The committee considers these studies informative, but not suitable for derivation of a health-based recommended OEL as these studies are not robust (e.g. lack of univocal case definitions) and these results need to be replicated.

No suitable occupational studies were retrieved in the additional literature search.

Overall, the recently published literature did not provide new insights regarding the critical health effects of CO.

8.3 DECOS' evaluation of previous reports and recent literature

Based on the assessments of carbon monoxide exposure and adverse effects published previously by other expert groups, the committee notes several aspects critical for selecting a starting point for derivation of a health-based recommended exposure level for carbon monoxide.

Methodological limitations

The committee has assessed both the scope and methodology of the abovementioned reports. The committee notes that the reports show little or no overlap in assessed information and for most reports the main information provided involved primary data sources which were systematically retrieved. Therefore, the committee considers these reports informative from an overall point of view, but not suitable as a single primary source for the committee's evaluation from a methodological point

of view. Only for the WHO outdoor air report, a systematic approach was applied and the search strategy was well reported. The WHO outdoor air report based its recommendation on two systematic reviews on ambient carbon monoxide exposure (in the order of hours up to seven days) and myocardial infarction in relation to hospital admissions, emergency department visits or mortality (Lee et al. (2020), and Mustafic et al. (2012)).[37,38] Importantly, the WHO based its conclusion on the actual findings reported in a peer reviewed publication whereas reports from other expert groups included non-reviewed, secondary sources.

Usability of COHb for HBR-OEL derivation

In principle, DECOS recommendations are expressed as the amount of substance in air. For carbon monoxide, the percentage of COHb is often used as exposure parameter in literature. The committee notes that COHb is likely not toxic as such but rather a biomarker for exposure to carbon monoxide (see Section 2.2.2. Biological exposure monitoring). COHb levels can be influenced by several other factors than occupational exposure to carbon monoxide, including smoking, environmental CO exposure and the factors mentioned above (altitude, sex, age, and exercise).[7] COHb measurements can be predictive but are confounded by differences in baseline exposure levels between individuals and by time and are not well correlated with subsequent adversities (see also Section 2.2.2 Biological exposure monitoring). For these reasons, the committee concludes that COHb measurements can be supportive, but are not a reliable basis to determine a biological limit value or to predict an occupational exposure limit in air. Therefore, only literature on carbon monoxide concentrations in air is considered for derivation of a HBR-OEL.

Use of occupational studies

As the committee's recommendations relate to the occupational situation, literature regarding occupational settings is of particular interest.
For carbon monoxide, limited information is available on adverse effects and occupational exposure. An occupational study (excluding case reports) has been included in the reports of the mentioned expert groups, namely the study by Sari et al. (2008).[34] However, in this study only COHb was measured for the assessment of exposure and therefore this study is not considered to derive HB-OELs but is only considered as supportive evidence by the committee.

Modes of action

Although hypoxia is historically considered as the main mode of action of carbon monoxide toxicity, various carbon monoxide-mediated, non-hypoxic mechanistic effects have been described (see Chapter 7 Mechanisms of toxicity). Particularly, these pathways have been implicated in adverse effects observed after prolonged exposure to low levels of carbon monoxide.

Critical endpoints

In reports of most expert groups, cardiovascular effects, neurological and neurodevelopment effects and developmental effects have been associated with prolonged exposure to relatively low levels of carbon monoxide. For these endpoints, different groups of higher risk are involved for which no clear toxicological threshold has been identified (either based on epidemiological or animal data). The committee is of the opinion that there is no single critical endpoint that should be considered for derivation of a health-based recommended OEL. Also, the committee considers these endpoints to have a toxicological threshold.

Conclusions

Based on the reports published by other expert groups, the committee considers cardiovascular effects, neurological effects and (neuro)developmental effects to be the critical endpoints that can be affected by exposure to low levels of carbon monoxide. Cardiovascular effects have been the basis for limit values derived by the MAK Commission, SCOEL, and WHO (see Table 9).

Table 9 Summary of 8-hours TWA and short term exposure limits and the related critical effects per organisation.

Year	Organisation	8-hours TWA	Critical effect	Short term exposure limit	Critical effect
1981	MAK Commission	35 mg/m^3 (30 ppm)	(Latent) cardiovascular disease	-	-
1995	SCOEL	23 mg/m^3 (20 ppm)	CNS activity and susceptibility to cardiovascular disease	15 min: 117 mg/m^3 (100 ppm)	Not specified
2010	WHO	10 mg/m^3 (9 ppm)	Reduced exercise tolerance and increased symptoms of ischaemic heart disease	15 min: 100 mg/m^3 (86 ppm)	Not specified
2012	ATSDR	-	-	-	-
2012	NEG	-	-	-	-
2017	Swedish criteria group	-	-	-	-
2021	WHO	24 hours: 4 mg/m^3 (3.4 ppm)	Myocardial infarction	-	-

Due to uncertainties related to various modes of action and limited data on other endpoints, a single critical endpoint cannot be established.
The committee concludes that the study of Lee et al. (2020)[37] provides the most robust starting point for quantitative hazard assessment, because it is a well-performed systematic review and quantitative meta-analysis on effects of low CO exposures and cardiovascular effects. In this study the relation between ambient carbon monoxide exposure and clinical cardiovascular outcome – a study also used by the WHO for its outdoor guideline – was assessed. Lee et al. assessed the overall certainty of the association between short-term exposure (up to 7 days) to carbon

monoxide and myocardial infarction and concluded the evidence to be of moderate certainty (outlined in appendix 7 of Lee et al.), because of potential confounding by other air pollutants. This moderate certainty was based on the judgement of various domains (limitations in studies, indirectness, inconsistency, imprecision, publication bias, large effect size, plausible confounding towards null, dose-response relation), that did not result in down- nor upgrading of the evidence. The committee evaluated the statistical analysis of the models applied by individual studies in the meta-analysis, and valued the corrections for other air pollutants to be of diverse quality between models. However, the committee does not see indications of a major influence on the risk estimates by other potential confounders. The committee underlines the benefit of such short-term evaluations over chronic studies making potential confounding by factors that do not change day-to-day (such as smoking and lifestyle factors) of less concern.

09 quantitative hazard assessment

The available data (as discussed in Section 8.3 DECOS' evaluation of previous reports and recent literature) indicates that three main endpoints should be considered for the quantitative hazard assessment of carbon monoxide: cardiovascular effects, neurological effects and (neuro)-developmental effects. The committee assumes that a toxicological threshold exists for these endpoints, which appears to be very low. However, the available studies have limitations and do not allow the determination of such a threshold.

