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Carbon monoxide criteria

With reference to effects on the heart, central nervous system and fetus

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1. Background

Reviews of scientific data on the health effects of exposure to polluted air have been presented on many occasions and standards and recommendations have been put forth in several countries. Air pollutants of various kinds have been the subjects of a series of criteria documents published in recent years by the World Health Organization (WHO), which include reviews of the effects of sulfur dioxide and suspended particulates (1979), oxides of nitrogen (1977) and carbon monoxide (1979).

In Sweden the responsibility of proposing standards for environmental air pollution lies with the Environment Protection Board (EPB). The EPB has initiated work on criteria documents in which information is evaluated with particular reference to specific conditions in Sweden. Examples of such conditions are the high frequency of inversions at many geographical locations in the country, the long period of the year when heating is required — from late September to early May — and local characteristics of industrial and motor vehicle exhaust.

The first document on air quality criteria was undertaken by an expert group at the Department of Environmental Hygiene at the EPB and dealt with sulfur dioxide and suspended particles (Camner *et al.*, 1973). In the presentation of its evaluation of epidemiological and experimental data on the health effects of these agents, the group concluded that the recommendations for air quality with reference to sulfur dioxide and smoke enumerated by the WHO should be used as tools in the planning of air pollution control in Sweden. In addition, it was recommended that values for sulfur dioxide and particulates should not exceed the values given as annual means for any significant length of time (i.e., a few months). It was not considered medically justifiable that the very low exposure present in Sweden during the summer months would allow for high exposure during winter months, even if the annual mean remained below the recommended level.

Subsequent to the criteria document of sulfur dioxide and particulates, the EPB has decided to produce a document on carbon monoxide. The task of producing this criteria document was given to the Department of Environmental Hygiene at the University of Gothenburg.

A first draft of the document was discussed during a seminar organized by the EPB on 4 September 1979. A second version of the document was then circulated for further comments in February 1980. Valuable comments were received from Lars Friberg, Magnus Piscator, Carl-Johan Göthe, Maths Berlin and Poul Astrup.

2. Scope of the work

There exists a number of criteria documents on carbon monoxide. One of the most recent of these was published by the National Academy of Sciences in the United States (1977). WHO has issued a report on carbon monoxide (1979) in its series of environmental criteria documents. In the present document, basic information on the chemical properties of CO, its presence in the environment and pharma-

cological effects has been collected from the above mentioned criteria documents.

In view of the abundance of reports and publications on the general toxicity of carbon monoxide and the effects encountered at high exposure levels, the emphasis in this report has been directed toward reviewing three major effects charged to be of primary significance in the evaluation of environmental standards at low exposure levels. These are cardiovascular effects, effects on the central nervous system and effects on the fetus. Research reports on these effects have been analyzed and conclusions are presented as to the relevance of this information for establishing carbon monoxide exposure criteria. Finally, evaluations and conclusions are presented, together with recommendations for further work.

The evaluation as presented in this document is based solely on health effects. The report is limited to an evaluation of *criteria,* defined as the tests which permit the determination of the nature and magnitude of the effects of carbon monoxide on man and his environment. *Guides* to air quality are those sets of concentrations and exposure times associated with the specific effects of varying concentrations of the pollutant on man. No proposals are given for *standards;* these must be developed later, with due attention paid to technical, economic and political considerations.

3. Environmental carbon monoxide

3.1 Properties of Carbon Monoxide

Carbon monoxide (CO) is a colorless, odorless and tasteless gas which is slightly lighter than air. Under normal conditions, it is stable and chemically inert. CO burns in air or oxygen. The physical properties of CO are reported in Table 3-1.

In all cases in which data in the original reports described here are given in parts per million (ppm), they can be changed into mg/m^3 by using the relationships given in Table 3-1.

3.2 Sources and Incidence of Carbon Monoxide

Methane oxidation in the atmosphere has been suggested as a source of natural CO but the major part of atmospheric CO derives from human activities.

Carbon monoxide is produced by the incomplete combustion of motor vehicle fuel occurring in petrol engines and to a much smaller extent in diesel engines. Heating and industrial processing are also important sources of CO.

Table 3-1. Physical properties of carbon monoxide (WHO, 1979).

Melting point	—250° C
Boiling point	—192° C
Density, at 0° C, 1 atmos	1.250 g/liter
Density, at 25° C, 1 atmos	1.145 g/liter
Specific gravity relative to air	0.967
Solubility in water, at 0° C	3.54 ml/100 ml (44.3 ppm mass)
Solubility in water, at 25° C	2.14 ml/100 ml (26.8 ppm mass)
Explosive limits in air	12.5 to 74.2 %
Conversion factors:	
at 0° C, 1 atmos	1 mg/m^3 = 0.800 ppm vol
	1 ppm vol = 1.250 mg/m^3
at 25° C, 1 atmos	1 mg/m^3 = 0.873 ppm vol
	1 ppm vol = 1.145 mg/m^3

Table 3-2. Ranges of carbon monoxide concentrations in air from various sources.

Source	CO (ppm)
fresh sea air	0.06—0.5
urban air	1—30
street corner	5—50
heavily trafficked interchange	50—100
automobile exhaust	30,000—80,000
cigarette smoke	20,000—60,000
cigarette smoke-filled room	2—16

The emission of CO is highest around densely populated areas. Measurements of ambient CO levels have been performed in several cities and concentrations are observed to be related to the vehicle traffic pattern. Figure 3-1 is an illustration of levels of carbon monoxide emission in automobile exhaust as a function of vehicle speed.

The most significant exposure to carbon monoxide occurs in urban settings, in industry, at home to CO produced by gas heating equipment and in cars to CO escaping from deficient exhaust systems or from exhaust systems of surrounding vehicles.

Estimations of CO concentrations under conditions with a high degree of pollution with cigarette smoke show that CO concentrations of up to 16 ppm may be attained (Corn, 1974).

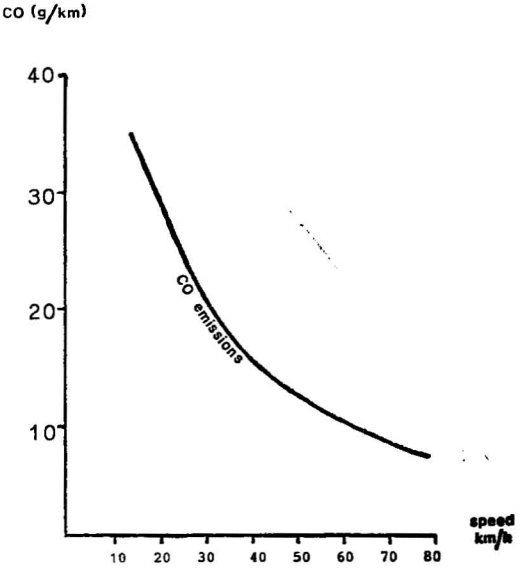


Figure 3-1. CO emission factor as a function of speed (A. M. Voorhees & Associates, Inc., 1976).

3.3 Environmental concentrations in Sweden

Levels of carbon monoxide in the ambient air of a number of Swedish cities have been measured on several occasions and data are continuously being obtained from different air monitoring programs. The following will serve as an illustration of the many programs reported or underway.

A report published in 1977 by the EPB (Statens Naturvårdsverk, PM 729, 1977) gives the results of an investigation of vehicle emissions carried out between 1969 and 1975 in 28 Swedish cities. The study concentrated particularly upon identifying levels of CO in street situations in order to determine peak CO levels and mean 8-hour daytime CO levels. Table 3-3 is an illustration of measurements made at various locations in Stockholm and Gothenburg. Carbon monoxide levels observed in Malmö are shown in Table 3-4 and a further demonstration of CO pollution levels in Stockholm is found in Table 3-5.

Other descriptions of carbon monoxide pollution are given in an EPB report on the development of a model for describing and predicting air pollution levels from auto emissions (Statens Naturvårdsverk, PM 891, 1977). Several factors were taken into consideration in setting up the model, among them auto emissions at different speeds and situations, traffic flow, traffic patterns, traffic volume and meteorological conditions. Some measurement data from Stockholm are illustrated in Figures 3-2 and 3-3 to outline the existing exposure situation.

Measurements have been made of concentrations of air pollutants, among them carbon monoxide, in certain areas of Stockholm by the city's Environmental and Health Care Administration (Miljö- och Hälsovårdsförvaltningen). Measurements were made twice during 1976 and once in 1977. Wind velocity and direction were measured, in addition to concentrations of a number of air pollutants.

The general purposes of the measurements were to identify the present pollution situation and to judge what the pollution situation would be if alterations were made in the traffic patterns in certain areas of the city. Air quality

Table 3-3. Carbon monoxide measurements made in Stockholm and Gothenburg.*

place year	ht. of surrounding buildings	width of street	street description	ht. of measuring apparatus	no. vehicles/day	no. measurement days	max ½ h (mean)	max 8 h (mean)	no. times CO exceeded 9 ppm in 8 h period
Stockholm: Norra Stationsg. 1973	20 m	12 m	buildings on both sides	3 m	46,000	11	19 ppm	10 ppm	3
Gothenburg: Västra Hamng. 1973	12 m	16 m	houses on both sides; park between	2.5 m	18,000	7	12 ppm	8 ppm	0
Gothenburg: Parkgatan 1973	6 m	10 m	buildings on one side	2.5 m	19,000	7	32 ppm	15 ppm	2
Gothenburg: Övre Husarg. 1973	20 m	12 m	buildings at irregular intervals, both sides	2.5 m	25,000	7	25 ppm	12 ppm	1

* From Statens Naturvårdsverk PM 729, 1977.

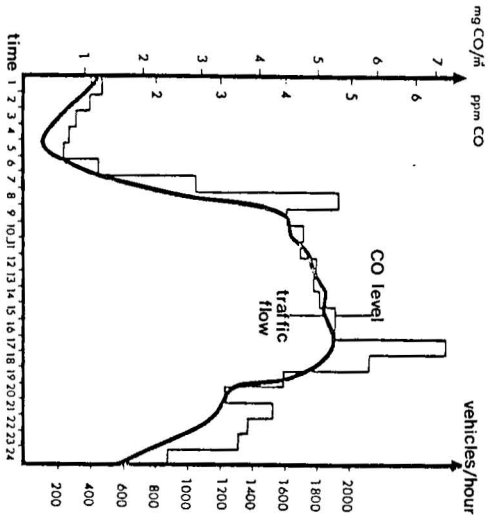


Figure 3-2. Mean carbon monoxide levels at Sveavägen's (Stockholm) east and west sides on Fridays in April, May and September, 1976. Shown in relation to traffic flow (Statens Naturvårdsverk, PM 729, 1977).

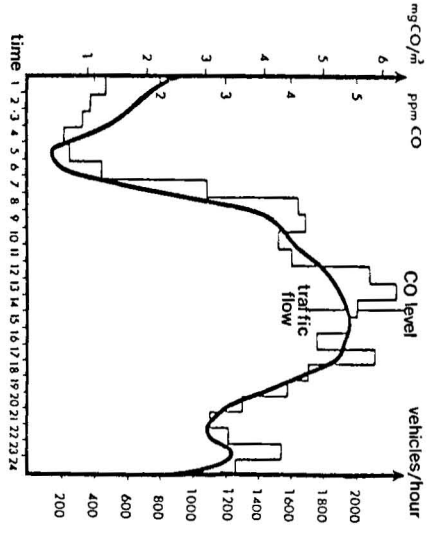


Figure 3-3. Mean carbon monoxide values on both sides of Sveavägen (Stockholm) during April, May and September, 1976, Mondays through Thursdays. Shown in relation to traffic flow (Statens Naturvårdsverk, PM 729, 1977).

measurements were carried out in February, 1979, at Arsenalsgatan, Stallgatan, Blasieholmskajen and in front of the National museum (Miljö- och Hälsovårdsförvaltningen, Stockholms Kommun, Report 1976-03-12). Traffic is light at Blasieholmskajen and in front of the museum — about 4,000 and 2,000 vehicles/day, respectively — and considerably heavier along Arsenalsgatan and Stallgatan (roughly 25,000 vehicles/day).

Table 3-4. Carbon monoxide measurements made at different locations in Malmö.*

place year	ht. of surrounding buildings	width of street	street description	no. vehicles/ day	maximum ½ h mean value
Sallerupsvägen 1971	12 m	26 m	houses on both sides of street	26,000	11 ppm
Nobelvägen 147 1972	12 m	33 m	houses on both sides of street	32,000	13 ppm
Amiralsgatan 1972	12 m	30 m	relatively open area	30,000	19 ppm
Nobelvägen 1973	6 m	33 m	relatively open area	32,000	8.5 ppm
Trelleborgsvägen 1973	6 m	26 m	relatively open area	16,000	7 ppm
Maiedalsvägen 1973	6 m	22 m	relatively open area	12,000	3 ppm
Nobelvägen 56 1973/1974	12 m	33 m	houses at irregular intervals on both sides of street	41,000	30 ppm

* From Statens Naturvårdsverk PM 729, 1977.

Table 3-5. Air pollution measurements made at Hantverkargatan, Hornsgatan, Norr Mälarstrand and Sveavägen in Stockholm, February—August, 1977.*

place month	CO values 1-hr max	CO values 8-hr max	traffic density	street description
Hantverkargatan			10,000/d	16 m wide street; 18 m high buildings, both sides of street
February	18 ppm	9 ppm		
May	9 ppm	5 ppm		
Hornsgatan			40,000/d	23 m wide street; 22 m high buildings, both sides of street
March	19 ppm	13 ppm		
June	12 ppm	10 ppm		
Norr Mälarstrand			30,000/d	buildings at irregular intervals on one side of street
March/April	11 ppm	7 ppm		
June/July	3 ppm	2 ppm		
Sveavägen			30,000/d	33 m wide street; 23 m high buildings, both sides of street
April/May	9 ppm	8 ppm		
July/August	9 ppm	8 ppm		

* From Miljö- och Hälsovårdsförvaltningen, Stockholms Kommun, Report 1978-02-06.

The area around the museum is open and winds were favourable during the measurement period. Peak concentrations of CO of approximately 4 ppm occurred at about 0900 and 1800. CO levels at Blasieholmskajen and Stallgatan were similar.

Concentrations of carbon monoxide were significantly higher at Arsenalsgatan. This is a narrow street with rather tall buildings on both sides and heavy weekday traffic. It is considered to be one of the most heavily polluted streets in the city. The highest 24-hour mean CO concentration measured was 15 ppm and the highest 8-hour mean value was 20 ppm.

Measurements of CO were made along Arsenalsgatan by the Administration's air quality control bus between November 25 and December 12, 1976 (Report 1977-02-04).