As noted in Section 8.2.5 Conclusions on recent literature, consistent data on neurological effects and corresponding exposure information are lacking. The committee therefore considers the available data on neuro-logical effects insufficient for a quantitative hazard assessment.

For developmental effects, only animal data are available (Annex A). The data indicate that continuous exposure to carbon monoxide during pregnancy can lead to several developmental effects, including reduced foetal weight, abnormal haematological parameters, abnormal behaviour of newborns and foetal mortality. The majority of the developmental studies do not allow for derivation of a proper exposure-response relationship, especially related to low exposure, due to methodological limitations (e.g. inclusion of only one test concentration, relatively high concentrations, and/or lack of quantified results). Also, in all developmental toxicity studies maternal animals were exposed continuously during pregnancy without a recovery period, whereas for occupational exposures a duration is assumed to last for 8 hours a day followed by a period of recovery. The committee therefore considers the available data on developmental effects insufficient for a quantitative hazard assessment.

For cardiovascular effects epidemiological data are available. The systematic review and meta-analysis by Lee et al. (2020)[37] included 26 articles that address the risk of myocardial infarction due to ambient carbon monoxide exposure. The committee notes that this study was properly conducted taking into account several potential confounders; however, the included studies do not involve occupationally exposed populations. Although sensitive groups (such as patients with coronary artery disease) are also present in the occupational population, the representation might well differ from the general population.

Based on the preference of the use of epidemiological data and taking into account the abovementioned considerations, the committee used the data on cardiovascular effects as starting point to derive a HBR-OEL.

9.1 Derivation and recommendation of a HBR-OEL (8-h TWA)

For derivation and recommendation of a HBR-OEL, the committee considers the systematic review and meta-analysis of Lee et al. (2020)[37],

which was also the basis for the updated WHO outdoor air quality guidelines for carbon monoxide published in 2021[9], to be the most reliable source for hazard quantification. This study is summarised in detail in Section 8.1.7 WHO report outdoor air quality.

Lee et al. (2020)[37] derived an updated pooled risk estimate for ambient carbon monoxide using random-effects meta-analysis. Based on the publication by Lee et al. (2020), the WHO recommended a 24-h guidance value of 4 mg/m^3 (3.4 ppm) for the general population in 2021. This value corresponds to an expected excess in myocardial infarctions of 5.4%, calculated by the WHO based on a RR of 1.019 for a population exposed to 4 mg/m^3 (3.4 ppm) during the day.

The committee considers the value of 4 mg/m^3 (3.4 ppm) recommended by the WHO, which would correspond with an estimated increase of 5.4% in myocardial infarctions in the general population, to be a reasonable starting point for a HBR-OEL. For the extrapolation to the working population, the committee applied the default factors as indicated in table 10 (See also the committee's *Guidance for recommending classifications and health-based occupational exposure limits*)[2].

Table 10 Applied default factors for extrapolation to the working population

Exposure duration (hours)	24/8 (/24 hours for general population/8 hours for workers) 7/5 (7 days for general population/5 days for worker)
Respiratory rate (m^3)	6.7/10 (standard conditions for general population/light exercise for workers)
Sensitivity of the population with differences in response between people of all ages due to differences in biological, life-style and environmental factors	10/5 (Heterogeneous general population/ more homogeneous working population)
Effect	1/3 (assessment factor NOAEL/LOAEL)

Taking these factors into account, the committee derives a HBR-OEL based on cardiovascular effects of:

4 mg/m^3 x (24/8 * 7/5 * 6.7/10 * 10/5 * 1/3) = 7.5 mg/m^3 (6.4 ppm)

The committee recommends a HBR-OEL for carbon monoxide of 7.5 mg/m^3 (6.4 ppm).

HBR-OEL compared to WHO value for the general population

The proposed limit value of 7.5 mg/m^3 (6.4 ppm) for the working population differs from the WHO guidance value of 4 mg/m^3 (3.4 ppm) for the general population. The committee notes that the different contexts of both values should be considered. The WHO guidance value pertains a certain risk of cardiovascular effects for the general population with the inclusion of various sensitive groups (See Section 8.1.7 WHO report

outdoor air quality). The HBR-OEL derived by the committee in this report indicates an exposure level at which no adverse effects should be expected in a working population exposed for 8 hours per day.
The advised limit of 7.5 mg/m^3 (6.4 ppm) is three times lower than the current applied limit of 23 mg/m^3 (20 ppm).

9.2 Short term exposure limit (STEL; 15-minute TWA)

The STEL is defined as the concentration that workers can be exposed to for a short period of time without risking acute effects, such as throat irritation, that will not be controlled by the application of an 8-hour OEL.[a] The committee notes that it is important to limit short-term exposures in view of the various severe effects that might occur later, even when complying to an 8-h TWA value.

As the committee has not identified literature suitable for derivation of a STEL, the committee cannot derive a STEL.

Previously, a STEL of 100 mg/m^3 has been set by the WHO (for the general population) and a STEL of 117 mg/m^3 by the SCOEL (for workers). The committee notes that these values were not substantiated by scientific studies.

[a] https://oshwiki.osha.europa.eu/en/themes/occupational-exposure-limit-values

9.3 Ceiling value

A ceiling exposure value is the maximum concentration of a substance that should never be exceeded under any circumstance. This value is used for substances for which short-term peaks of exposure could result in serious health effects, as is the case for carbon monoxide.

The committee has not found literature suitable for derivation of a ceiling value. Therefore, a reliable ceiling value cannot be established.
The NIOSH has established a Ceiling concentration of 200 ppm and an Immediately Dangerous to Life or Health (IDLH) concentration of 1200 ppm.[b] The committee notes that in the Netherlands, a value *(alarmerings-grenswaarde)* of 490 mg/m^3 (421 ppm)[c] is applied. This value, however, is used for incident response and indicates the air concentration (during 10 minutes) above which irreversible or other serious health effects can occur, or at which exposure to the substance makes people less able to keep themselves safe.

9.4 Skin notation

No data were available on dermal absorption of carbon monoxide. However, as with other gases that are extensively absorbed via the lungs, no substantial contribution is expected from possible absorption through

[b] CDC - Immediately Dangerous to Life or Health Concentrations (IDLH): Carbon monoxide - NIOSH Publications and Products https://www.cdc.gov/niosh/idlh/630080.html
[c] https://www.rivm.nl/ggd-richtlijn-mmk-koolmonoxide/gezondheidseffecten-koolmonoxide/advieswaarden-grenswaarden

intact skin. The committee therefore concludes that a skin notation is not warranted.

9.5 Groups at extra risk

With regard to the occupational situation, several groups at extra risk have been identified.[7] Pregnant women and their offspring are considered to have a higher sensitivity for carbon monoxide induced-toxicity.
Also, specific working conditions can lead to a higher risk of developing adverse health effects, such as working under heavy exercise and working at low oxygen pressure, including high altitude. Workers who smoke and workers who are co-exposed to chemicals that are metabolised to carbon monoxide in the body (e.g. dichloromethane) are at extra risk due to higher internal carbon monoxide exposure.
The committee notes that with respect to employees who are at extra risk, both employer and employee have responsibilities and obligations to ensure safe working conditions protection.

references

[1] Gezondheidsraad. *Gezondheidsrisico's door lage concentraties koolmonoxide*. Den Haag: Gezondheidsraad, 2019; publicatienr. 2019/11.

[2] Health Council of the Netherlands. *Guidance for recommending classifications and health-based occupational exposure limits*. The Hague, 2021.

[3] MAK Commission. *The MAK collection for occupational health and safety - Carbon monoxide*. 1981.

[4] Scientific Expert Group on Occupational Exposure Limits. *Recommendation from the Scientific Expert Group on Occupational Exposure Limits for Carbon monoxide*. 1995; SEG/SUM/57. Geraadpleegd: 27 February 2019.

[5] WHO. World Health Organization. *WHO guidelines for indoor air quality: selected pollutants*. WHO Regional Office for Europe, 2010; ISBN 978 92 890 0213 4.

[6] ATSDR. U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry *TOXICOLOGICAL PROFILE FOR CARBON MONOXIDE*. 2012.

[7] Nordic Expert Group (NEG). The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *147. Carbon monoxide*. 2012; nr 2012;46(7); ISBN 978-91-85971-41-1; ISSN 0346-7821.

[8] Swedish Criteria Group for Occupational Standards EJM. Swedish Work Environment Authority, S-112 79 Stockholm, Sweden *Scientific Basis for Swedish Occupational Standards XXXV Cutting fluid aerosols, Carbon monoxide*. 2017; No 2017;51(5), ISBN 978-91-85971-63-3, ISSN 0346-7821

[9] WHO. *WHO global air quality guidelines*. Copenhagen, Denmark, 2021. https://apps.who.int/iris/handle/10665/345329.

[10] European Chemicals Agency (ECHA). *Carbon monoxide*. https://echa-term.echa.europa.eu/en/web/guest/registration-dossier/-/registered-dossier/15368/4/12. Geraadpleegd: 31 August 2021.

[11] INCHEM. *Carbon monoxide ICSC: 0023*. 2007. https://inchem.org/documents/icsc/icsc/eics0023.htm. Geraadpleegd: 31 August 2021.

[12] WHO. World Health Organization. *CARBON MONOXIDE*. Environmental Health Criteria, 1999/2004; ISBN 92 4 157213 2

[13] Barn P, Giles L, Heroux ME, Kosatsky T. *A review of the experimental evidence on the toxicokinetics of carbon monoxide: the potential role of pathophysiology among susceptible groups*. Environ Health 2018; 17(1): 13.

[14] Veronesi A, Pecoraro V, Zauli S, Ottone M, Leonardi G, Lauriola P, et al. *Use of carboxyhemoglobin as a biomarker of environmental CO exposure: critical evaluation of the literature*. Environ Sci Pollut Res Int 2017; 24(33): 25798-25809.

[15] Hampson NB, CHRN SLD. *Symptoms of carbon monoxide poisoning do not correlate with the initial carboxyhemoglobin level*. Undersea & Hyperbaric Medicine 2012; 39(2): 657.

16 Motterlini R, Foresti R. *Biological signaling by carbon monoxide and carbon monoxide-releasing molecules*. Am J Physiol Cell Physiol 2017; 312(3): C302-C313.

17 EPA. *Air quality criteria for carbon monoxide.* Washington DC: DC: US Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, 2000; EPA 600/P-99/001F.

18 EPA. *Integrated Science Assessment for Carbon Monoxide*. United States Environmental Protection Agency, 2010; EPA/600/R-09/019F.

19 Mukhopadhyay S, Hirsch A, Etienne S, Melnikova N, Wu J, Sircar K, et al. *Surveillance of carbon monoxide-related incidents - Implications for prevention of related illnesses and injuries, 2005-2014*. Am J Emerg Med 2018; 36(10): 1837-1844.

20 SER. The Social and Economic Council of the Netherlands (SER) *Occupational Exposure Limits Carbon monoxide https://www.ser.nl/en/grenswaarden/koolmonoxide.aspx*. Geraadpleegd: 19 April 2018.

21 Institut für Arbetsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA). *GESTIS International Limit Values*. https://limitvalue.ifa.dguv.de/WebForm_ueliste2.aspx.

22 European Commission. *Commission regulation (EU) 2018/669 of 16 april 2018*. 2018. http://publications.europa.eu/resource/cellar/7243e2bd-4f66-11e8-be1d-01aa75ed71a1.0016.03/DOC_1.

23 DFG. MAK- und BAT-Werte-liste 2021. Bonn: Deutsche Forschungsgemeinschaft, 2021. https://series.publisso.de/sites/default/files/documents/series/mak/lmbv/Vol2021/Iss1/Doc001/mbwl_2021_deu.pdf.

24 Weaver LK, Howe S, Hopkins R, Chan KJ. *Carboxyhemoglobin half-life in carbon monoxide-poisoned patients treated with 100% oxygen at atmospheric pressure.* Chest 2000; 117(3): 801-808.

25 Raub JA, Benignus VA. *Carbon monoxide and the nervous system.* Neurosci Biobehav Rev 2002; 26(8): 925-940.

26 Ryter SW, Ma KC, Choi AMK. *Carbon monoxide in lung cell physiology and disease.* American Journal of Physiology - Cell Physiology 2018; 314(2): C211-C227.

27 Queiroga CSF, Vercelli A, Vieira HLA. *Carbon monoxide and the CNS: Challenges and achievements.* British Journal of Pharmacology 2015; 172(6): 1533-1545.

28 Rose JJ, Wang L, Xu Q, McTiernan CF, Shiva S, Tejero J, et al. *Carbon monoxide poisoning: Pathogenesis, management, and future directions of therapy.* American Journal of Respiratory and Critical Care Medicine 2017; 195(5): 596-606.