It was seen that the 9 ppm CO concentration recommended by the WHO as the highest mean value permissable for an 8-hour period was exceeded along Arsenalsgatan nearly every weekday and occasionally even on Saturdays. The highest 8-hour mean concentration observed during this measurement period was 24 ppm CO — that is, 2.7 times higher than the WHO's recommended maximum.

4. Carbon monoxide in humans

4.1 Pharmacological Effects of Carbon Monoxide

Carbon monoxide levels in the body reflect endogenous production of the gas as well as exogenous CO, which reaches the body via inhalation. Endogenous CO is formed by the breakdown or catabolism of hemoglobin and other heme containing pigments. Sjöstrand (1949) demonstrated that carbon monoxide is released when protoporphyrin degrades to bilirubin.

CO is rapidly absorbed through the lungs and the rate of absorption is directly related to the alveolar ventilation. About 60 % of the inhaled CO is absorbed in the blood. Above minute volumes of 20 liters, the uptake is 10—15 % lower than expected from true proportionality (Forbes 1970).

In the blood, CO binds reversibly with hemoglobin (Hb) — forming carboxyhemoglobin (COHb) — and with certain heme proteins. A strong coordination bond is formed between CO and the iron atom in protoheme. The latter molecule is a ferrous ion complex of a protoporphyrine which, when combined with the protein globin, constitutes hemoglobin.

The principal factors related to the amount of CO present in the body after inhalation exposure are:

— concentration of CO inspired
— endogenous CO production
— amount of exercise
— body size
— lung health, including diffusion capacity
— barometric pressure

Coburn *et al.* (1965) developed a mathematical model for calculating the formation of COHb. Experimental data obtained by Peterson and Stewart (1970) largely

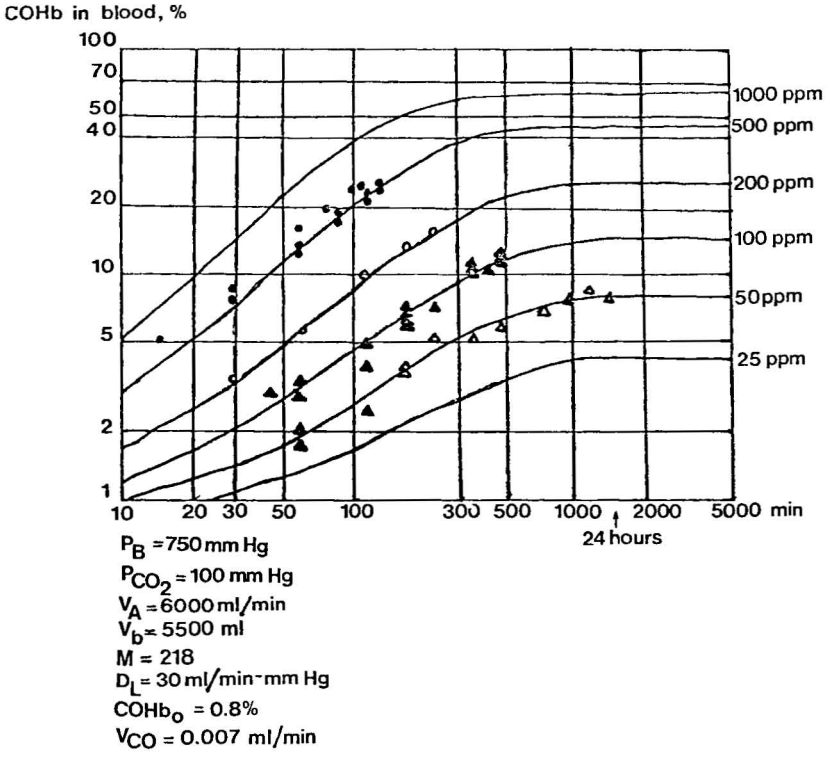


Figure 4-1. Absorption of carbon monoxide with relation to exposure duration and sampled carbon monoxide in resting individuals. (figure modified from U.S. Environmental Protection Agency, Air Quality Criteria for Carbon Monoxide, EPA-600/8-79-022).

confirm the accuracy of the model. As Coburn indicated, the equation cannot be used to calculate COHb levels above about 15 %. The model presupposes that the oxyhemoglobin value is constant, which is not the case at higher levels of CO in blood. In a later analysis of the model, Peterson and Stewart (1975) underline this by stating that the equation has no uniform solution, but that »trial and error» must be used for the calculation. Further details of the application of the model are given in Appendix 1.

Table 4-1 illustrates expected COHb values in the blood of resting individuals at different exposure durations and ambient carbon monoxide concentrations.

As the affinity of Hb for CO is approximately 200 to 250 times its affinity for oxygen, exposure to even lower concentrations of carbon monoxide can result in a clinically significant reduction of the oxygen-carrying capacity of the blood. Furthermore, the presence of COHb in the blood shifts the oxyhemoglobin dissociation curve to the left, so that tissue oxygen tensions must fall to much lower levels in order for the oxyhemoglobin to release its oxygen. Following CO exposure, the resultant decrease in the oxygen-carrying capacity of the blood, together with the impaired release of oxygen to the tissues, gives rise to a relatively greater degree of tissue oxygen deficiency than would arise from an equivalent reduction in ambient pO_2 (oxygen tension), or an equivalent reduction in Hb secondary to anemia (see figure 4-2).

Table 4-1. Examples of expected COHb values after different exposure times and at different ambient carbon monoxide levels. See Appendix 1 for complete data.

exposure time	35 ppm		5 ppm	
	rest	heavy work	rest	heavy work
30 min	0.9	1.8	0.5	0.6
60 min	1.3	2.7	0.6	0.7
6 hours	3.6	5.1	0.8	0.8
24 hours	5.3	5.3	1.0	1.0

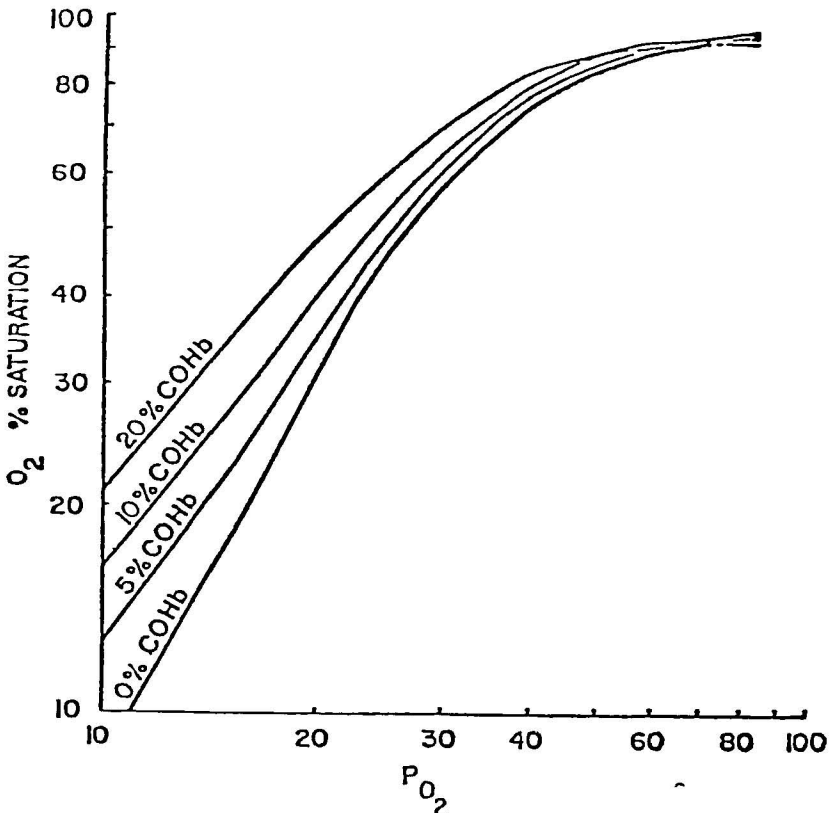


Figure 4-2. Blood oxygen dissociation curves at pH 7.4 at various COHb values (U.S. Environmental Protection Agency, Air Quality Criteria for Carbon Monoxide, EPA-600/8-79-022).

Hb and myoglobin are structurally related and react with CO in a similar manner. Identical CO exposures produce different degrees of saturation of myoglobin depending upon the partial pressures of O_2 in the tissue. This has practical consequences for the myocardial tissue with its high oxygen consumption.

Man has the ability to compensate in part for the reduction in the oxygen-carrying capacity of the blood resulting from chronic exposure to CO by increasing his red blood cell mass.

CO is eliminated nearly completely by the lungs. Less than 1 % of the gas is oxidized within the body to CO_2. The biological half-life of the gas in healthy, sedentary adults at sea level is 4—5 hours. 100 % oxygen administered by face mask reduces the biological half-life to approximately 80 minutes (Stender *et al.*, 1977). In the hyperbaric setting, the administration of 100 % oxygen at 3 ATA reduces the biological half-life of the gas to 23.5 minutes (Stewart 1975).

The excretion of CO becomes slower with time and the lower the initial level of COHb, the slower the rate of disappearance (U.S. EPA-600/8-79-022).

As the major effect of the presence of CO in the body is related to the capacity for transporting oxygen to the tissues, all organs for which a continuous high oxygen supply is necessary to maintain normal function become critical organs. The three most important of these are the heart, the central nervous system and the fetus.

4.2 Levels in the Population

Several investigations have been performed concerning the CO levels present in various populations. This has been done either by measuring the COHb level in the blood or by taking measurements of CO in the expired air.

Kahn *et al.* (1974) measured COHb levels in 16,649 blood samples from blood donors in the St. Louis metropolitan population. The mean COHb level was 2.3 %. Of all samples, 70.1 % contained less than 3 % and 1.2 % contained 10 % COHb or more. COHb values in smokers were 5 times higher than for non-smokers (4.58 versus 0.85 %). There was also a difference between inhaling and non-inhaling smokers (4.7 versus 2.2 %).

The COHb levels were related to the distance travelled by car prior to giving the blood sample, and an increase in COHb level was found related to travel distance. This increase was small, however, compared to the smoker/non-smoker differences.

The correlation between ambient CO levels and COHb values was negative for average 24 and 12 hour values between 0600 and 1800 hours. Average hourly values of ambient CO at 2 hours previous to the blood sampling correlated with the COHb levels obtained at the time of the sampling. The winter COHb values in non-smokers were higher than spring, summer and autumn values, although the ambient air CO levels were highest during the autumn.

In another study of COHb levels in blood samples from the populations of Chicago, Milwaukee, New York and Los Angeles (Stewart *et al.*, 1973), between 26 and 76 % of the samples from the different cities had COHb levels in excess of 1.5 %. Samples from persons from urban areas with high vehicle density consistently had higher COHb levels than those from low density areas. It was also observed that the COHb levels increased in connection with a weather inversion over the New York area.

A U.S. national survey was performed 1969—1972 by Stewart *et al.* (1974) to determine the range of COHb levels in the population. Venous blood samples were obtained from 29,000 blood donors in urban, suburban and rural communities.

45 % of all non-smoking blood donors had levels higher than 1.5 %. Tobacco smoking and geographical location, as well as occupation and meteorological conditions, were associated with COHb levels.

Non-smoking donors living in urban areas consistently had higher COHb values than donors in rural areas. The difference in COHb saturation between non-smokers and smokers was relatively constant when rural and urban areas were compared, implying that the environment does further increase the total CO burden of smokers. This is in contrast to a previous theory that CO concentrations in ambient air do not further affect the levels

of COHb which smokers have acquired through smoking. The analytical findings suggest that smokers with high COHb levels had a higher hemoglobin concentration — an indication that the smoker compensates for the anoxic stress caused by smoking by increasing his red blood cell mass — and this was also true for non-smokers living in areas with high ambient CO levels.

Taxi drivers had the highest COHb levels of all occupational groups. Eight non-smoking drivers in New York had an average of 2.5 % COHb (range 1.3—5.8 %). In smoking taxi drivers, the average value was 6.9 %, with a range of 3—13 %. A poor correlation was found between ambient air CO concentrations and blood bank COHb values.

In Sweden no data are available on COHb levels in the general population, and the COHb levels after exposure to various concentrations of environmental CO have not been studied. Some data are available on certain occupational groups, however.

Göthe *et al.* (1969) measured COHb in 76 traffic policemen after controlling traffic during rush hours. No estimations of environmental CO levels and COHb levels before the exposure were made. COHb levels were higher in smokers as compared to non-smokers (3.6 versus 1.1 %). In smokers the COHb levels tended to decrease with increasing time on duty. The authors concluded that heavy exposure to vehicle exhaust may cause a small increase in COHb levels.

4.3 Confounding Exposures

An important confounding variable when relating COHb and environmental CO levels is tobacco smoking. Measurements made of different brands of cigarettes smoked by a smoking machine under specified conditions demonstrate that the smoke contains between 4 % and 5 % carbon monoxide per puff (Wald and Smith 1973).

The COHb level is elevated in cigarette smokers. Results of a study on COHb levels in cigar and pipe smokers (Goldman 1977) showed that past smoking history is less significant in determining COHb levels than are inhalation habits and what is smoked. In this investigation, COHb levels in cigarette smokers were 5 % and in cigar smokers about 12 %.

Significant exposures to carbon monoxide are also found in a number of specific environments and are seen to markedly elevate the COHb levels of exposed persons.

An investigation done in New York City to determine the CO exposure of bridge and tunnel workers reported a 30-day average of 63 ppm CO, with a maximum hourly concentration of 217 ppm at one facility (Ayres *et al.*, 1973). COHb levels above 3 % were found in 85 % of all smoking workers and in 47 % of non-smoking workers. They estimated that the average bridge and tunnel worker was exposed to concentrations of air pollutants five times greater than the levels recommended for community air by the U.S. EPA.

In a two-year study on the exposure situation of toll booth workers in Boston it was seen that the concentration of CO during the second year of the study averaged 35 ppm CO during more than one-third of the time (Burgess *et al.*, 1977). Average concentrations for two summer seasons and two winter seasons ranged between 24 and 30 ppm, with a peak of 90 ppm in one area during one winter season.

Breath-held alveolar air samples were measured in the same study for their CO concentrations. A small group of non-smokers was measured before and immediately after a two-hour shift in a tunnel. A doubling of the alveolar CO concentration was observed, from 15 ppm to 30 ppm, corresponding to an increase of COHb of roughly 1 %. However, even the post-exposure level was lower than the alveolar air concentrations of CO of the smoking workers.

Exposure to particular CO sources may also influence the COHb level in the general population. An example of an exposure to carbon monoxide unrelated to automobile exhaust or smoking is reported by Johnson *et al.* (1975) from ice-skating rinks in Seattle, Washington. The machines used for re-surfacing the ice in the rinks were fueled with propane and ventilation inside the buildings was often inadequate. Measurements of CO concentrations were taken after complaints had been made that

15 children who had skated at the rink suffered from headaches, 4 of whom also felt sick and 2 of whom had vomited. Hourly averages of CO during the hours 1600 to 2400 ranged between 157 and 304 ppm at one rink.

Effects of exposure to liquid paint removed containing the organic solvent methylene chloride are reported by Stewart and Hake (1976). When absorbed, this chemical is quickly metabolized to CO, rapidly raising COHb levels. The authors describe the case of a 66-year-old man who died from heart failure when using a paint remover containing methylene chloride in an unventilated basement workshop.

Two additional cases of exposure to methylene chloride in a degreasing and metal cleaning factory are reported in an unpublished paper by Benzon *et al.* (Northwestern Medical School, Chicago). One 40-year-old man lost consciousness after an exposure to methylene chloride fumes from an industrial leak. A 50-year-old man exposed on the same occasion did not lose consciousness but complained of dizziness and nausea. Both men had COHb levels of nearly 20 % after the exposure and were hospitalized for several days. The authors stated that approximately 70,000 workers in the United States are exposed annually to methylene chloride in industry.

5. Effects on the cardiovascular system

5.1 Physiological Background

For a number of reasons, the myocardium is more sensitive than any other muscle tissue to the decrease in amount of available oxygen in blood caused by formation of COHb. The myocardium depends almost entirely on aerobic metabolism for energy production. At rest, it normally extracts about 70 % of the oxygen present in the coronary circulation and coronary sinus blood is only 30 % saturated. The oxygen extraction reserve for the myocardium is lower than for most other tissues (James *et al.*, 1979).

Coronary circulation responds to low oxygen tension by increasing the flow rate rather than increasing oxygen extraction. The ability to increase oxygen consumption by increasing flow allows performance of continuous contractile work at rest and also provides the ability to increase cardiac work with exercise.

Coronary vascular disease may prevent an increase in local coronary blood flow in response to need. In this situation, the myocardium is forced to extract more oxygen but does this at the expense of a markedly reduced coronary venous and tissue oxygen tension. The patient with coronary heart disease is thus particularly vulnerable to the stresses induced by carbon monoxide because the rigid atheromatis vascular bed may not adequately dilate in response to cellular hypoxia (Ayres *et al.*, 1970).

Carbon monoxide decreases myocardial oxygen tension by 3 mechanisms:

1. Decreased oxygen extraction.
2. Increased ventricular work and oxygen demand due to stimulation of the adrenergic system.
3. Decreased capillary oxygen tension because of the leftward shift of the oxyhemoglobin dissociation curve.

The formation of carboxymyoglobin is also of importance. At a COHb level of 10 %, roughly 30 % of the cardiac myoglobin is saturated with CO.

At low COHb concentrations, the ratio between the carboxymyoglobin and COHb concentrations is about 3 to 1. With decreasing arterial pressure of oxygen, this ratio gradually increases, reaching 7 to 1 at a pO_2 value below 40 mm Hg.

Experimental studies on animals and man and epidemiological studies have given evidence concerning effects of CO on the cardiovascular system. At low exposure doses, effects on the heart muscle and aorta and functional effects in terms of limitations to maximum exercise effort have received particular attention.

Table 5-1. Effects of CO exposure on the cardiovascular system of animals.

CO and/or COHb level	Duration	Animal	Effects	Investigators Year
1500 ppm 23 % COHb	30 min	dogs	decrease in arterial oxygen saturation and oxygen consumption; increase in coronary arterial blood flow and heart rate.	Adams *et al.*, 1973
0.01 % vol 21 % COHb	5.75 h, 6 d/ wk, 11 wks	dogs	myocardial degeneration and fibrosis.	Ehrich *et al.*, 1944
90 ppm	3 months	rabbits	myocardial degeneration.	Wanstrup *et al.*, 1969
180 ppm	2 wks	rabbits	myocardial damage at the ultrastructural level.	Kjeldsen *et al.*, 1972
50, 100, 180 ppm	4—24 h	rabbits	no qualitative change in myocardium at 50 ppm; myocardial damage in some animals at 100 ppm; myocardial damage in nearly all animals at 180 ppm.	Thomsen and Kjeldsen, 1974
100 ppm	24 wks	monkeys	significant, persistent elevation in hematocrit, hemoglobin, and red blood cells; increased P wave amplitudes; higher incidence of T wave inversion in animals with induced infarction.	De Bias *et al.*, 1973
500 ppm 4.9—17 % COHb	5, 5—6 min exposures, 4 min apart	dogs	COHb levels as low as 4.9 % exaggerated the severity of myocardial ischemia after coronary litigation.	Becker and Haak, 1979
100 ppm 6 % COHb	2 h	dogs	electric current needed to provoke ventricular fibrillation significantly decreased after CO exposure.	Aronow *et al.*, 1979
0.018 % vol	2 wks	rabbits	toxic effect on arterial walls, increased endothelial permeability, formation of edema.	Kjeldsen *et al.*, 1972
170—350 ppm 15—33 % COHb	10 wks	rabbits	increased degree of atheromatosis and total cholesterol content in aortic tissue after cholesterol feeding and CO exposure.	Astrup *et al.*, 1967
180—220 ppm 16—18 % COHb	continuously or 12 h		no significant influence in uptake of injected plasma radioactivity or accumulation of free or esterified cholesterol in aortic wall in cholesterol-fed animals after CO exposure.	Stender *et al.*, 1977
250 ppm 9—26 % COHb	4 h/d, 5 d/ wk, 7 months	squirrel monkeys	atherosclerosis induced in coronary arteries aggravated by CO exposure by a factor of 2.	Webster *et al.*, 1970
200 ppm	6 wks	rabbits	study of CO effect on cholesterol in aortic wall. CO-exposed normocholesterolemic rabbits had higher cholesterol concentration in aortic arch. No significant differences in uptake of labelled plasma cholesterol by inner layer of aortic wall.	Stender *et al.*, 1977

5.2 Studies on Animals

A number of studies has been conducted using animal models in order to determine the effects of carbon monoxide exposures on the myocardium. Adams *et al.* (1973) measured cardiac function in dogs exposed to 1500 ppm CO for a period of 30 minutes. They found that arterial oxygen saturation decreased linearly with increasing COHb levels, from 97 % in controls to 73 % at 20 % COHb. Although mean coronary sinus oxygen saturation increased from 22.7 % to 32.3 %, the O_2 content across the heart decreased from 13.6 ml O_2 to 7.4 ml O_2/100 ml. Coronary arterial blood flow and heart rate were seen to increase in relation to COHb levels. A significant decrease in O_2 consumption was noted, beginning at a level of 10 % COHb and reaching a 21 % decrease at 20 % COHb.

In 1944, Erich *et al.* showed that an exposure to low concentrations of CO for a period of several months led to myocardial degeneration and fibrosis in dogs. Wanstrup *et al.* (1969) found similar changes in the myocardium in rabbits after a 3 month exposure to 180 ppm CO, and Kjeldsen *et al.* (1972) observed myocardial damage at the ultrastructural level in rabbits after a 2 week exposure to 180 ppm CO (16—18 % COHb).

Studies on rabbits were performed by Thomsen and Kjeldsen (1974) to determine the threshold limit for myocardial damage produced by CO exposure. It was found that a 50 ppm CO exposure for 4 to 24 hours, yielding 4—5 % COHb, did not result in qualitative changes in the myocardium, though an increase in the number of lipid droplets was found in several of the myocardial preparations. A 180 ppm CO exposure for 4 hours or more produced myocardial degeneration in nearly all animals. At a 100 ppm CO exposure for 4 to 24 hours (8—10 % COHb), some animals showed a normal myocardial ultrastructure while other demonstrated myocardial damage.

De Bias and co-workers (1973) reported on a study of normal monkeys and monkeys with induced myocardial infarction. The animals were exposed continuously to 100 ppm for 24 weeks. In both groups, significant and persistent characteristic elevations in the hematocrit, hemoglobin and red blood cells were seen after 3 weeks. Electrocardiograms demonstrated increased P-wave amplitudes in both groups. Infarcted animals showed a higher incidence of T-wave inversion than the non-infarcted animals. The authors suggested that this indicated a greater degree of myocardial ischemia in the infarcted monkeys breathing carbon monoxide.

The same problem was treated by Becker and Haak (1979) in a study on dogs. They demonstrated that COHb levels as low as 4.9 % exaggerated the severity of myocardial ischemia seen after coronary ligation. The authors stated that the burden on the heart produced by COHb formation was at least twice that incurred by a simple reduction in oxyhemoglobin.

The effect of carbon monoxide exposure on the ventricular fibrillation threshold was reported by Aronow *et al.* (1979). Dogs were exposed to 100 ppm CO for 2 hours, resulting in a COHb level of about 6 %. The electric current needed to provoke ventricular fibrillation was significantly decreased after CO exposure and increased when the dogs resumed breathing fresh air.

The importance of cholesterol for the induction of aortic wall damage after carbon monoxide exposure has been reported in several studies. In an experiment by Kjeldsen *et al.* (1972), rabbits were continuously exposed to 180 ppm CO for 2 weeks, causing COHb concentrations to rise to 16—18 %. A variety of pathological changes was found in the aortic walls of the exposed animals, suggesting increased endothelial permeability and formation of edema. The authors stated that the changes were indistinguishable from early atherosclerosis.

Astrup *et al.* (1967) studied the development of atherosclerosis in rabbits exposed to 170—350 ppm CO (15—33 % COHb) and simultaneously fed cholesterol. They reported an increased degree of atheromatosis and total cholesterol content in the aortic tissue in the CO exposed group.

In a more recent study by the same research group (Stender *et al.*, 1977), animals were exposed to 180—220 ppm CO (16—18 % COHb) continuously or for periods of 12 hours. One group of animals received cholesterol in their diet. The CO exposure did not significantly influence

Table 5-2. Effects of CO exposure on cardiovascular system in man.

CO and/or COHb level	Duration	Effects	Investigators Year
5 % CO 9 % COHb	30—120 sec	increase in coronary blood flow and oxygen extraction ratio and decrease in coronary sinus oxygen tension in subjects with normal hearts; no significant increase in coronary heart disease subjects at high COHb levels; oxygen extraction ratio increased and coronary sinus tension decreased in heart patients; altered lactate and pyruvate metabolism seen at high COHb levels.	Ayers *et al.*, 1970
100 ppm 4.08 % COHb	1 h	significant decrease in exercise time until marked dyspnea in subjects with chronic obstructive pulmonary disease.	Aronow *et al.*, 1977
42—63 ppm 5.08 % COHb	90 min	exercise time until onset of angina decreased significantly in angina pectoris patients; systolic blood pressure and heart rate at angina also significantly decreased.	Aronow *et al.*, 1972
50 and 100 ppm 2.9 and 4.5 % COHb	4 h	exercise time until onset of angina in angina pectoris patients reduced even at low COHb level; systolic blood pressure and heart rate also decreased at angina.	Anderson *et al.*, 1973
7 and 20 % COHb		maximal exercise time for healthy subjects decreased with increasing COHb levels; no difference in blood lactate concentrations between exposed and control groups; maximum oxygen uptake decreased with increased COHb.	Ekblom and Huot, 1972
100 ppm 3.95 % COHb	1 h	mean exercise time until exhaustion decreased in middle-aged, healthy non-smokers. reduced work time for exposed non-smokers; no reduction in exposed smokers; respiratory pattern changes noted in smokers.	Aronow and Cassidy, 1975 Drinkwater *et al.*, 1975
50 ppm		study of »admission case fatality rate» in hospitals divided into high and low pollution areas: significant difference found for fatality rates between high and low area hospitals in 9 of 10 weeks when ambient CO levels were above a weekly mean of 9 ppm.	Cohen *et al.*, 1969
		significant low-level association observed between ambient CO levels and frequency of initial cardiorespiratory complaints at an emergency room of a hospital in Denver, Colorado, during high pollution months.	Kurt *et al.*, 1974

the uptake of injected plasma radioactivity or the accumulation of free or esterified cholesterol in the aortic wall. The authors suggested that the previously reported findings of such an effect of CO could have been caused by the higher serum cholesterol level in the exposed group.

The absence of an effect of CO on cholesterol accumulation in aortic walls was also reported by Webster *et al.* (1970), who studied squirrel monkeys given a diet containing cholesterol and exposed to approximately 250 ppm CO for 4 hours per day, 5 days a week for 7 months. In these animals (COHb values 9—26 % during the period), atherosclerosis induced in the coronary arteries was aggravated by the CO exposure by a factor of 2.

Stender *et al.* (1977) concluded that CO exposure is probably a very weak stimulus on the aortic wall compared with hypercholesterolemia induced by cholesterol feeding.

The evidence from animal studies on CO effects on the cardiovascular system thus demonstrates that acute oxygen deficiency of the myocardium makes this the most critical tissue.

5.3 Experimental Studies on Humans

Ayers *et al.* (1970) exposed 41 patients to CO during diagnostic cardiac catheterization. In subjects who inhaled 5 % CO for a period of 30—120 seconds, the COHb value increased from 0.98 to 8.96 %. This resulted in an increased cardiac output and cardiac oxygen extraction ratio. In subjects inhaling 0.1 % CO for 8—15 minutes, the COHb level increased to 7.9 % without an increase in cardiac output.

The mixed venous oxygen tension fell in both groups, and the decrease was correlated with the increase in COHb levels down to below 5 %. In the same report in investigations with dogs, the authors demonstrated an increase in coronary blood flow when COHb increased to 25 % (Ayers *et al.*, 1970). The coronary arterio-venous oxygen difference decreased to a greater extent than the coronary blood flow increased, resulting in a decrease in myocardial oxygen consumption.

The authors concluded that patients with coronary artery disease are particularly vulnerable for these effects and suggested that the myocardium surrounding a diseased vascular supply might become critically hypoxic at extremely low levels of COHb.

Aronow *et al.* (1977) studied 10 patients with chronic obstructive pulmonary disease during a 1 hour exercise performance test. The subjects had no history of cardiovascular disease at the time of the study. The patients were given air with 100 ppm CO or purified air for 1 hour. The mean COHb level was 1.48 % in the control group. In the exposed group, the COHb value increased from 1.43 to 4.08 %.

No ischemic S-T segment depression was found during exercise. The mean exercise time until marked dyspnea appeared decreased from about 220 seconds in the control period to 147 seconds (33 % decrease) after breathing carbon monoxide for 1 hour. The authors suggested that the decreased exercise performance after CO exposure was a cardiovascular rather than a respiratory limitation.

Aronow *et al.* (1972) administered cardiac tests to 10 men with angina pectoris after they had been driven for 90 minutes on a freeway in Los Angeles during morning rush hour traffic. The tests were repeated on a subsequent morning with the men breathing compressed, purified air during freeway travel. The 3 smokers in the group were instructed not to smoke for 8 hours prior to the experiment.