29 Levy RJ. *Carbon monoxide and anesthesia-induced neurotoxicity.* Neurotoxicol Teratol 2017; 60: 50-58.

30 Guzman JA. *Carbon monoxide poisoning.* Crit Care Clin 2012; 28(4): 537-548.

31 Institute of Medicine. *Damp indoor spaces and health.* Washington, DC: National Academies Press, 2004.

[32] Stern FB, Halperin WE, Hornung RW, Ringenburg VL, McCammon CS. *Heart disease mortality among bridge and tunnel officers exposed to carbon monoxide.* Am J Epidemiol 1988; 128(6): 1276-1288.

[33] Ely EW, Moorehead B, Haponik EF. *Warehouse workers' headache: emergency evaluation and management of 30 patients with carbon monoxide poisoning.* Am J Med 1995; 98(2): 145-155.

[34] Sari I, Zengin S, Ozer O, Davutoglu V, Yildirim C, Aksoy M. *Chronic carbon monoxide exposure increases electrocardiographic P-wave and QT dispersion.* Inhal Toxicol 2008; 20(9): 879-884.

[35] National Research Council (US) Committee on Acute Exposure Guideline Levels. *Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 8*. National Acadamies Press (US) 2010.

[36] Tvedt B, Kjuus H. *[Chronic CO poisoning. Use of generator gas during the second world war and recent research]*. Tidsskr Nor Laegeforen 1997; 117(17): 2454-2457.

[37] Lee KK, Spath N, Miller MR, Mills NL, Shah ASV. *Short-term exposure to carbon monoxide and myocardial infarction: A systematic review and meta-analysis.* Environment International 2020; 143: 105901.

[38] Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, et al. *Main air pollutants and myocardial infarction: a systematic review and meta-analysis.* Jama 2012; 307(7): 713-721.

[39] Davoodabadi Z, Soleimani A, Pourmoghaddas A, Hosseini SM, Jafari-Koshki T, Rahimi M, et al. *Correlation between air pollution and hospitalization due to myocardial infarction.* ARYA Atheroscler 2019; 15(4): 161-167.

[40] Pothirat C, Chaiwong W, Liwsrisakun C, Bumroongkit C, Deesomchok A, Theerakittikul T, et al. *Acute effects of air pollutants on daily mortality and hospitalizations due to cardiovascular and respiratory diseases.* J Thorac Dis 2019; 11(7): 3070-3083.

[41] Liu X, Bertazzon S, Villeneuve PJ, Johnson M, Stieb D, Coward S, et al. *Temporal and spatial effect of air pollution on hospital admissions for myocardial infarction: a case-crossover study.* CMAJ Open 2020; 8(4): E619-e626.

[42] Liu Y, Pan J, Fan C, Xu R, Wang Y, Xu C, et al. *Short-Term Exposure to Ambient Air Pollution and Mortality From Myocardial Infarction.* J Am Coll Cardiol 2021; 77(3): 271-281.

[43] Zhang H, Yi M, Wang Y, Zhang Y, Xiao K, Si J, et al. *Air pollution and recurrence of cardiovascular events after ST-segment elevation myocardial infarction.* Atherosclerosis 2022; 342: 1-8.

[44] Zhu Y, Fan Y, Xu Y, Xu H, Wu C, Wang T, et al. *Short-term exposure to traffic-related air pollution and STEMI events: Insights into STEMI onset and related cardiac impairment.* Sci Total Environ 2022; 827: 154210.

[45] Trentini JF, O'Neill JT, Poluch S, Juliano SL. *Prenatal carbon monoxide impairs migration of interneurons into the cerebral cortex.* Neurotoxicology 2016; 53: 31-44.

[46] Lukina AO, Burstein B, Szyszkowicz M. *Urban air pollution and emergency department visits related to central nervous system diseases.* PLoS One 2022; 17(6): e0270459.

[47] Thilakaratne RA, Malig BJ, Basu R. *Examining the relationship between ambient carbon monoxide, nitrogen dioxide, and mental health-related emergency department visits in California, USA.* Sci Total Environ 2020; 746: 140915.

[48] Prigge E, Hochrainer D. *Effects of carbon monoxide inhalation on erythropoiesis and cardiac hypertrophy in fetal rats.* Toxicol Appl Pharmacol 1977; 42(1): 225-228.

[49] Carratu MR, Renna G, Giustino A, De Salvia MA, Cuomo V. *Changes in peripheral nervous system activity produced in rats by prenatal exposure to carbon monoxide.* Arch Toxicol 1993; 67(5): 297-301.

[50] Carratu MR, Cagiano R, Desantis S, Labate M, Tattoli M, Trabace L, et al. *Prenatal exposure to low levels of carbon monoxide alters sciatic nerve myelination in rat offspring.* Life Sci 2000; 67(14): 1759-1772.

[51] Di Giovanni V, Cagiano R, De Salvia MA, Giustino A, Lacomba C, Renna G, et al. *Neurobehavioral changes produced in rats by prenatal exposure to carbon monoxide.* Brain Res 1993; 616(1-2): 126-131.

[52] Giustino A, Cagiano R, Carratu MR, Cassano T, Tattoli M, Cuomo V. Prenatal exposure to low concentrations of carbon monoxide alters habituation and non-spatial working memory in rat offspring. Brain Res 1999; 844(1-2): 201-205.

[53] De Salvia MA, Cagiano R, Carratu MR, Di Giovanni V, Trabace L, Cuomo V. I*rreversible impairment of active avoidance behavior in rats prenatally exposed to mild concentrations of carbon monoxide.* Psychopharmacology (Berl) 1995; 122(1): 66-71.

[54] Storm JE, Fechter LD. *Prenatal carbon monoxide exposure differentially affects postnatal weight and monoamine concentration of rat brain regions.* Toxicol Appl Pharmacol 1985; 81(1): 139-146.

[55] Storm JE, Valdes JJ, Fechter LD. *Postnatal alterations in cerebellar GABA content, GABA uptake and morphology following exposure to carbon monoxide early in development.* Dev Neurosci 1986; 8(4): 251-261.

[56] Penney DG, Baylerian MS, Thill JE, Yedavally S, Fanning CM. *Cardiac response of the fetal rat to carbon monoxide exposure.* Am J Physiol 1983; 244(2): H289-297.

[57] Astrup P, Olsen HM, Trolle D, Kjeldsen K. *Effect of moderate carbon-monoxide exposure on fetal development.* Lancet 1972; 2(7789): 1220-1222.

[58] Singh J. *Early behavioral alterations in mice following prenatal carbon monoxide exposure.* Neurotoxicology 1986; 7(2): 475-481.

[59] Singh J, Scott LH. *Threshold for carbon monoxide induced fetotoxicity.* Teratology 1984; 30(2): 253-257.