The CO concentration in the car during travelling ranged from 42 to 63 ppm. The mean COHb levels after breathing freeway air were 5.08 % immediately after driving and 2.91 % after 2 hours. Two of the smokers had high values before the test — 3.5 % versus 0.6 % among the remaining 8 subjects. When those 2 persons were excluded from the after-exposure determinations, the values became 4.6 % immediately after freeway exposure and 2.7 % after 2 hours. The COHb values after the subjects had breathed purified air during freeway travel were 0.65 % and 0.75 %, respectively.

The mean exercise performance from the control test to immediately after and 2 hours after breathing freeway air was reduced from the control value of 249 seconds by 75 and 38 seconds, respectively. Resting blood pressure and heart rates

were not affected by the freeway exposure. At the time when angina occurred there was a significant decrease in the systolic blood pressure and heart rate in the group exposed to freeway air.

FEV_1/FVC decreased in one test person but was unchanged in the others. 3 of the 10 persons developed ischemic S-T segment abnormalities during the exposure; no such changes were seen in persons breathing purified air.

In a later study, Aronow *et al.* (1973) examined 10 patients with angina pectoris in an exercise performance test. At a COHb level of 2.7 % (exposure to 50 ppm for 2 hours) the mean exercise time until onset of angina decreased from 224 to 188 seconds. S-T segment depression occurred earlier after the onset of angina when the persons were exposed to CO.

It has been reported that exposure to carbon monoxide can also impair exercise performance in persons with normal health. Ekblom and Huot (1972) studied 10 healthy subjects, of whom 5 performed submaximal and 5 maximal treadmill and bicycle exercise tests. The subjects breathed air containing CO for 15 minutes, calculated to bring COHb levels to 7 % for a low level and 20 % for a high level. Mean maximal work time on the treadmill and bicycle ergometer was reduced with increasing COHb levels. At the heavy work load, a significant correlation was found between heart rate increase and COHb level.

In another experiment, 10 middle-aged healthy non-smokers (Aronow and Cassidy 1975) breathed either compressed, purified air or air with 100 ppm CO for 1 hour. COHb levels increased from 1.67 % before exposure to 3.95 % after exposure. Immediately after the exposure the subjects performed a treadmill exercise test. The mean time until exhaustion decreased significantly in the group exposed to CO, from 698 seconds to 663 seconds. Ischemic S-T segment depression was not observed in the control experiments, but developed in one subject after carbon monoxide exposure.

The maximal aerobic power of 20 healthy young men, including both smokers and non-smokers, was tested by Drinkwater *et al.* (1974). The subjects were exposed to 50 ppm CO, 0.27 ppm peroxyacetyl nitrate (PAN) or a combination of the two. After a 5 minute exposure, the maximum aerobic power was determined in an exercise test. COHb levels were 2.5 % among non-smokers and 4.1—4.4 % among smokers. Exposure to CO resulted in a decrease in exercise time among non-smokers, though no effect was seen among smokers. Smokers' respiration rates were higher, however, than those of the non-smokers. Heat stress (35 °C) had a stronger effect on exercise time than exposure to carbon monoxide.

The combination of CO and PAN produced no noticeable effects on the responses — PAN exposure itself was also without effects on the exercise performance.

5.4 Epidemiological Studies

Cohen *et al.* (1969) studied the case fatality rate for patients admitted with myocardial infarction to 35 Los Angeles hospitals in 1958. Based upon 3,080 admissions, the »admission case fatality rate» and the »man day at risk case fatality rate» was calculated. Data on CO levels were obtained from regular control stations using daily average values.

Using CO data, the hospitals were divided into those in low CO pollution areas (less than 8 ppm) and high CO pollution areas (more than 8 ppm). Hospitals in the high CO pollution areas received 2,484 myocardial admissions and 596 cases were admitted in low pollution areas. No seasonal trends were found for case fatality rates and admissions of deaths.

Weekly case fatality rates were calculated separately for high and low CO areas. The difference between areas was determined, and it was found that on 35 out of 52 weeks (instead of the expected 26), the admission case fatality rate was higher for high CO area hospitals. A significant difference was only found for the highest CO quartile, and the differences occurred only during periods of relatively increased CO pollution. An analysis of socio-economic variables could not demonstrate any difference between persons admitted to the high and low CO hospitals. No COHb measurements were performed. Data on smoking habits and occupations,

which could have influenced the results, were not included in the study.

In another study, 8,556 patients were interviewed by questionnaire at the emergency room of Colorado General Hospital from November 1975 to February 1976 (Kurt *et al.*, 1979). 95 % of the patients lived within a 15-km radius of the hospital. CO levels (mean of the maximum 1 hour period for each 24 hour period and the 24 hour mean) were recorded at a monitoring station 300 m from the hospital. No COHb levels were determined.

Higher CO levels tended to occur during inversions with warmer ground temperatures. One hour maximum levels reached 40 ppm and 24 hour values 13—14 ppm. A visual evaluation of the relation between cardiovascular complaints and CO levels over the study period suggests a co-variation. There were, however, several periods when high levels of CO were not accompanied by a corresponding increase in complaints.

When the 1 hour mean maximum levels were divided into 4 exposure classes for CO, an increase in cardiac complaints was found between the 2 lowest classes ($\leqslant 11$ and 11 to $\leqslant 17$ ppm), but not for higher exposure classes (≥ 23 ppm).

Two day trends of CO elevation correlated with the frequency of cardiorespiratory complaints. Ambient levels of other air pollutants (ozone, oxides of nitrogen and sulphur compounds) did not correlate with cardiorespiratory complaints.

No measurements of COHb levels in the patients were made in this study. Neither is any information given as to the activities of patients at the time of complaints (for example exercise activities) and the representation of CO levels at one monitoring station for the situation in a large area is not discussed.

The relation between general weather conditions and heart disease has been studied by several authors. Sarna *et al.* (1977) reported that the myocardial infarction rate was related to climate conditions. Their material included 1,216 cases of acute myocardial infarction (AMI) during 1 year in Helsinki. The incidence of AMI was found to be most likely to occur with temperatures just below freezing and high relative humidity.

In typical winter weather with moderately cold temperatures and high atmospheric pressure, the incidence of AMI was 15 % below average. The highest case fatality rate was found on very cold winter days. There was no indication that respiratory infection attributed to the cardiac mortality observed. No measurements of air pollution levels were made in this study.

The present state of knowledge concerning environmental CO and mortality is summarized by Cassel *et al.* (1972), who reviewed in depth several of the studies on the problem. They concluded that observations on the relationship between air pollution, weather and illness had not presented evidence on specific causes.

6. Effects on the central nervous system

The central nervous system (CNS) has a high oxygen consumption and may thus be considered one of the critical organs in terms of exposure to carbon monoxide.

Many researchers have investigated effects on the CNS under different CO exposure conditions and with a variety of different tests. These may all be considered as tests of behavioral effects, but can be divided into two broad categories. One consists of vigilance tests, such as the estimation of short time intervals, reaction to visual or auditory stimuli, discrimination between different visual or auditory signals and maintaining attention or concentration. The second is motor tests, which consist of tests of the performance of physical tasks. Researchers frequently use several tests within the framework of one study and occasionally also combine

Table 6-1. Results obtained from human performance of vigilance tests during exposure to carbon monoxide.

CO/COHb level (exposure duration)	Test	Effects	Investigator Year
0, 50, 100, 175, 250 ppm (4 h)	time perception	sound duration discrimination decrement observed in subjects exposed to a minimum of 50 ppm for 90 min.	Beard and Wertheim 1967
0, 50, 100, 175, 200 ppm (4 h)	time perception	overestimation of 30-sec intervals and sound duration discrimination noted after exposure to 50 ppm for 90 min.	Beard and Wertheim 1969
2, 50, 100, 200, 500 ppm (5 h)	time estimation	no decrement noted, even with levels up to 20 % COHb.	Stewart *et al.*, 1973
1, 25, 50, 100, 200, 500, 1000 ppm (0.5 — 24 h)	time estimation	no performance decrements after 8 h exposure to 100 ppm; delayed headaches, changes in VER and decrease in manual co-ordination seen at COHb levels between 15—20 %.	Stewart *et al.*, 1970
50, 100, 150, 200, 250 ppm (3 h)	time estimation, tracking	no performance decrements noted.	O'Donnell, *et al.*, 1971
75, 150 ppm; 5.9 and 12.7 % COHb (9 h)	mental arithmetic, time estimation, tracking & visual tests	subjects exposed during sleep; tests administered upon awakening; no performance decrements observed; sleep change of less light sleep and more deep sleep noted in subjects.	O'Donnell, *et al.*, 1971 [b]
650, 950 ppm, 7.6 & 11.2 % COHb (45 min)	depth perception, reaction time, visual discrimination	no performance decrements noted except for reaction time, which was significantly longer; decrement essentially the same for both exposure groups.	Ramsey 1973
17 % O_2 or 114 ppm		no performance decrements observed.	Christenson *et al.*, 1977
1, 25, 50, 100, 200, 500, 1000 ppm (0.5—24 h)	visual evoked response	changes in the visual evoked response above 20 % COHb; increases in amplitude of 2—2—4-wave complex and negative-going shift in 5a—6 waves seen at 20—22 % COHb.	Hosko 1970
35, 70 ppm, 3.0, 5.0 % COHb (4 h)	eye-hand tracking, visual monitoring, pitch discrimination	interaction of low-level CO exposure observed with task difficulty and duration to accelerate loss of vigilance and affect performance efficiency of difficult tasks.	Putz *et al.*, 1976
3.2—8 % COHb	auditory time perception	no influence by CO of auditory duration discrimination.	Wright & Shephard 1978
75, 150 ppm (2.3 h)	time discrimination	no CO-related impairment of performance at 3.77 and 7.81 % COHb.	Otto *et al.*, 1979
26, 111 ppm (140 min)	monitoring, vigilance	no influence on monitoring tasks found, but a negative effect seen on vigilance test at levels of 6.6 % COHb.	Horvath *et al.*, 1971
10, 20 % COHb	driving performance (visual tests)	increase in reaction time to taillight intensities and relative speeds; increase in normal driving speed also noted, and a decrease in accuracy of maintaining a fixed distance between cars.	Ray and Rockwell, 1970

Table 6-2. Results obtained from human performance of motor tests during exposure to carbon monoxide.

CO/COHb level (exposure duration)	Test	Effects	Investigators Year
6, 11 and 17 % COHb	driving performance	subjects with 6 % COHb demonstrated no negative effects on driving ability; CO-related decrement in peripheral vision reported but no serious efefct on driving ability detected even at higher COHb levels.	McFarland 1973
		comparison of motor vehicle accident frequency and CO concentration in ambient air during two high-CO pollution periods; no direct association or lag association was found.	Ury *et al.*, 1972
10 and 20 % COHb	driving performance	increase in reaction time to taillight intensities and relative speeds; increase in normal driving speed also noted, and a decrease in accuracy of maintaining a fixed distance between cars.	Ray and Rockwell 1970
0, 25, 50, 75, 100 ppm (4.5 h)	critical tracking	no effects on performance observed.	Hanks 1970

elements of different tests to make one more complex test.

As the number of reports on CO-related CNS effects is large, a thorough review cannot be given in this report. Complete reviews on the subject have been published earlier (U.S. Environmental Protection Agency, 1980, Laties and Merigan, 1979).

An analysis will be made in the following of reports in which effects have been described among humans at low exposure levels approximating those which may be found in environmental air.

Beard and Wertheim (1967) reported on experiments with non-smoking university students exposed to 50, 100, 175, or 250 ppm CO for up to 4 hours. Levels of COHb in the subjects were not measured. During the exposure period, the subjects were given an auditory discrimination test in which they were asked to compare a test signal with a previously given reference signal of a 1-sec duration and to indicate whether it was shorter or longer than the reference signal. 600 trials were carried out in 4-hour sessions.

The authors reported a dose-related reduction of correct judgements for all exposure levels and for both 325 and 125 msec test tones. When 50 ppm of CO was added to the chamber air, a significant decrement was noted after 90 minutes of exposure. This trend continued, showing decrements at proportionally shorter times for higher CO levels.

In another study by the same researchers (Beard and Wertheim, 1969) similar decrements were observed in the estimation of 30-second time intervals and during sound duration discrimination tests, again when subjects were exposed to concentrations of CO as low as 50 ppm for 90 minutes. Decrements increased linearly with increasing concentrations of CO. COHb levels were not measured in the subjects. The authors concluded that exposure to low levels of CO did affect human performance of vigilance tests.

When repeating the study using a double-blind procedure they were however unable to reproduce the original findings (Beard 1970).

Several researchers have tried to verify the findings from the initial observations reported by Beard and Wertheim. Stewart *et al.* (1973) exposed 27 university students

to < 2, 50, 100, 200 and 500 ppm CO for periods up to 5 hours. Three different time estimation tests were administered, one of which was similar to the one previously used by Beard and Wertheim. At COHb concentrations of up to 20 %, no correlations were found between the results from the time estimation tests and COHb levels for any of the tests. The authors concluded that their results strongly indicated that time preception is one of the most resistant functions of man's brain to negative effects of carbon monoxide.

In a following study, Stewart and coworkers (1970) exposed 18 healthy males between the ages of 24 and 42 to CO concentrations of < 1, 25, 50, 100, 200, 500 and 1,000 ppm CO for periods of 30 minutes to 24 hours. A battery of different tests involving motor task, visual and time estimation performance was administered. No effects of CO exposure were noted among subjects exposed to up to 200 ppm (16 % COHb). At higher COHb values, acute headaches developed among certain subjects. When COHb saturations were above 15 %, the subjects demonstrated delayed headaches, changes in the visual evoked response and a decrease in manual coordination.

O'Donnell *et al.* (1971) studied 9 male non-smoking students exposed to 50 and 125 ppm CO for 3 hours (COHb 2.98 and 6.64 %). Results of time estimation, ataxia testing and tracking tests failed to demonstrate any effect of the exposure. The same negative effects were found in a pilot study on a smaller number of persons where the CO levels were 200 and 250 ppm (10.35 and 12.37 % COHb). Differences were noted in the pattern of the tracking task, although no variations in performance were found.

In another investigation, O'Donnell and co-workers (1971 b) exposed 4 non-smoking subjects to either 75 or 150 ppm CO during sleep for 9 hours. Mean COHb levels were 5.9 % and 12.7 %, respectively. Using sleep patterns as an indicator of CNS condition, EEG recordings were made. Critical flicker fusion was measured and a neutral arithmetic test was performed by subjects after awakening. Monitoring and time discrimination capability were also determined.

In the results no indications or trends to the effect that CO produced a decrement in time estimation could be found. Flicker fusion and the mental task were also negative for CO effects. EEG evaluations showed no pronounced effects of CO, although a tendency toward a deeper sleep during the first 3 hours of exposure during CO nights was reported. The authors suggested that these changes present in the early phase of the exposure when COHb levels were below 8 % might be a reflection of some primary physiological adaptative mechanism to CO exposure.