[60] Loder RT, Hernandez MJ, Lerner AL, Winebrener DJ, Goldstein SA, Hensinger RN, et al. *The induction of congenital spinal deformities in*

mice by maternal carbon monoxide exposure. J Pediatr Orthop 2000; 20(5): 662-666.

61 Kwak HM, Yang YH, Lee MS. *Cytogenetic effects on mouse fetus of acute and chronic transplacental in vivo exposure to carbon monoxide: induction of micronuclei and sister chromatid exchanges.* Yonsei Med J 1986; 27(3): 205-212.

62 Dominick MA, Carson TL. *Effects of carbon monoxide exposure on pregnant sows and their fetuses.* Am J Vet Res 1983; 44(1): 35-40.

63 Morris GL, Curtis SE, Simon J. *Perinatal piglets under sublethal concentrations of atmospheric carbon monoxide.* J Anim Sci 1985; 61(5): 1070-1079.

Committee

Members of the Dutch Expert Committee on Occupational Safety for the advisory report

Carbon monoxide

- Prof. F.G.M. Russel, Professor of Pharmacology and Toxicology, Radboud University Medical Center, Nijmegen, *chairman*
- Prof. H. Bouwmeester, Associate Professor of Toxicology, Wageningen University and Research Centre, Wageningen
- Dr. ir. W. Fransman, Senior Scientist, TNO, Zeist
- Prof. I. Kreis, Professor in Epidemiology, Royal College of Surgeons, London, the UK
- Dr. E.D. Kroese, Toxicologist, TNO, Zeist
- Dr. A.L. Menke, toxicological pathologist, TNO Metabolic Health Research, Leiden
- Dr. S. Peters, Epidemiologist / Scientific Researcher, Institute for Risk Assessment Sciences, Utrecht
- Dr. M. Rooseboom, Principal Toxicologist, Shell Product Stewardship, Shell Global Solutions International B.V., The Hague
- Dr. G.B.G.J. van Rooy, Occupational Physician/Toxicologist, Arbo Unie Expert Centre for Chemical Risk Management, and Radboud UMC Outpatient Clinic for Occupational Clinical Toxicology, Nijmegen
- Prof. L.A. Smit, Professor One Health and Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht

Observers

- Dr. R. Renirie, Ministry of Social Affairs and Employment, The Hague
- D. Theodori MSc, Social and Economic Council, The Hague

Scientific secretary

- Dr. R.H. Mennen, Health Council of the Netherlands, The Hague
- Dr. S.R. Vink, Health Council of the Netherlands, The Hague

annexes

A developmental toxicity studies

Table A1 Reproductive and developmental effects in animals after exposure to carbon monoxide.

Reference	Species	Exposure	Maternal Toxicity	Mean maternal blood COHb (%)	Reproduction toxic effects	Remarks
Prigge et al. (1977)[48]	SPF Wistar rats N=10-80 litters/ group; males and females	0, 68, 143, 286, 572 mg/m^3 Continuously throughout GDs 0-21, after which foetuses were removed by caesarean section. No gross necropsy	N.R.	N.R.	*Developmental toxicity*: 68 mg/m^3: increase in foetal haematocrit (p<0.05) and heart weight (absolute [p<0.05] and relative [p<0.01]). N=12-13 litters 143 mg/m^3: increase in foetal heart weight (absolute [p<0.05] and relative [p<0.001]). N= 10 litters 286 mg/m^3: decrease in foetal haemoglobin (p<0.001), haematocrit (p<0.001), body weight (p<0.001). Increase in heart weight (absolute [p<0.001] and relative [p<0.001]). N=10-19 litters 572 mg/m^3: decrease in foetal haemoglobin (p<0.001), haematocrit (p<0.001), body weight (p<0.001). Increase in relative heart weight (p<0.001). N=22-25 litters	No information on N pups or dose-response statistics. If not stated, no effect on haemoglobin, haematocrit, body weight.
Carratu et al. (1993)[49]	Wistar rats N=5 litters; 6 pups/litter; 1 pup/litter/ exposure group (males only)	0, 86, 172 mg/m^3 Continuously on GDs 0-20, after birth pups assigned to non-exposed mothers. No gross necropsy.	N.R.	172 mg/m^3: 15 (pilot studies)	*Developmental toxicity*: At both concentrations: Increase in time constant of sodium current inactivation (on PD40, p<0.01), % of maximum number of activatable sodium channels at normal resting potential (on PD40, p<0.01) and negative shift of equilibrium potential (on PD 40 and 270, p<0.01) in myelinated nerve fibres. No effects on time to the peak of sodium current, mortality or weight gain.	No information on maternal toxicity and concentration -dependent statistics. Just male pups.
Carratu et al. (2000)[50]	Wistar rats N=20 litters/ group; 6 pups/ litter (males only)	0, 86, 172 mg/m^3 Continuously on GDs 0-20, after birth pups assigned to non-exposed mothers. No gross necropsy.	N.R.	GD10: 0 mg/m^3: 0.97±0.02 86 mg/m^3: 7.20±0.12 172 mg/m^3: 14.42±0.52 GD20: 0 mg/m^3: 1.62±0.10 86 mg/m^3: 7.43±0.62 172 mg/m^3: 16.08±0.88	*Developmental toxicity*: At both concentrations: decrease in myelin sheath thickness of sciatic nerve fibres on PD40 and PD90 (p<0.01). No difference in regression line of myelin sheath thickness. No effect on axon diameters, motor activity, pup weight gain and postnatal mortality. *Reproductive toxicity*: No effect on dam weight gain, number of dams giving birth, pregnancy length and litter size.	No information on maternal toxicity. Just male pups. Data confirms elevated HbCO during gestation (0 mg/m^3) due to increased endogenous CO production.

Reference	Species	Exposure	Maternal Toxicity	Mean maternal blood COHb (%)	Reproduction toxic effects	Remarks
Di Giovanni et al. (1993)[51]	Wistar rats N=24 dams; 8 litters/group; 6 pups/litter, N=118-119 pups/group (males only)	0, 86, 172 mg/m^3 Continuously on GDs 0-20, after birth pups assigned to non-exposed mothers. No gross necropsy.	N.R.	172 mg/m^3: ~15 (pilot studies)	*Developmental toxicity*: 172 mg/m^3: reduction in minimum frequency of ultrasonic calls (p<0.05) and responsiveness (rate of calling) to a challenge dose of diazepam in male pups (p<0.01). Impaired acquisition of an active avoidance task at adult age in males (p<0.005). Not concentration -dependent. No effect on locomotor activity or d-amphetamine-induced hyperactivity, pup weight gain and postnatal mortality. *Reproductive toxicity*: No effect on dam weight gain, number of dams giving birth, pregnancy length and litter size at birth.	No information on maternal toxicity. Just male pups.
Giustino et al. (1999)[52]	Wistar rats N=6 pups/litter; 1 pup/litter/ exposure group; 10 pups/exposure group (males only)	0, 86, 172 mg/m^3 Continuously on GDs 0-20, after birth pups assigned to non-exposed mothers. No gross necropsy.	N.R.	(Mean ±SEM) 0 mg/m^3: 1.62±0.10 86 mg/m^3: 7.3±0.20 172 mg/m^3: 16.08±0.88	*Developmental toxicity*: Decrease in habituation (novel exploration object test; overall p<0.001; 86 mg/m^3: p<0.05; 172 mg/m^3: p<0.01) and working memory. No effect on spontaneous motor activity, pup weight gain and post-natal mortality. *Reproductive toxicity*: No effect on dam weight gain, number of dams giving birth, pregnancy length and litter size at birth.	No information on maternal toxicity.
De Salvia et al. (1995)[53]	Wistar rats N= 6 pups/litter (males only)	0, 86, 172 mg/m^3 Continuously throughout gestation, after birth pups assigned to non-exposed mothers. No gross necropsy.	N.R.	172 mg/m^3: ~15 (pilot studies)	*Developmental toxicity*: No effect on pup weight gain and postnatal mortality. 172 mg/m^3: impaired acquisition of a two-way active avoidance task in 3-month (p<0.001) and 18-month (p<0.01) rats and an impaired reacquisition in 18-month-old rats (p<0.02). No effects on intertrial activity and escape response latencies. *Reproductive toxicity*: No effect on dam weight gain, number of dams giving birth, pregnancy length and litter size at birth.	No information on N pups, maternal toxicity and concentration-dependent statistics. Just male pups.

Reference	Species	Exposure	Maternal Toxicity	Mean maternal blood COHb (%)	Reproduction toxic effects	Remarks
Storm et al. (1985)[54]	Long Evans rats N=6-15 litters/ group; N=8 pups/litter, males and females	0, 86, 172, 344 mg/m^3 Continuously throughout gestation. No gross necropsy.	No effect on weight gain	0 mg/m^3: 2.5±0.7 86 mg/m^3: 11.5±1.6 172 mg/m^3: 18.5±2.3 344 mg/m^3: 26.8±5.4	*Developmental toxicity*: 344 mg/m^3: decrease in birth weight (p<0.01) Significant differences in neurotransmitter concentrations. PD21: No effect on body weight, pons/medulla, neocortex and hippocampus weight. Dose-dependent decrease in cerebellar weight (p<0.001). 172 mg/m^3: decrease in cerebellum weight (p<0.05) 344 mg/m^3: decrease in cerebellum weight (p<0.05) PD42: No effect on body weight, pons/medulla, neocortex and hippocampus weight. Dose-dependent linear trend of decreasing cerebellar weight (p<0.01). 344 mg/m^3: decrease in cerebellum weight (p<0.05)	Limited information on maternal toxicity.
Storm et al. (1986)[55]	Long Evans rats N=7-9 litters/ group; N=10-12 pups/ group	0, 86, 172, 344 mg/m^3 Continuously throughout gestation + PDs 1-10. No gross necropsy.		0 mg/m^3: 2.5 86 mg/m^3: 11.5 172 mg/m^3: 18.5 344 mg/m^3: 26.8	*Developmental toxicity*: 172 and 344 mg/m^3: Significant effects on cerebellar GABA contents. PD10: dose-dependent decrease in body weight and cerebellar weight (p<0.01) 86 mg/m^3: decrease in body weight (p<0.05) 172 and 344 mg/m^3: decrease in body weight (p<0.05) and cerebellar weight (p<0.01) PD21: dose-dependent decrease in cerebellar weight (p<0.01), no effects on body weight. 86 mg/m^3: decrease in cerebellar weight (p<0.01) 344 mg/m^3: decrease in cerebellar weight (p<0.01) and number of fissures in cerebella (p<0.05)	No information on maternal toxicity. If not stated, no effect on cerebellar weight. Seem to be same rats as Storm and Fechter, 1985 (based on COHb levels).

Reference	Species	Exposure	Maternal Toxicity	Mean maternal blood COHb (%)	Reproduction toxic effects	Remarks
Penney et al. (1983)[56]	Caesarean originated barrier sustained (COBS) rats N=24 dams/ experiment; 7-14 pups/ group	0, 180, 190, 229 mg/m^3 Continuously throughout GDs 4-22	N.R.	Mothers: 229 mg/m^3: 24.9 Newborns: 0 mg/m^3: 0.5-0.8 180 mg/m^3: 24.9 190 mg/m^3: 21.8 229 mg/m^3: 31.0-33.5	*Reproductive toxicity*: No effect on number of foetuses/dam or pups/litter. *Developmental toxicity*: Killed at birth: 180 mg/m^3: Increase in corpuscular haemoglobin (p<0.05), corpuscular haemoglobin volume (p<0.05), heart/body weight ratio (p<0.001), placental weight (p<0.001) and placental/body weight ratio (p<0.001). Decrease in body weight (p<0.001). 190 mg/m^3: Increase in heart weight (p<0.01), heart/body weight ratio (p<0.001), placental weight (p<0.05), placental/body weight ratio (p<0.001). Decrease in haemoglobin concentration (p<0.01), haematocrit ratio (p<0.05), red blood cell count (p<0.001), body weight (p<0.001). 229 mg/m^3: Increase in corpuscular haemoglobin (p<0.01), corpuscular haemoglobin concentration (p<0.05), heart weight (p<0.001), heart/body weight ratio (p<0.001), placental weight (p<0.01), placental/body weight ratio (p<0.001). Decrease in red blood cell count (p<0.05), body weight (p<0.05). Killed few hours before birth: 180 mg/m^3: Increase in corpuscular haemoglobin (p<0.01).	Separate experiments for the different concentrations, no concentration-response statistics. No information on maternal toxicity, sex. Not clear which type of rats are used. If not stated, no effect on haemoglobin, haematocrit, heart weight, red blood cell count.
Astrup et al. (1972)[57]	Rabbits N=81 N=14 dams (males and females)	0, 103, 206 mg/m^3 Continuously throughout gestation. No gross necropsy.	N.R.	103 mg/m^3: 8-9 206 mg/m^3: 16-18	*Developmental toxicity*: 103 mg/m^3: decreased birth weights by 11% and increased neonatal mortality. (9.9% vs 4.5% in control). 206 mg/m^3: decreased birth weights by 20% and increased neonatal mortality (35% vs 1% in control).	Two separate experiments for two exposures, differences in rabbits between experiments (age, previous pregnancy, control rats not in exposure chambers). No information on maternal toxicity and statistics.