Wright and Shephard (1978) designed an auditory duration discrimination test to replicate that of Beard and Wertheim in order to explore experimental conditions which might have influenced the results. In one of the experimental settings, an increase in the number of errors was found at COHb levels of 3.2 %. No effect was seen at COHb levels up to slightly above 8 %. Task difficulty, environment, and arousal of the test persons markedly influenced the results and a psychophysical analysis suggested that auditory duration discrimination was not influenced by CO.

Otto *et al.* (1979) tried to duplicate the Beard-Wertheim experiments more precisely than previous authors. They exposed 13 non-smoking male subjects to 75 and 150 ppm CO for 2.33 h (COHb 3.77 and 7.81 %). The experiments took place in a small audiometric chamber. A time discrimination task of exactly the same design as the Beard-Wertheim experiments was used. Differences in the experimental design related mainly to activities between the time discrimination task and the attaching of electrodes for collection of EEG recordings.

Data were treated using several different principles but no evidence of a CO related impairment in performance could be found. The authors claimed that the experiment had been repeated using similar procedures for measuring the possible effect and that the modifications in the experimental set-up should have decreased the variance for this type of effect.

The discrepancy between the Beard-Wertheim results and those of other authors could be due to methodological differences in the various experiments.

However, no convincing conclusions which support this concept can be found when comparing the different studies, notably that of Otto *et al.* (1979). O'Donnell *et al.* (1971b) suggested that the results presented by Beard and Wertheim were due to or confounded by sensory restriction effects. However, Otto *et al.* (1979) conducted their experiments in a similar chamber without being able to confirm the results.

In view of this series of negative results on CO effects related to time perception, as well as the inability of Beard and Wertheim to reproduce their own results, time perception cannot be considered as a valid criterion for environmental CO exposure.

Ramsey (1973) tested 20 male university students exposed to 650 ppm CO for 45 minutes (7.6 % COHb) and another group exposed to 950 ppm (11.2 % COHb). 20 other students acted as controls. Tests for depth perception, visual discrimination, reaction time and flicker fusion were administered. Of the various tests, only reaction time showed a significant mean decrement. The increase in reaction time was less than 10 % of the control value. The effect occurred at both exposure levels with no trend toward a dose-response relationship.

Horvath *et al.*, (1971) used 10 non-smoking males, administering exposures of 26 and 111 ppm CO for 140 minutes (2.3 and 6.6 % COHb). During the exposure, the subjects performed a monitoring task with light pulses as the stimulus. No influence was found on the monitoring task, but at the 111 ppm CO level subjects identified fewer signals in the following vigilance test. The authors concluded that the CO exposure produced a negative effect on monitoring in vigilance. These results could not, however, be reproduced in a study by Winneke *et al.* (1977).

Christensen *et al.* (1977) studied the effect of different atmospheric conditions and an exposure to CO on vigilance tests as performed by 10 subjects. Each subject was tested under 4 conditions: filtered air (21 % O_2), CO (114 ppm), low O_2 (17 %) and a combination of 113 ppm CO and 17 % O_2. The CO exposure gave COHb levels of about 5 % at the end of a 2-hour session. The vigilance test was a light pulse discrimination type, conducted in a small chamber. Decreased performance was observed among subjects breathing the low oxygen atmosphere, but no effect was found related to CO exposure.

In experiments on male subjects using exposures of 1, 25, 50, 100, 200, 500 and 1,000 ppm CO for periods of 0.25 to 24 hours, Hosko (1970) found that COHb levels above 20 % produced changes in the visual evoked response (VER). Increases in the amplitude of 2, 3, 4 wave complex were observed and were accompanied by a negative shift in the 5b and 5c segments of the VER at 20—22 %.

A study by U.S. Department of Health, Education and Welfare (Putz *et al.*, 1976) was carried out to determine whether the level of human attention would be reduced by CO levels producing 5 % COHb or less. Another purpose of the investigation was to incorporate some recent methodological refinements in order to assess the presence of effects reported in earlier CO research. Auditory evoked response was also examined under conditions of low-level CO exposure and during a complex auditory discrimination task requiring attention and active information processing.

A total of 30 subjects between the ages of 18 and 26 years was exposed to levels of 35 and 70 ppm CO for 4 hours, calculated to bring COHb levels to 3 and 5 %, respectively. The subjects were tested for their performance of a dual task, consisting of eye-hand tracking as a central task and brightness monitoring as a peripheral task. Pitch discrimination was used to study the auditory evoked response.

The results demonstrated that in the dual task, attention or arousal levels were reduced by CO exposure and that CO caused poorer performance under the high frequency tracking condition and dim peripheral-light condition than under the easier low frequency tracking and bright peripheral light test conditions. For the high CO exposure group, response times for peripheral monitoring increased at a significantly faster rate than was the case in either the low CO exposure group or the control group after the first hour of exposure. However, detection accuracy and the number of misses or false alarms were unaffected.

In addition, tracking accuracy did not remain stable, as predicted, but deteriorated in the fourth hour of high frequency tracking when COHb reached 5 %.

Results from the test of auditory evoked response tentatively indicated a CO-induced disruption of amplitudes of auditory evoked potentials recorded in response to stimuli of significance to the subjects. The authors felt that the data suggested that the extra mental effort required for discrimination increases the suspicion of disruption of sensory evoked potentials by CO.

The authors concluded that the data demonstrated that a level of about 5 % COHb interacts with task difficulty and duration to accelerate the loss of vigilance and adversely affects the efficiency of difficult task performance, such as tracking. They further concluded that the same COHb level can significantly influence the level of brain potentials of exposed individuals who are engaged in extended and repetitious decision-making activity.

McFarland (1973) conducted studies to determine whether exposure to carbon monoxide negatively affects driving performance. 27 subjects were exposed to CO until COHb levels of 6, 11 and 17 % were obtained. They were then tested for their ability to perform selected driving related laboratory tests of visual response. In laboratory studies, subjects performed a complex psychomotor task with control of the field of vision. No effects on the rate of correct responses or reaction time were seen at any of the COHb levels. Visual peripheral responses were more frequently omitted at COHb levels of 17 %.

In following driving experiments, a visual interruption apparatus was used, allowing a 0.5 second view of the highway at desired intervals. The authors claimed that at 17 % COHb the subjects needed relatively more road viewing time at 50 miles per hour. No data were reported in the articles.

A comparison was made in Los Angeles of the frequency of motor vehicle accidents and the concentration of CO in ambient air during two high CO pollution periods (Ury *et al.*, 1972). No association was found to exist between the frequency of automobile accidents and the CO pollution level. Comparisons were made of CO concentrations and number of accidents which occured 1 or 3 hours after the presence of a certain CO level, but no association could be demonstrated.

Ray and Rockwell (1970) found responses at 10 and 20 % COHb in the performance of automobile driving, including increased response time to tail-light intensities and relative speeds, an increase of normal driving speed and a decreased accuracy in maintaining a 200-foot separation distance. In another investigation, subjects were given a critical tracking task after exposure to 0, 25, 50, 75 and 100 ppm CO for 4.5 hours (Hanks 1970). No effects on performance were observed after the exposure.

The above demonstrates that several investigators have presented data which suggest that task performance may be influenced by CO exposure. This effect can then be used as a criteria for environmental carbon monoxide exposure.

7. Effects on the fetus

7.1 Physiological Background

Production of carbon monoxide in the body varies between men and women. During the estrogenic phase of the menstrual cycle, endogenous production in women is the same as for normal men. During the progestational or secretory phase of the cycle, CO production almost doubles. The rate of CO production in-

creases even further during pregnancy and then rapidly decreases in the post-partum period (see Table 7—1).

The cause of the increase in CO production during these different periods is unclear. In pregnant women, about 15 % of the increase results from endogenous CO production by the fetus. Another 30 to 40 % of the increase may be accounted for by the increase in red cell mass of the mother (Longo 1977).

Maternal COHb levels normally range between 0.5 and 1.0 % (Longo 1977). It has been reported that the normal concentrations of COHb in human fetal blood vary between 0.7 and 2.5 %, and that the ratio of fetal to maternal COHb varies from 0.6 to 1.6 (Longo 1970).

Fetal uptake of CO takes place more slowly than maternal uptake. After an acute exposure, maternal COHb values reach half their steady state value in 2 hours, whereas this value is not reached in the fetus until 7 hours after the onset of the exposure. Final equilibrium is reached 36 to 48 hours after the onset of exposure. The COHb level in the fetal blood is then slightly above that of the mother due to particular characteristics of the fetal Hb.

CO exchanges across the placenta by simple diffusion. The carboxyhemoglobin concentrations in fetal blood vary as a function of maternal COHb concentrations, the rate of fetal CO production, the diffusing capacity of the placenta for CO, the relative affinity of hemoglobin for CO as compared to O_2 and the affinity of blood for O_2 and for CO (Longo 1970). A mathematical model for the CO exchange between human fetus and mother has been presented by Hill *et al.* (1977).

Table 7-1. Rate of endogenous production of CO reported for men and women.

	$\dot{V}CO$ (ml/hr)
normal men §	0.42
non-pregnant women, estrogen phase *	0.32
non-pregnant women, progesterone phase *	0.62
pregnant women	0.92
postpartum, 24 h +	1.40
postpartum, day 4 +	0.39

§ Coburn *et al.*, 1963
* Delivoria-Papadopoulos *et al.*, 1974
\+ Linderholm and Lindström 1969

An illustration of the interaction between maternal and fetal COHb levels is given in a study by Longo and Hill (1977). They estimated the relation of COHb concentrations in fetal sheep to the COHb concentration of the pregnant mother after inhalation of various concentrations of carbon monoxide.

The authors found that when the pregnant sheep inhaled air containing 30 ppm CO for between 24 and 48 hours, the COHb levels rose from 1.1 % to a constant level of about 4.6 % after 8 to 10 hours. The fetal COHb levels rose from 1.8 % to a steady state value of about 7.4 %, which was reached after 36 to 48 hours. The decrease in COHb levels was markedly slower from the fetal blood.

Effects on the fetus may be related to direct oxygen deprivation without a significant increase of COHb levels in the fetal blood. When exposed to high concentrations of CO, the oxyhemoglobin saturation curve of the mother shifts to the left, reducing the O_2 pressure in the blood in the placenta. The fetal arterial pO_2 levels are probably close to critical values and the compensatory mechanisms in adults — increased cardiac output, coronary blood flow and tissue blood flow — are probably not present in the fetus.

In the previously cited experiment on sheep (Long and Hill, 1977), the pO_2 in the fetal descending aorta decreased from 20.5 to 14.7 mm Hg at 10 % maternal COHb. Inferior vena cava pO_2 decreased from 16 to 11.5 mm Hg.

CO may exert a direct effect on the placental cells, interfering with their metabolic and transport function (Longo 1977). Detailed descriptions of the influence of various factors on fetal COHb and its relationship to maternal COHb are given in broad reviews on the subjects (Longo 1970 and 1977, National Academy of Sciences 1977).

7.2 Studies on Animals

Many animal experiments have been carried out to investigate the effects of CO exposure on pregnant females and on the

Table 7-2. Fetal effects of maternal carbon monoxide exposure: animal experiments.

CO/COHb level (exposure duration)	Animal model	Effects	Investigator Year
90 ppm, 9—10 % COHb (30 d continuous)	pregnant rabbits	litters of exposed mothers had significantly lower birthweights; great increase in stillborn births and number of neonates who died within first 24 h; no differences in mortality between exposed and control groups at days 6 and 21; some neonates born without a leg.	Astrup 1972
0.1—0.3 % inspired CO (1—3 h)	pregnant rhesus monkeys	pregnant mothers sustained up to 60 % COHb without clinical sequalae; fetuses whose arterial oxygen content fell below 2.0 ml/100 ml for at least 45 min showed severe brain damage.	Ginsberg and Myers 1974
0.1—0.3 % inspired CO (exposed until fetuses obtained a »moderate» or »severe» hypoxia + 1 hour)	pregnant rhesus monkeys	widespread cerebral necrosis in fetuses whose arterial oxygen content fell to 1.6—1.8 ml/100 ml.	Ginsberg and Myers 1976
15 % COHb (entire pregnancy)	pregnant rats	no differences in number of offspring per litter, mortality rate at day 1 or any gross teratologic effects; insignificant difference in birthweight between exposed and controls, which became significant at day 4; markedly lower brain protein levels in CO neonates; changes in CHS in connection with prenatal CO exposure.	Fechter and Annau 1977
30 or 90 ppm or low oxygen (continuous exp)	pregnant rats	great reduction in number of successful pregnancies; fetuses exposed to low O_2 showed increased hematocrit; no differences in number of live, recently dead or visibly abnormal fetuses.	Garvey and Longo 1978
30, 50, 100 ppm (24—48 h), 300 ppm (2—3 h)	pregnant sheep	fetal COHb levels rose more slowly than maternal, took longer to wash out, and were at maximum considerably higher than maternal levels.	Longo and Hill 1977
250 ppm, 10—15 % COHb (7 or 24 h/d, 6—15 or 6—18 d of gestation)	pregnant rabbits and mice	mean body weight of mice fetuses higher in 7 h/d group and lower in 24 h/d group than controls; 2 of 18 in 24 h/d group had malformations; exposed had more lumbar ribs and spurs than controls.	Schwetz *et al.*, 1979

fetus. Most of the studies have used rather high levels of CO. In the study by Longo and Hill (1977), 5 of 11 fetuses died when fetal COHb levels reached about 20 % (100 ppm CO exposure for 24 hours). Astrup (1972) exposed pregnant rabbits for 30 days continuously to 90 ppm CO (COHb levels of 9 to 10 %). Birthweights decreased 11 % and neonatal mortality increased 10 %. The death rate during the first 21 days was also increased. In another group exposed to 180 ppm CO (16 to 18 % COHb), birthweight and neonatal mortality effects were more pronounced. In addition, 3 out of 17 newborns had leg deformities.

Brain damage has been reported in monkey fetuses after maternal CO intoxication. Ginsberg and Myers (1974) performed experiments on 9 pregnant rhesus monkeys, exposing them to 0.1 to 0.3 % inspired CO over a 1 to 3-hour period. Fetal hypoxia developed within minutes after the onset of maternal CO exposure. The authors concluded that fetal brain damage first resulted when the arterial O_2 content fell below 2.0 ml/100 ml for at least 45 minutes during maternal CO exposure. In these cases severe brain damage appeared, consisting of brain swelling associated with hemorrhagic necrosis of the cerebral hemispheres.