Reference	Species	Exposure	Maternal Toxicity	Mean maternal blood COHb (%)	Reproduction toxic effects	Remarks
Singh (1984)[58]	CD-1 mice, N=14 litters/ group, males and females	0, 74, 143 mg/m^3 Continuously throughout GDs 7-18.	No apparent signs of maternal toxicity.	N.R.	*Developmental toxicity*: No effect on mean number of live pups born/litter and birth weight. 74 mg/m^3: decrease in aerial righting score on PD14 (p<0.05). No effect on righting reflex and negative geotaxis. 143 mg/m^3: increase in time required for righting reflex on PD1 (p<0.05) and for negative geotaxis on PD10 (p<0.05), decrease in aerial righting score on PD14 (p<0.05)	No information on N pups or dose-response statistics.
Singh and Scott (1984)[59]	CD-1 mice, N=17 litters/ group, males and females	0, 74, 143, 286, 572 mg/m^3 Continuously throughout GDs 7-18, after which animals were sacrificed and foetuses examined. Gross malformations of uterine horns examined	No apparent signs of maternal toxicity	N.R.	*Reproductive toxicity*: 572 mg/m^3: increase in no. of dead or resorbed foetuses (p<0.01 vs control and other dose groups) *Developmental toxicity*: 143 mg/m^3: decrease in foetal body weight (p<0.01) 286 mg/m^3: decrease in foetal body weight (p<0.01) 572 mg/m^3: increase in foetal mortality and decrease in foetal body weight (p<0.01 vs control). Small number of skeletal anomalies (lack of ossification) in foetuses of all groups, but not dose dependent.	No information on N pups. If not stated, no effect on foetal mortality, no. of dead or resorbed foetuses and foetal body weight.
Loder et al. (2000)[60]	DBA/1J mice N=214 in total; 24-70 pups/ group	0, 229, 458, 687 mg/m^3 7-hour/day on GD 8.5, 9.5 or 10.5 (concentration-response at GD 9.5). No gross necropsy.	N.R.	N.R.	*Developmental toxicity*: Concentration-dependent increase in the number of congenital spinal deformities (p<0.05), most sensitive time of exposure was GD 9.5.	No information on sex, N litters, maternal toxicity. Extensive statistics.

Reference	Species	Exposure	Maternal Toxicity	Mean maternal blood COHb (%)	Reproduction toxic effects	Remarks
Kwak et al. (1986)[61]	ICR mice N=20-64/ exposure group	1,718 mg/m^3, 2,864 mg/m^3 and 4,010 mg/m^3 on GDs 5, 11 and 16 for 10 minutes (acute) 572 mg/m^3 on GDs 0-6, 7-13 and 14-20 for 1 hour (chronic).	Concentration-dependent increase in micronuclei in maternal bone marrow (acute [p<0.01] and chronic [p<0.05]) and sister chromatid exchange in maternal cells (acute [p<0.01] and chronic [p<0.05])	N.R.	*Developmental toxicity*: Concentration-dependent increase in micronuclei in foetal blood (acute [p<0.01] and chronic [p<0.05]) and in sister chromatid exchange in foetal cells (acute [p<0.01] and chronic [p<0.05])	Some questions about validity of the report, like timing between exposure and cell harvesting. Very brief information, no information on sex, N pups.

Reference	Species	Exposure	Maternal Toxicity	Mean maternal blood COHb (%)	Reproduction toxic effects	Remarks
Dominick and Carson (1983)[62]	Miniature and domestic swines, N=20 sows	0, 172, 229, 286, 344, 401, 458 mg/m^3 48-96h between GDs 108 and 110 Necropsy of all pigs	N.R.	0 mg/m^3: 1.4 ± 0.3 172 mg/m^3: 14.7±0.8 229 mg/m^3: 20.4±3.1 286 mg/m^3: 24.2±1.2 344 mg/m^3: 29.3±1.9 401 mg/m^3: 30.4±1.2 458 mg/m^3: 34.2 (n=1)	*Developmental toxicity*: A significant correlation was found between CO exposure level and maternal COHb (p<0.01), CO exposure level and stillbirth rate (p<0.05) and maternal COHb and stillbirth rate (p<0.05). Maternal/Piglets COHb concentrations (%): 286 mg/m^3 : 22.5/25.1±1.3 344 mg/m^3: 32.0/37.1±2.8 Necropsy showed multiple abnormalities: At unclear dosage: multiple foci of mononuclear cells in the liver (hyperchromatic nuclei with prominent nucleoli, focally high mitotic indices and high nucleus/cytoplasm ratio). Clusters of cells were considered erythrocyte precursors. No significant relationship between number of embryonic mean corpuscular haemoglobin and level or duration of maternal exposure. ≥286 mg/m^3: diffuse discoloration of subcutaneous tissue, muscle, and abdominal and thoracic viscera in all stillborn pigs ≥344 mg/m^3: majority of stillborn pigs had moderate autolysis 229 mg/m^3 for 72 hours from 1 sow: 1 stillborn pig had focal cortical malacia of hemispheral white and grey matter, infiltrated by numerous gitter cells and reactive glial cells. 344 mg/m^3 for 96 hours from 1 sow: 6 weak, depressed pigs showed multifocal haemorrhages and vacuolation of the neuropile throughout cortical white matter and brain stem. 1 pig had pale, poorly demarcated focus of haemorrhage had oedema with swollen oligocytes and astrocytes in the cerebellum 401 mg/m^3 for 48 hours from 1 sow: 2 weak, depressed and incoordinated pigs, 4 stillborn. Focal necrosis with foamy gitter cells of the left hemispheral white matter in live pigs. Peripheral to necrotic focus, extensive glial-vascular proliferation, haemorrhage and gitter cell infiltration.	No information on maternal toxicity, N pups, sex.