The same authors (Ginsberg and Myers 1976) performed experiments with rhesus monkeys, inducing a variety of different levels of fetal hypoxia by exposing pregnant mothers to CO. The observed effects were correlated to the fetal arterial blood oxygen content. In animals in which oxygen in arterial blood was kept at a level between 2.1 and 2.4 ml/100 ml during the most severe period of hypoxia, no brain damage was observed.

Widespread cerebral necrosis was seen in animals whose oxygen content was maintained at 1.6—1.8 ml/100 ml. Less severe brain injury was seen in an intermediate exposure group.

The authors concluded that the monkey fetus is able to sustain significant reductions in arterial oxygen content for periods up to and more than an hour without neurologic sequelae, but that reductions in blood oxygen past a certain critical level result in severe and irreversible brain injury. Should the blood oxygen drop lower, even if only slightly, such severe brain edema occurs that the entire cerebrum becomes necrotic and the newborns therefore die early.

Garvey and Longo (1978) exposed two groups of pregnant rats continuously to 30 and 90 ppm CO and to a low oxygen atmosphere (13 %) in order to investigate the growth and development of the fetus. Maternal COHb levels were 4.8 and 8.8 % and fetal levels 11.3 and 17 %.

The animals were sacrified after 20 days gestation. The number of successful pregnancies was seen to decrease in relation to the exposure levels. Animals exposed to 13 % oxygen showed increased hematocrit erythrocyte count and hemoglobin values. Neither of the CO exposed groups demonstrated this hematologic response. No differences were observed in the number of fetuses alive, recently dead or visibly abnormal for any of the exposure groups.

The 13 % oxygen groups showed a decrease in fetal body weight, which the authors interpreted to be due to the 26 % reduction in food intake in this group. The two CO-exposed groups showed no reduction in weight or food consumption. Fetal body growth was not affected by either CO level, but was significantly affected in fetuses exposed to 13 % oxygen.

Fetal brain wet weight was increased 14 % in the group exposed to 90 ppm CO. Decreased concentrations of brain protein, DNA, norepinephrine and serotonin were observed, as well as a reduced dry-wet weight ratio. No changes were seen in the 30 ppm or in the 13 % oxygen groups.

Fechter and Annau (1977) studied the offspring of pregnant rats exposed to 150 ppm CO for the duration of the gestation period. COHb levels in the mothers were 15 %. Within 12 hours after birth, the animals and litters were removed from exposure.

The authors did not observe any differences in the number of offspring per litter or the mortality rate on day 1, or any gross teratologic effects. There was a slight, though not significant, difference in birth weight between exposed and control neonates. This difference inceased during the preweaning period and was statistically significant at the fourth day.

A 25 % decrease in brain protein level was found in CO neonates as compared to

controls, though the absolute brain weight of the two groups did not differ. A lower activity level was seen in CO-exposed neonates at all ages tested, both spontaneously and after the injection of L-dopa, which elicits vigorous activity. The activity levels were related to whole brain dopamine concentration. No difference was seen for norepinephrine or 5-hydroxytryptamine. The authors suggested that the results indicated changes in the function of the central nervous system in connection with prenatal exposure to carbon monoxide.

Schwetz *et al.* (1979) exposed mice and rabbits to 250 ppm CO for 7 and 24 hours per day (10—15 % COHb) during the gestation period. The mean body weight of fetuses of mice exposed 7 h/day was higher and, in the group exposed 24 h/day, lower than in control animals. Two out of 18 in the 24 h group had malformations as compared to 1 out of 17 in the control group. Litters in the exposed group had a singificant increase in the number of lumbar ribs and spurs. No differences were found between exposed and control rabbits.

7.3 Studies on Humans

No extensive studies on pregnant females exposed to low environmental levels of CO have been performed, though several studies have been made to study possible differences between smoking and non-smoking mothers. As previously indicated, COHb levels differed between these groups. Some of the major studies are described briefly below.

Data were collected on the smoking habits of 253 pregnant women in Copenhagen (Astrup *et al.*, 1972) and measurements taken of their COHb levels. Later, the birth weights of the newborns were measured. Among the 253 pregnant women, 177 were non-smokers, demonstrating a mean COHb level of 0.87 %, and 176 were smokers, showing a mean of 1.92 % COHb. The mean birth weight of babies of non-smoking mothers was 3,225 g and smokers' babies had a mean birth weight of 2,990 g. There were no incidences of congenital deformities in either group, and none of the babies died.

A total of 6,989 pregnant women was included in a prospective investigation in France of effects of smoking during pregnancy (Goujard *et al.*, 1975). An increase in the number of stillbirths occurred among mothers who smoked (23.3 against 9.2 per 1,000 births). A large proportion of this increase was due to abruptio placentae, the percentage of smokers in this category being 46 % while it was only 12 % in the group of livebirths.

Meyer and co-workers (1976) performed further analyses of data collected in the Ontario Perinatal Mortality Study (Ontario Department of Health, 1967). They found that maternal smoking had the strongest effect on birth weight and that birth weights of 2,500 g or less increased directly with the level of smoking, by 20 % up to 3.4 times increase over 37 of the different data subgroups. For smokers of less than one pack a day and smokers of more than one pack a day, gestation periods lasting 38 weeks or less, and adjusted for 7 other factors, increased by 20 % and 50 %. Cases of perinatal mortality increased by 20 % and 50 %, respectively.

Except for mothers pregnant for the first time who smoked less than one pack per day, placental complications also increased in relation to the level of smoking in the 37 subgroups. Finally, the adjusted rates for placenta previa increased 25 % and 92 %, and adjusted rates for abruptio placentae increased 23 % and 86 % for the two groups of smokers. Both complications show a high risk for perinatal mortality.

Using data collected from the 1958 British Perinatal Mortality Survey (Butler and Bonham 1963) and its follow-up study, the National Child Development Study (Pringle *et al.*, 1966), Fedrich and co-workers (1971) investigated the possibility of a connection between maternal smoking and the incidence of congenital heart disease in the population. Questionnaires were completed for 98 % of all births in England, Scotland and Wales during the first of March, 1958. Of a total of 17,418 births, the authors found 86 cases of congenital heart disorder. Among 7,822 stillbirths and neonatal deaths recorded in England, Scotland and Wales during the months of March, April and May, 1958, 204 singletons with congenital heart di-

Table 7-3. Fetal effects of maternal carbon monoxide exposure: studies in humans.

Investigators Year	Description	Effects
Astrup *et al.*, 1972	smoking habits and COHb levels of 253 pregnant women recorded; birthweights and conditions of neonates later recorded.	mean birthweight of neonates of non-smoking mothers was 3,225 g. and of smoking mothers 2,990 g
Goujard *et al.*, 1975	prospective investigation of 6,989 pregnant women.	250 % increase observed in number of stillbirths among smoking mothers; a large proportion of the increase was due to abruptio placentae.
Meyer *et al.*, 1976	further analysis of data collected in Ontario Perinatal Mortality Study.	neonatal birthweight and length of gestation seen to be directly related to mothers' smoking habits; placental complications increased with the level of smoking, except for mothers pregnant for the first time smoking less than 1 pack/day, particularly for placenta previa and abruptio placentae.
Fedrich *et al.*, 1971	further analysis of data collected in 1958 British Perinatal Mortality Study and National Child Development Study, with reference to identifying possible connections between maternal smoking and incidence of congenital heart disease.	analysis demonstrated that the occurrence of congenital heart disease in babies was 50 % greater among smoking mothers than non-smoking mothers; sample too small, however, to allow for firm conclusions.
Buncher 1969	data collected from obstetrical wards in Naval hospitals in U.S.; effects of smoking during pregnancy studied.	observed difference in length of pregnancy between non-smoking and smoking mothers (more than 1 pack/day) was 29 to 24 h; it was suggested that about 10 % of the known reduction in birthweight could be attributed to this shortened gestation period.

sease were found. Analysis of the figures demonstrated that the incidence of congenital heart disease among the babies of smoking mothers was 7.3 per 1,000 births, while the incidence in babies of non-smoking mothers was 4.7/1,000 — an increase of 50 % in babies of smokers. Though the number of cases of congenital heart disease in any particular category was small, the authors felt that the results did warrant further investigations into a possible connection between smoking during pregnancy and the occurrence of congenital heart disease in neonates.

In a study using data collected from obstetrical wards in Naval hospitals in the U.S. (Buncher 1969), the length of pregnancy in smoking mothers was seen to be shorter than that in non-smoking mothers. The difference in the average length of pregnancies between non-smoking mothers and mothers who smoked one pack of cigarettes per day was 29 to 34 hours. The authors suggested that about 10 % of the known reduction in birth weights of babies born to smoking mothers may be attributed to the shortened period of gestation.

8. Evaluation

The emphasis of this review of carbon monoxide criteria has been to evaluate the effects of CO on the cardiovascular system, the central nervous system and the fetus. As a basis for identifying standards, this section summarizes the ways in which different conditions of CO pollution are related to biologically significant approaches for measurement strategies and to exposure related effect criteria.

8.1 Exposure Strategies

Unlike such pollutants as SO_2 and particulates, CO is not evenly spread over large areas, but is concentrated along streets with heavy vehicular traffic. Concentrations are often significantly lower very short distances away from these streets. This causes difficulties in terms of evaluating data collected from ordinary (stationary) air pollution monitoring stations. Such stations are frequently situated away from areas with high traffic density, and great differences have been observed in CO concentrations as measured by mobile stations on sidewalks along heavily trafficked streets and at permanent monitoring stations only a few blocks away.

The amount of CO in the ambient air of cities at a given time varies directly with the traffic density. Concentrations are highest at rush hour and lowest during the night when there is little traffic. In terms of meaningful measurement periods, a 24-hour mean value cannot give a very precise picture of actual daytime concentrations, when traffic is heaviest and the majority of people are likely to be exposed. An average over a time period when levels are elevated and including the two peak events — morning and evening rush hours — is thus preferable.

Several researchers have demonstrated that short time averaged air pollution concentrations tend to be lognormally distributed over a longer time period. Measurements expressed as average of the different levels present during the day are thus not sufficient indicators of risks from CO exposures. The effects on man may occur after a relatively short term exposure to a higher concentration which may not necessarily affect the average long term value. With consideration taken to protection, a standard should thus include values for both a longer time period as well as for a shorter time period.

In those countries which have set limits for the highest allowable amount of carbon monoxide in ambient air, standards have usually been made as 8-hour and 1-hour levels. The WHO has also expressed their recommended limits in these time frames.

A 30-minute or 1-hour period is adequate to describe the short term exposure — no increase in the possibility to protect sensitive individuals is obtained by using shorter time periods.

The 8-hour mean usually applied to describe the situation over the day has a disadvantage in that both daily traffic peak periods are not included. A more practical time period might be 10 or 12 hours, which would include both morning and evening rush hours.

For each series of measured data, a certain portion of values in excess of a decided threshold must be accepted. In the United States, the 1-hour standard requires rank ordering of 1-hour measurement values for a year and comparison of the second highest value with the 1-hour standard (currently 40 mg/m^3 or 35 ppm). If the second highest value is less than 40 mg/m^3, the standard has been met. A rank ordering is also performed for the 8-hour standard (currently 10 mg/m^3 or 9 ppm); the second highest value is used as the critical level.

Measured carbon monoxide data can also be presented by using log-normal cumulative frequency distribution plots. With the aid of such data, the frequency of equalling or exceeding any specific CO concentration can be determined.

Environmental CO limits for different countries are shown in table 8-1.

8.2 Conditions in Sweden

The review of the CO exposure situation in Sweden based upon data from measurements in several cities shows results consistent with observations from other countries. The high concentrations occur near or in streets with heavy traffic and maximum levels are reached during rush hours. There is no reason to believe that climatic or other conditions in Sweden are so different as to call for specific considerations when carbon monoxide standards are set.

8.3 Exposure Criteria

Fetal effects, with relation to both survival and development, have been demonstrated in animals exposed to high levels of CO. As such rapidly growing tissues as the fetus are extremely sensitive to decreases in their oxygen supply, and considering that maternal exposure will cause a prolonged and elevated level in the fetus, the risk for such effects is also present in humans.

No studies have been carried out on females exposed to low concentrations of CO over longer time periods, but significant effects have been detected in fetuses of smoking mothers. Some of these effects are similar to those found after prolonged hypoxia or CO exposure and it can thus be suspected that they are caused by the carbon monoxide content in the inhaled smoke. Smokers are, on the other hand, also exposed to high concentrations of other potentially toxic agents in the smoke, such as nicotine, polycylic hydrocarbons and hydrogen cyanide. Accurate conclusions as to the causative agent for the effects observed in smoking mothers can thus not be drawn.

At present, no data which can be used for dose-response relationships concerning fetal effects of CO exposure at levels found in environmental air are available. The data obtained in animal experiments and from investigations of smoking mothers suggest, however, that COHb levels in excess of those resulting from the carbon monoxide levels recommended by the

Table 8-1. Examples of limits for environmental CO exposure in ppm and corresponding COHb values at rest and heavy physical work (WHO 1979).

	current 1-hour standards	estimated COHb value at rest/exercise		current 8-hour standards	estimated COHb value at rest/exercise	
WHO	35	1.3 %	3.0 %	9	1.4 %	1.6 %
USA	35	1.3 %	3.0 %	9	1.4 %	1.6 %
Canada	30	1.2 %	2.6 %	13	1.9 %	2.1 %
Japan	20	1.0 %	1.8 %	10	1.5 %	1.7 %

WHO are required for the occurrence of fetal effects.

The relation between low level CO exposure and *effects on the central nervous system* have been the subject of much controversy. Reported CNS effects occurring at low COHb levels are a slowing of responses and a decreased ability to perform multi-faceted, complex tasks. The increase in reaction time is similar to effects found in animals, and implies that the presence or absence of a positive effect is critically dependent upon the type of test used, the experimental conditions and the status of the experimental subject.

Information available at present concerning behavioral effects of CO exposure has been summarized by Otto *et al.* (1979): *»In general, the evidence concerning the behavioural effects of CO is inconclusive. Although significant decrements in vigilance performance during low-lovel CO exposure have been reported by several laboratories, subsequent efforts to replicate these findings have consistently failed. Results of one vigilance study have been challenged on statistical grounds.*

One factor which has not been systematically varied is the population selected for study. Normal, healthy, young adults have been used in practically all CO behavioural studies. This population is least likely to show any adverse effects, since healthy young adults have maximal reserve capacity to compensate for reduced oxyhemoglobin availability. Susceptible populations with impaired oxygen uptake have been used effectively to document the deleterious effects of low-level CO on cardiovascular function. A similar strategy should prove useful in resolving the behavioural consequences of CO exposure.»

In spite of the uncertainties involved in the interpretation of the results from CNS effects after CO exposure, it can at presently be concluded that no deleterious effects have been demonstrated at COHb levels below 5 %. The WHO standard provides sufficient protection for this type of effect.

A review of the information on *cardiovascular effects* demonstrates that the functioning of the heart muscle is affected even at very low levels of CO. The evidence is obtained from toxicological studies on man undertaken by several research groups. Essentially, no contradictory data are reported, and the conclusions from clinical studies on man are supported by toxicological studies on animals.

With relation to survival data on patients with critical heart disease, methodological limitations in the epidemiological studies make it difficult to draw any conclusions as to casual relationships. Increases in air pollution levels usually occur under very specific meteorological conditions which also include decreases or increases in ambient air temperature, alterations in the level of airborne particulates and changes in humidity. It is not possible to ascertain whether any one of these specific alterations or combinations of two or several factors may be responsible for the slight differences in cardiovascular deaths seen between areas with varying degrees of carbon monoxide pollution.

Persons with chronic obstructive lung disease or with compromised cardiac function are particularly vulnerable to the functional limitations induced by CO exposure. It is conceivable that no threshold level exists for this group. Every degree of exposure will theoretically induce an increased burden on the cardiovascular system through increased functional requirements and deplete the oxygen supply for the heart muscle.

When the ability to compensate is overpowered, such as during strenuous exercise or when limitations in the blood supply are present, myocardial tissue anoxia will result. This means that even a very low concentration of COHb will cause effects to appear among particularly sensitive persons. Among the Swedish population, it has been estimated that about 13,700 persons suffer from severe angina pectoris (Hagman 1978). The incidence among males in the age group 47—57 years has been estimated to be 0.4 %.

No epidemiological studies have been performed where the presence of acute symptoms of angina pectoris among known sufferers has been related to COHb levels induced by environmental exposure and to what extent symptoms occur under everyday conditions. If such effects were present, particularly in cities, the WHO recommendations would not protect every

sensitive individual simultaneously experiencing physical stress. It does not seem likely that the number thus affected is large, but precise information is lacking.

Even if the concept of »no threshold» is accepted as regards the appearance of cardiac symptoms in predisposed persons exposed to environmental carbon monoxide, the same symptoms could be present in a given population due to other strains without CO exposure. The level of CO at which these other factors become more important than the carbon monoxide exposure is not known.

8.4 Further Research

Abundant information is available on carbon monoxide and its toxic effects, including those occurring among vulnerable groups and related to critical organs in the body. Field measurements, particularly in cities, have also demonstrated that carbon monoxide levels reach a plateau limited by the number of vehicles which can accumulate at a given surface area at any time. Due to other pollutants in vehicle exhaust, notably lead, action is also underway in several places to limit the amount of car exhaust.

In view of the above, extensive further research on the toxic effects of carbon monoxide does not have a high priority from an environmental point of view. In a few specific areas, however, additional information is needed. These are elaborated below.

1. Estimation of COHb levels in urban populations have only been made using blood samples from donors. No precise data on environmental CO levels have been obtained in these studies. Although the equations on the relation between CO exposure and COHb levels are reliable under carefully controlled laboratory conditions, their application to a normal day's exposure in cities has not been sufficiently evaluated.

It is desirable to perform COHb measurements of persons exposed to CO in different urban environments. Suitable test persons could be a group remaining for prolonged periods on the street or persons regularly working close to the street, such as employees in shops on the ground level.

2. Additional information on risk groups, such as persons with blood vessel insufficiencies demonstrated by angina pectoris or intermittent claudication, would give further information as to the protection obtained with the WHO standard. Prospective studies should be performed, and the presence of symptoms in daily life related to COHb levels and ambient air CO levels.

3. Although the few experiments that have been reported in the literature do not indicate a synergistic effect between CO and other agents such as alcohol, drugs and toxic substances, additional information should be sought in this area, initially by performing animal experiments which can be executed at relatively high levels of exposure. When choosing agents suspect of synergism, particular attention should be paid to substances which influence the oxygen saturation of the blood, the availability of oxygen or the oxygen demand of the sensitive tissue.

Appendix

Relation between exposure to carbon monoxide and carboxyhemoglobin (COHb)

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A number of scientists have suggested equations for measuring the relation between exposure to carbon monoxide and the resulting level of carbon monoxide in blood. Several such equations are described in the WHO document *Environmental Health Criteria 13: Carbon Monoxide* (1979), and calculations have been made on the basis of the various models. The equation recommended by WHO is based on the model developed by Coburn,

Forster and Kane (1965). The model was used to study endogenous production of CO, and gives correct relations at low COHb values. However, when used for high exposures the method gives rise to serious errors (partly discussed in the WHO criteria document). The calculations made in Annex 1 of WHO's criteria document show a considerable overestimation of the amount of COHb when measuring the relation between this value and exposure to high concentrations (200 ppm) of CO. An even greater overestimation is shown by Peterson and Stewart (1970) when they use the Coburn-Forster-Kane model to study COHb levels after exposures to still higher concentrations of carbon monoxide.

In later work, Peterson and Stewart (1975) are aware of the errors which can occur as a consequence of the fact that both CO and oxygen compete for available hemoglobin. It is pointed out that the equation given has no clear-cut solution; rather, a trial and error method must be used. Under certain given conditions, however, such a procedure yields very little error.

Peterson and Stewart (1975) base their own calculations on the Coburn-Forster-Kane model according to the following:

$$\frac{A\,(HbCO)_t - B\dot{V}co\,P_{ICO}}{A\,(HbCO)_0\,B\dot{V}co\,P_{ICO}} = \exp\,(-tA/V_bB)$$

where:

A = $PcO_2/M\,(HbO_2)$
B = $1/D_Lco + P_L/\dot{V}_A$
M = ratio of the affinity of blood for CO to that for O_2
(HbO_2) = ml of O_2 per ml of blood
$(HbCO)_t$ = ml of CO per ml of blood at time »t»
$(HbCO)_0$ = ml of CO per ml of blood at the beginning of the exposure interval
PcO_2 = average partial pressure of oxygen in lung capillaries, mmHg
$\dot{V}co$ = rate of endogenous CO production, ml/min
D_{LCO} = diffusivity of the lung for CO, ml/min mmHg
P_L = barometric pressure minus the vapor pressure of water at body temperature, mmHg
V_b = blood volume, ml
P_{ICO} = partial pressure of CO in the inhaled air, mmHg
$\dot{V}_A$ = alveolar ventilation rate, ml/min
t = exposure duration, min
exp = 2.7182 ... the base of natural logarithms raised to the power of the bracketed expression

Table 1 gives the relation between carbon monoxide exposure and carboxyhemoglobin under standard conditions at rest, light work and strenuous work. Table 2 illustrates the corresponding calculations (light work) with a COHb value of 5 %. The relationships for a small person with small blood volume and low hemoglobin value under conditions of light work are given in Table 3.

All calculations have been made with a Hewlett Packard 41 C calculator.

Table 1, Expected COHb values under different conditions according to Peterson and Stewart (1975) at rest (alveolar ventilation: 6 l/min, diffusion capacity: 30 ml/min), light work (alveolar ventilation: 18 l/min, diffusion capacity: 40 ml/min) and heavy work (alveolar ventilation: 30 l/min, diffusion capacity: 60 ml/min). Height: 175 cm; weight: 75 kg (blood volume: approx 5.5 l), hemoglobin: 15 g/100 ml; barometric pressure: 750 mmHg; affinity constant for CO: 218; $COHb_0$: 0.5 %.

duration	200 ppm			100 ppm			75 ppm			50 ppm		
	r	lw	hv	r	lw	hv	r	lw	hv	r	lw	hv
15 min	1.7	3.2	4.7	1.1	1.8	2.6	0.9	1.5	2.0	0.8	1.2	1.5
30 min	2,8	5.7	8.3	1.7	3.1	4.4	1.4	2.4	3.4	1.1	1.7	2.4
45 min	3.9	7.9	11.2	2.2	4.2	5.9	1.8	3.2	4.5	1.3	2.3	3.1
60 min	5.0	9.8	13.6	2.7	5.2	7.1	2.2	4.0	5.4	1.6	2.8	3.7
90 min	6.9	13.1	17.2	3.7	6.8	9.1	2.9	5.2	6.9	2.1	3.6	4.7
2 h	8.7	15.6	19.5	4.6	8.2	10.4	3.6	6.3	8.0	2.5	4.3	5.5
4 h	14.3	21.0	23.0	7.5	11.4	12.8	5.7	8.8	9.9	4.0	6.0	6.8
6 h	17.8	22.9	23.7	9.5	12.7	13.4	7.3	9.8	10.4	5.0	6.7	7.2
8 h	20.0	23.5	23.8	10.8	13.2	13.5	8.3	10.2	10.5	5.7	7.1	7.3
24 h	23.8	23.9	23.9	13.6	13.6	13.6	10.6	10.6	10.6	7.3	7.3	7.3

duration	35 ppm			25 ppm			10 ppm			5 ppm		
	r	lw	hv	r	lw	hv	r	lw	hv	r	lw	hv
15 min	0.7	0.9	1.2	0.6	0.8	1.0	0.5	0.6	0.7	0.5	0.5	0.5
30 min	0.9	1.4	1.8	0.8	1.1	1.4	0.6	0.7	0.8	0.5	0.6	0.6
45 min	1.1	1.7	2.3	0.9	1.3	1.7	0.6	0.8	0.9	0.6	0.6	0.6
60 min	1.3	2.1	2.7	1.0	1.6	2.0	0.7	0.9	1.0	0.6	0.6	0.7
90 min	1.6	2.6	3.4	1.3	2.0	2.5	0.8	1.0	1.2	0.6	0.7	0.7
2 h	1.9	3.1	3.9	1.5	2.3	2.9	0.8	1.1	1.3	0.6	0.7	0.7
4 h	2.9	4.3	4.9	2.2	3.1	3.5	1.1	1.4	1.5	0.7	0.8	0.8
6 h	3.6	4.8	5.1	2.7	3.5	3.7	1.3	1.5	1.6	0.8	0.8	0.8
8 h	4.1	5.1	5.2	3.1	3.7	3.8	1.4	1.6	1.6	0.9	0.9	0.8
24 h	5.3	5.3	5.3	3.9	3.9	3.9	1.6	1.6	1.6	1.0	1.0	1.0

r = rest
lw = light work
hw = heavy work

Table 2, Expected COHb values under different conditions according to Peterson and Stewart (1975) at light work (alveolar ventilation: 18 l/min; diffusion capacity:40 ml/min) och $COHb_0$: 5 %. Height: 175 cm; weight: 75 kg (blood volume: approx 5.5 l); hemoglobin: 15 g/100 ml; barometric pressure: 750 mmHg; affinity constant for CO: 218.

	200 ppm	100 ppm	75 ppm	50 ppm	35 ppm	25 ppm	10 ppm	5 ppm
15 min	7.3	5.9	5.6	5.2	5.0	4.9	4.7	4.6
30 min	9.3	6.7	6.1	5.4	5.1	4.8	4.4	4.3
45 min	11.1	7.5	6.6	5.6	5.1	4.7	4.1	4.0
60 min	12.7	8.1	7.0	5.8	5.1	4.6	3.9	3.7
90 min	15.3	9.2	7.7	6.1	5.1	4.5	3.5	3.2
2 h	17.4	10.1	8.2	6.3	5.2	4.4	3.2	2.8
4 h	21.6	12.2	9.6	6.9	5.2	4.1	2.4	1.8
6 h	23.1	13.0	10.2	7.1	5.3	4.0	2.0	1.3
8 h	23.6	13.4	10.4	7.2	5.3	3.9	1.8	1.1
24 h	23.9	13.6	10.6	7.3	5.3	3.9	1.6	0.9

Table 3, Expected COHb values under different conditions according to Peterson and Stewart (1975) at light work (alveolar ventilation: 18 l/min; diffusion capacity: 40 ml/min) for a small person (height: 165 cm; weight: 55 kg; blood volume: approx 4 l) with low hemoglobin value (11 g/100 ml). Barometric pressure: 750 mmHg; affinity constant for CO: 218; $COHb_0$: 0.5 %.

	200 ppm	100 ppm	75 ppm	50 ppm	35 ppm	25 ppm	10 ppm	5 ppm
15 min	5.3	2.9	2.3	1.7	1.3	1.1	0.7	0.6
30 min	9.3	4.9	3.8	2.6	2.0	1.5	0.8	0.6
45 min	12.5	6.5	5.0	3.5	2.5	1.9	1.0	0.7
60 min	15.0	7.9	6.0	4.1	3.0	2.2	1.1	0.7
90 min	18.5	9.8	7.5	5.1	3.7	2.7	1.2	0.7
2 h	20.6	11.1	8.5	5.8	4.2	3.1	1.4	0.8
4 h	23.4	13.1	10.2	7.0	5.0	3.7	1.6	0.9
6 h	23.8	13.5	10.5	7.3	5.2	3.8	1.6	0.9
8 h	23.9	13.6	10.6	7.3	5.3	3.8	1.6	0.9
24 h	23.9	13.6	10.6	7.3	5.3	3.9	1.6	0.9

References

J. D. Adams, H. H. Erickson and H. L. Stone. Myocardial metabolism during exposure to carbon monoxide in the conscious dog. J Appl Physiol *34:* 238—242, 1973.

E. W. Anderson, R. J. Andelman, J. M. Strauch, W. J. Fortuin and J. H. Knelson. Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris: a study in 10 patients with ischemic heart disease. Ann Int Med *79:* 46—50, 1973.

W. S. Aronow, C. N. Harris, M. W. Isbell, R. N. Rokaw and B. Imparato. Effect of freeway travel on angina pectoris. Ann Int Med *77:* 669—676, 1972.

W. S. Aronow and J. Cassidy. Effect of carbon monoxide on maximal treadmill exercise: a study in normal persons. Ann Int Med *83:* 496—499, 1975.

W. S. Aronow, J. Ferlinz and F. Glauser. Effect of carbon monoxide on exercise performance in chronic obstructive pulmonary disease. Amer J Med *63:* 904—908, 1977.

W. S. Aronow, E. A. Stemmer and S. Zweig. Carbon monoxide and ventricular fibrillation threshold in normal dogs. Arch Environ Health *34:* 184—186, 1979.

P. Astrup. Some physiological and pathological effects of moderate carbon monoxide exposure. Br Med J *4:* 447—452, 1972.

P. Astrup, K. Kjeldsen and J. Wanstrup. Enhancing influence of carbon monoxide on the development of atheromatosis in cholesterol-fed rabbits. J Atheroscler Res *7:* 343—354, 1967.

P. Astrup, H. M. Olsen, D. Trolle and K. Kjeldsen. Effect of moderate carbon monoxide exposure on fetal development. The Lancet, December 9, 1972, 1220—1222.

S. M. Ayres, R. Evans, D. Licht, J. Griesback, F. Reinold, E. F. Ferrand and A. Criscitiello. Health effects of exposure to high concentrations of automotive emissions: studies in bridge and tunnel workers in New York City. Arch Environ Health *27:* 168—178, 1973.