Reference	Species	Exposure	Maternal Toxicity	Mean maternal blood COHb (%)	Reproduction toxic effects	Remarks
Morris et al. (1985)[63]	Crossbred gilts (pigs) N=4-6 litters; 123 piglets in total; 13-24 piglets/ group (males and females)	0, 229, 286 mg/m^3 Continuously from GD 109. Histopathological examination of piglets	N.R.	In gilts 24h after exposure began: 0 mg/m^3: 0±0 229 mg/m^3: 13.6±0.46 286 mg/m^3: 17.1±0.86 In piglets at birth: 0 mg/m^3: 0±0 229 mg/m^3: 19.8±1.1 286 mg/m^3: 22.4±0.8	*Developmental toxicity*: No effect on stillbirth rate for both concentrations; no histopathological abnormalities. 229 mg/m^3: decrease in total blood haemoglobin (p<0.05) 2h and 24h after birth and haematocrit 24h after birth (p<0.05). comprised performance in behaviour test: open field test 48h after birth (p<0.06). 286 mg/m^3: decrease in total blood haemoglobin (p<0.05) at birth, 2h and 24h after birth, oxyhaemoglobin (p<0.05) at birth and haematocrit (p<0.05) at birth and 24h after birth. Comprised performance in behaviour tests: negative geotaxis test 24h after birth (p<0.05) and open field test 24h (p<0.05) and 48h after birth (p<0.06).	No information on maternal toxicity, no concentration-response statistics.
Trentini et al. (2016)[45]	CD mice N=4-7 litters/8-12 pups/group	175 mg/m^3 87 mg/m^3 (75 ppm) did not reach sufficiently high COHb levels and 583 mg/m^3 (500 ppm) induced clear maternal toxicity in a dose range finding study	N.R.	N.R.	*Developmental toxicity*: Thinning of cerebral wall at post-natal day 4 (p<0.05). altered distribution of early (E12) and late (E16) embryonic neocortical cells (p<0.05) Functional impairment in behavioral tests after birth, specifically the pre-pulse inhibition test and the hot plate test (p<0.05)	Only one dose tested

PD = postnatal day, GD = gestational day, N.R.=not reported

B search strategies

B1 Cardiovascular studies

Pubmed

1. myocardial infarct*.mp.
2. heart attack*.mp.
3. exp Acute Coronary Syndrome/
4. acute coronary syndrome*.mp.
5. exp Myocardial Infarction/
6. exp heart infarction/
7. (“cardiac infarct*” or “cardial infarct*” or (“coronary arter*” adj3 occlusion) or (heart adj2 infarct*) or “myocardium infarct*” or “premonitory infarction sign” or “subendocardial infarct*” or “myocardial stunning” or “cardiogenic shock”).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
8. or/1-7
9. exp air pollution/
10. ((air or atmosphere or atmospheric) adj (pollution* or polluted or pollutant* or contamination or contaminated)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
11. exp Carbon Monoxide/
12. exp Carbon Monoxide Poisoning/
13. (“CO” adj3 (pollut* or contamin* or particulate or poisoning)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
14. (“carbon monoxide” or “carbonmonoxide”).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
15. 9 or 10 or 11 or 12 or 13 or 14
16. 8 and 15
17. limit 16 to human
18. limit 17 to dc= 2018/09/30-2022/10/31

After screening titles and abstracts by using PECOS criteria (see below), 6 articles remained.

PECOS	Inclusion criteria	Exclusion criteria
Population	• General adult human population (age >18 years), developed and developing areas, both urban and rural. No geographical restrictions. • Exposure to the pollutant of interest via inhalation through ambient air predominantly.	Exposure to the pollutant of interest in occupational settings or as a result of indoor exposure exclusively
Exposure	Short-term exposure (in the order of hours to 7 days) to ambient air CO from any source expressed in a concentration unit (mg/m3).	No exclusion criteria applied based on adjustment for co-pollutants.
Comparator	Increase in concentration unit of exposure to the air pollutant of interest in the same or in a similar population.	
Outcome	Health outcomes selected for short-term exposure include emergency department visits/ hospital admissions and mortality due to myocardial infarction (ICD-9 code: 410 or ICD-10 codes: I21-I22)	

Study	• Human epidemiological studies including:
	  • time series
	  • case-crossover
	  • systematic reviews of the above studies to scan for references (or as a basis for an update)
	• Published (or accepted for publication i.e. in press) studies in peer reviewed indexed journals in any language (abstract in English language). If suitable articles are identified published in languages not known by the SR team, further assistance will be sought after (members of the GDG or external review team from different regions, colleagues, researcher networks, etc)
		• Qualitative studies
		• Studies without individual level data i.e. fully ecological covariates
		• Reviews and methodological papers
		• Non-human studies (in vivo, in vitro, other)
		• Studies with complete geographical and temporal over-lap during meta-analysis (to avoid inclusion of patients across multiple studies)

B2 Developmental studies

A general PubMed literature search was conducted using the terms 'reproductive toxicity' AND 'carbon monoxide', from 2012 (publication year of the reports of the NEG and the ATSDR) until March 2023. 91 hits were retrieved. After selection using the following exclusion criteria:

- Review or case study;
- Indirect effects studied, e.g. involving other substances or pharmaceuticals;
- Effects of air pollution;
- Clinical studies on poisoning;
- Non-representative occupations with high acute (co-)exposures, such as firemen;
- Lack of quantitative exposure data;
- Effects studied not considered adverse;
- Absence of effects;
- Study designs not involving humans or (accepted) animal models;

Only 1 article remained.

B3 Neurological studies

Similar search terms were used as for cardiac effects, but cardiac related terms were replaced by: Central nervous system[MeSH] OR central nervous system[tiab] OR cerebrospinal Axis [Title/Abstract]

- Only human species
- This resulted in **763 hits** (no time restriction)
- Selection article types meta-analysis and systematic review resulted in **5 hits** that were not useful
- Applying a time restriction – starting search from 01-01-2012 (as NEG and ATSDR date from this year) resulted in **244 hits**
- Needs further selection by sifting through titles/abstracts to see whether concentrations were given

Selection criteria:

NOT

Case reports

Review

In vitro

Animal studies

Cigarette smoke/ nicotine

Infants

No exposure mentioned

Methodological papers

YES

Concentration

Occupation

Hospital/emergency visits

Mortality or death

B4 Occupational studies

A general PubMed literature search was conducted using the terms ‘occupational exposure’ AND ‘carbon monoxide’, from 2012 (publication year of the reports of the NEG and the ATSDR) until March 2023. 191 hits were retrieved. After selection using the following exclusion criteria:

- Review or case study;
- Indirect effects studied, e.g. involving other substances or pharmaceuticals;
- Effects of air pollution;
- Clinical studies on poisoning;
- Non-representative occupations with high acute (co-)exposures, such as firemen;
- Lack of quantitative exposure data;
- Effects studied not considered adverse;
- Study designs not involving humans or (accepted) animal models;

No relevant articles remained.

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Fisheries, Food Security and Nature. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity.
The reports are available to the public.

This publication can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Carbon monoxide.
The Hague: Health Council of the Netherlands, 2024; publication no. 2024/12.