R. R. Beard and G. A. Wertheim. Behavioral impairment associated with small doses of carbon monoxide. Amer J Pub Health *57:* 2012—2022, 1967.

R. R. Beard and G. A. Wertheim. Behavioral manifestations of carbon monoxide absorption. Paper presented at the 16th International Conference on Occupational Health, Tokyo, 1969.

R. R. Beard. First annual conference on environmental toxicology, September 8—11, 1970. Statement made to the audience of scientists during the discussion of his paper.

L. C. Becker and E. D. Haak. Augmentation of myocardial ischemia by low level carbon monoxide exposure in dogs. Arch Environ Health *34:* 274—279, 1979.

C. R. Buncher. Cigarette smoking and duration of pregnancy. Amer J Obstet Gynecol *103:* 942—946, 1969.

W. A. Burgess, L. DiBerardinis and F. E. Speizer. Health effects of exposure to automobile exhaust: V. exposure of toll booth operators to automobile exhaust. Amer Ind Hyg Ass J *38:* 184—191, 1977.

N. R. Butler and D. G. Bonham. Perinatal Mortality. Livingstone, Edinburgh, 1963.

P. Camner, G. Andersson, P. Boston, C. Brosset, R. Cederlöf, L. Friberg, G. Persson and R. Rylander. Air quality criteria and guides for Sweden in regard to sulfur dioxide and suspended particulates. Nordisk Hygienisk Tidskrift, 1973.

E. J. Cassell, M. Lebowitz and J. R. McCarroll. The relationship between air pollution, weather and symptoms in an urban population: clarification of conflicting findings. Amer Rev Respir Dis *106:* 677—683, 1972.

C. L. Christenson, J. A. Gliner, S. M. Horvath and J. A. Wagner. Effects of three kinds of hypoxias on vigilance performance. Aviation, Space and Environ Med *6:* 491—496, 1977.

R. F. Coburn, W. S. Blakemore and R. E. Forster. Endogenous CO production in man. J Clin Invest 42: 1172—1176, 1963.

R. F. Coburn, R. E. Foster and P. Kane. Considerations of the physiological variables that determine the blood COHb concentration in man. J Clin Invest *44:* 1899—1910, 1965.

S. I. Cohen, M. Deane and J. R. Goldsmith. Carbon monoxide and survival from myocardial infarction. Arch Environ Health *19:* 510—517, 1969.

D. A. DeBias, C. M. Banerjee, N. C. Birkhead, W. V. Harrer and L. A. Kazal. Carbon monoxide inhalation effects follwing myocardial infarction in monkeys. Arch Environ Health *27:* 161—167, 1973.

M. Delivoria-Papadopoulos, R. F. Coburn and R. E. Forster. Cyclic variation of rate of CO production in normal women. J Appl Physiol *36:* 49—51, 1974.

B. L. Drinkwater, P. B. Raven, S. M. Horvath, J. A. Gliner, R. O. Ruhling, N. W. Bolduan and S. Taguchi. Air pollution, exercise and heat stress. Arch Environ Health *28:* 177—181, 1974.

W. E. Ehrich, S. Bellet and F. H. Lewey. Cardiac changes from carbon monoxide poisoning. Amer J Med Sci *208:* 511—523, 1944.

B. Ekblom and R. Huot. Response to submaximal and maximal exercise at different levels of COHb. Acta Physiol Scand *86:* 474—482, 1972.

L. D. Fechter and Z. Annau. Toxicity of mild prenatal carbon monoxide exposure. Science *197:* 680—682, 1977.

J. Fedrick, E. D. Alberman and H. Goldstein. Possible teratogenic effect of cigarette smoking. Nature *231:* 529—530, 1971.

W. H. Forbes. Carbon monoxide uptake via the lungs. Ann NY Acad Sci *171:* 72—75, 1970.

D. J. Garvey and L. Longo. Chronic low-level maternal carbon monoxide exposure and fetal growth and development. Biol Reprod *19:* 8—14, 1978.

M. D. Ginsberg and R. E. Myers. Fetal brain damage following maternal carbon monoxide intoxication: an experimental study. Acta Obstet Gynecol Scand *53:* 309—317, 1974.

M. D. Ginsberg and R. E. Myers. Fetal brain injury after maternal carbon monoxide intoxication. Neurology *26:* 15—23, 1976.

A. L. Goldman. COHb levels in primary and secondary cigar and pipe smokers. Chest *72:* 33—35, 1977.

J. Goujard, C. Rumeau and D. Schwartz. Smoking during pregnancy, stillbirth and abruptio placentae. Biomed *23:* 20—22, 1975.

C-J. Göthe, B. Fristedt, L. Sundell, B. Kolmodin, H. Ehrner-Samuel and K. Göthe. Carbon monoxide hazard in city traffic: an examination of traffic policemen in three Swedish towns. Arch Environ Health *19:* 310—314, 1969.

M. Hagman. The prevalence of angina pectoris patients under 70 years of age in Sweden based on epidemiological studies in Gothenburg. Stockholm: Svenska Läkarsällskapets Handlingar, 1978. p. 79. In Swedish.

E. P. Hill, J. R. Hill, G. G. Power and L. D. Longo. Carbon monoxide exchanges between the human fetus and mother: a mathematical model. Amer J Physiol *232:* H311—H323, 1977.

S. M. Horvath, T. E. Dahms and J. F. O'Hanlon. Carbon monoxide and human vigilance. Arch Environ Health *23:* 343—347, 1971.

M. J. Hosko. The effect of carbon monoxide on the visual evoked response in man and the spontaneous encephalogram. Arch Environ Health *21:* 174—180, 1970.

W. E. James, C. E. Tucker and R. F. Grover. Cardiac function in goats exposed to carbon monoxide. J. Appl Physiol *47:* 429—434, 1979.

C. J. Johnson, J. C. Moran, S. C. Paine, H. W. Anderson and P. A. Breysse. Abatement of toxic levels of carbon monoxide in Seattle ice-skating rinks. AJPH *65:* 1087—1090, 1975.

A. Kahn, R. B. Rutledge, G. L. Davis, J. A. Altes, G. E. Gantner, C. A. Thornton and N. D. Wallace. COHb sources in the metropolitan St. Louis population. Arch Environ Health *29:* 127—135, 1974.

K. Kjeldsen, H. K. Thomsen and P. Astrup. The effects of carbon monoxide on the myocardium: ultrastructural changes in rabbits after a moderate, chronic exposure. Circ Res *34:* 339—348, 1974.

K. Kjeldsen, P. Astrup and J. Wanstrup. Ultrastructural intimal changes in the rabbit aorta after a moderate carbon monoxide exposure. Atheroscler *16:* 67—82, 1972.

T. L. Kurt, R. P. Mogielnicki, J. E. Chandler and K. Hirst. Ambient carbon monoxide levels and acute cardiorespiratory complaints: an exploratory study. Amer J Pub Health *69:* 360—363, 1979.

V. G. Laties and W. H. Merigan. Behavioral effects of carbon monoxide on animals and man. Ann Rev Pharmacol Toxicol *19:* 357—392, 1979.

H. Linderholm and P. Lindström. Endogenous CO production and blood loss at delivery. Acta Obstet Gynecol Scand *48:* 356—362, 1969.

L. Longo. Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Ann NY Acad Sci *174:* 313—341, 1970.

L. Longo. The biological effects of carbon monoxide in the pregnant woman, fetus and newborn infant. Amer J Obstet Gynecol *129:* 69—103, 1977.

L. Longo and E. Hill. Carbon monoxide uptake and elimination in fetal and maternal sheep. Amer J Physiol *232:* H324—H330, 1977.

R. A. McFarland. Low-level exposure to carbon monoxide and driving performance. Arch Environ Health *27:* 355—359, 1973.

M. B. Meyer, B. S. Jonas and J. A. Tonascia. Perinatal events associated with maternal smoking during pregnancy. Amer J Epidemiol *103:* 464—474, 1976.

Miljö- och Hälsovårdsförvaltningen, Stockholms Kommun. Report 1976-03-12. Air pollution measurements at Blasieholm, 1976-02-06—26. In Swedish.

Miljö- och Hälsovårdsförvaltningen, Stockholms Kommun. Report 1977-02-04. New vehicle emission measurements at Arsenalsgatan. In Swedish.

Miljö- och Hälsovårdsförvaltningen, Stockholms Kommun. Report 1978-02-06. Summary of air pollution measurements in traffic situations at certain streets in Stockholm. In Swedish.

National Academy of Sciences, Committee on Medical and Biologic Effects of Environmental Pollutants. Carbon Monoxide. Washington D.C.: 1977.

R. D. O'Donnell, P. Mikulka, P. Heinig and J. Theodore. Low-level carbon monoxide exposure and human psychomotor performance. Toxicol Appl Pharmacol *18:* 593—602, 1971.

R. D. O'Donnell, P. Chikos and J. Theodore. Effect of carbon monoxide exposure on human sleep and psychomotor performance. J Appli Physiol *31:* 513—517, 1971 b.

Ontario Department of Health: Second Report of the Perinatal Mortality Study in Ten Teaching Hospitals in Ontario, Toronto, Canada. Ontario Perinatal Mortality Study Committee Toronto, Canada, 1967.

D. A. Otto, G. A. Benignus and J. D. Prak. Carbon monoxide and human time discrimination: failure to replicate Beard-Wertheim experiments. Aviation, Space Environ Med *50:* 40—43, 1979.

J. E. Peterson and R. E. Stewart. Absorption and elimination of carbon monoxide by inactive young men. Arch Environ Health *21:* 165—171, 1970.

J. E. Peterson and R. D. Stewart. Predicting the COHb levels resulting from CO exposures. J Appl Physiol *39:* 633—638, 1975.

M. L. K. Pringle, N. R. Butler and R. Davie. Eleven Thousand Seven-Year-Olds. London: Longmans, 1966.

V. R. Putz, B. L. Johnson and J. V. Setzer. Effects of carbon monoxide on vigilance performance. U.S. Department of Health, Education and Welfare (NIOSH) Pub No 77—124, 1976.

J. M. Ramsey. Effects of single exposure of carbon monoxide on sensory and psycho-

motor response. Amer Ind Hyg Ass J *34:* 212—216, 1973.

A. M. Ray and T. H. Rockwell. An exploratory study of automobile driving performance under the influence of low levels of COHb. Ann NY Acad Sci *174:* 396—408, 1970.

S. Sarna, M. Romo and P. Siltanen. Myocardial infarction and weather. Ann Clin Res *9:* 222—232, 1977.

B. A. Schwetz, F. A. Smith, B. K. Leong and R. E. Staples. Teratogenic potential of inhaled carbon monoxide in mice and rabbits. Teratology *19:* 385—392, 1979.

T. Sjöstrand. Endogenous formation of carbon monoxide in man under normal and pathological conditions. Scand J Clin Lab Invest *1:* 201—214, 1949.

Statens Naturvårdsverk, PM 729, 1977. Automobile exhaust investigation in Swedish cities 1969—1973. In Swedish.

Statens Naturvårdsverk, PK 891, 1977. Automobile exhaust in the street environment — model and model testing. In Swedish.

S. Stender, P. Astrup and K. Kjeldsen. The effect of carbon monoxide on cholesterol in the aortic wall of rabbits. Atheroscler *28:* 357—367, 1977.

R. D. Stewart. The effects of low concentrations of carbon monoxide in man. Scand J Respir Dis, Suppl *91:* 56—61, 1974.

R. D. Stewart. The effect of carbon monoxide on humans. Ann Rev Pharmacol *15:* 409—423, 1975.

R. D. Stewart, J. E. Peterson, E. D. Baretta, R. T. Bachard, M. J. Hosko and A. A. Herrmann. Experimental human exposure to carbon monoxide. Arch Environ Health *21:* 154—164, 1970.

R. D. Stewart, E. D. Baretta, L. R. Platte, E. B. Stewart, J. H. Kalbfleisch, B. Van Yserloo and A. A. Rimani. COHb concentrations in blood donors in Chicago, Milwaukee, New York and Los Angeles. Science *182:* 1362—1364, 1973.

R. D. Stewart, P. E. Newton, M. J. Hosko and J. E. Peterson. Effect of carbon monoxide on time perception. Arch Environ Health *27:* 155—160, 1973.

R. D. Stewart, E. D. Baretta, L. R. Platte, E. B. Stewart, J. H. Kalbfleisch, B. Van Yserloo and A. A. Rimani. COHb levels in American blood donors. JAMA *229:* 1187—1195, 1974.

R. D. Stewart and C. L. Hake. Paint-remover hazard. JAMA *235:* 398—401, 1976.

R. D. Stewart, R. S. Stewart, W. Stamm and R. P. Seelen. Rapid estimation of the COHb level in fire fighters. JAMA *235:* 390—392, 1976.

H. K. Thomsen and K. Kjeldsen. Threshold limit for carbon monoxide-induced myocardial damage. Arch Environ Health *29:* 73—78, 1974.

H. K. Ury, N. M. Perkis and J. R. Goldsmith. Motor vehicle accidents and vehicular pollution in Los Angeles. Arch Environ Health *25:* 314—322, 1972.

U. S. Environmental Protection Agency. Air Quality Criteria for Carbon Monoxide, EPA 600/8-79-022. U. S. Government Printing Office.

Alan M. Voorhees & Associates, Ind. »Users Guide for Highway Vehicle Emissions Model». Draft report prepared for county of San Diego, California, July, 1976.

N. Wald and P. G. Smith. Smoking tables for CO? The Lancet, October 20, 1973, 907—908.

J. Wanstrup, K. Kjeldsen and P. Astrup. Acceleration of spontaneous changes in the rabbit aorta by a prolonged, moderate carbon monoxide exposure. Acta Pathol Microbiol Scand *75:* 353—362, 1969.

W. S. Webster, T. B. Clarkson and H. B. Lofland. Carbon monoxide aggravated atherosclerosis in the squirrel monkey. Exp Molec Pathol *13:* 36—50, 1968.

G. Winneke, G. G. Fodor and H. W. Schlipkoter. Carbon monoxide, trichloroethylene, and alcohol: Reliability and validity of effects. In: D. Otto (Ed.), Multidisciplinary Perspectives in Event-Related Brain Potential Research. EPA 600/9-77-043. U. S. Government Printing Office.

World Health Organization. Nitrogen Oxides. Environmental Health Criteria 4. Geneva, 1977.

World Health Organization. Sulfur Oxides and Suspended Particulate Matter. Environmental Health Criteria 8. Geneva, 1979.

World Health Organization. Carbon Monoxide. Environmental Health Criteria 13. Geneva, 1979.

G. R. Wright and R. T. Shephard. Carbon monoxide exposure and auditory duration discrimination. Arch Environ Health *32:* 226—235, 1978.