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ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

CARBON MONOXIDE (CAS Reg. No. 630-08-0)

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PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. AEGL-2 and AEGL-3 levels, and AEGL-1 levels as appropriate, will be developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and will be distinguished by varying degrees of severity of toxic effects. It is believed that the recommended exposure levels are applicable to the general population including infants and children, and other individuals who may be sensitive or susceptible. The three AEGLs have been defined as follows:

AEGL-1 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing odor, taste, and sensory irritation, or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL level, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL level. Although the AEGL values represent threshold levels for the general public, including sensitive subpopulations, it is recognized that certain individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL level.

TABLE OF CONTENTS

LIST OF TABLES

131 **LIST OF FIGURES**

EXECUTIVE SUMMARY

Carbon monoxide (CO) is a tasteless, non-irritating, odorless and colorless gaseous substance. The main source of CO production is the combustion of fuels. Exposure at the workplace occurs in blast furnace operations in the steel industry and when gasoline- or propane-powered forklifts, chain-saws or other machines are used in confined spaces, such as companies, tunnels and mines. Environmental exposure to CO can occur while traveling in motor vehicles (9-25 and up to 35 ppm), visiting urban locations with heavily traveled roads (up to 50 ppm), or cooking and heating with domestic gas, kerosene, coal or wood (up to 30 ppm) as well as in fires and by environmental tobacco smoke. Endogenous CO formation during normal metabolism leads to a background carboxyhemoglobin concentration (COHb) of about 0.5-0.8 %. Smokers are exposed to considerable CO concentrations leading to a COHb of about 3-8 %.

CO binds to hemoglobin forming COHb and thereby renders the hemoglobin molecule less able to bind oxygen. Due to this mechanism, the oxygen transport by the blood and the release of bound oxygen in the tissues are decreased. Tissue damage results from local hypoxia. Organs with a high oxygen requirement, such as the heart and the brain, are especially sensitive for this effect.

AEGL-1 values were not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population.

Patients with coronary artery disease show health effects at lower COHb levels than children, pregnant women or healthy adults and, thus, constitute the most susceptible subpopulation. For the derivation of AEGL-2 values a level of 4 % COHb was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion (Allred et al., 1989; 1991). In the available studies, the CO exposure alone (i.e. with subjects at rest) did not cause angina, while exercise alone did so. However, since all studies used patients with stable exertional angina, who did not experience angina while at rest, it cannot be ruled out that in more susceptible individuals (a part of the patients with unstable angina pectoris might belong to this group) CO exposure alone could cause or increase angina symptoms. The changes in the electrocardiogram (ST-segment depression of 1 mm (corresponding to 0.1 mV) or greater) associated with angina symptoms were considered reversible, but is indicative of clinically relevant myocardial ischemia requiring medical treatment. An exposure level of 4 % COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. Ventricular arrhythmias have been observed at COHb of 5.3 %, but not at 3.7 % (Sheps et al., 1990; 1991), while in another study no effect of CO exposure on ventricular arrhythmia was found at 3 or 5 % COHb (Dahms et al., 1993). This exposure level, which corresponds to COHb values of 5.0-5.6 % in newborn and children was considered protective of acute neurotoxic effects in children, such as syncopes, headache, nausea, dizziness and dyspnea (Klasner et al., 1998; Crocker and Walker, 1985), and long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children (Klees et al., 1985). A mathematical model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a COHb of 4 % in adults at the end of exposure periods of 10 and 30 minutes and 1, 4 and 8 hours. A total uncertainty factor of 1 was used. A level of 4 % COHb was the NOEL for AEGL-2 effects in patients with coronary artery disease, while the LOEL was estimated at 6-9 %. In comparison, the LOEL was about 10-15 % in children and 22-25 % in pregnant women. Since AEGL-2 values were based on experimental data on the most susceptible subpopulation, they were considered protective also for other subpopulations and a total uncertainty factor of 1 was used.

It is acknowledged that apart from emergency situations, certain scenarios could lead to CO concentrations which may cause serious effects in persons with cardiovascular diseases. These scenarios include e.g. extended exposure to traffic fume emissions (e.g., in tunnels or inside cars with defect car exhaust systems), charcoal or wood fire furnaces, and indoor air pollution by tobacco smoking.

The derivation of AEGL-3 values was based on observations in humans. Several case reports indicate that in patients with coronary artery disease, CO exposure can contribute to myocardial infarction (which was considered an AEGL-3 endpoint). In the published cases of myocardial infarction, the following COHb values were measured after transport to the hospital: 52.2 % (Marius-Nunez, 1990), 30 %, 22.8 % (Atkins and Baker, 1985), 21 % (Ebisuno et al., 1986), 15.6 % (Grace and Platt, 1981). Case reports on stillbirths after CO poisoning of pregnant women reported measured maternal COHb of about 22-25 % or higher (Caravati et al., 1988; Koren et al., 1991). These anecdotal reports on cases affecting susceptible subpopulations were considered as important supporting information, but not as an adequate basis for the derivation of AEGL-3 values because of uncertainties about the end of exposure COHb levels, and whether repeated and/or prolonged exposures caused the infarction. The analysis of 101 cases of lethal poisoning and 158 cases of non-lethal poisoning by Pach et al. (1878; 1979) was used as the basis for derivation of AEGL-3 values. In the group of surviving patients only those were included from which blood for COHb analysis had been obtained within 2 hours from cessation of exposure. The COHb at the end of exposure was calculated by the authors of the report. Analysis revealed that only about 2 % of deceased subjects had COHb levels below 40 %. Of the patients that survived about 16 % had a COHb above 40 %. From this study a threshold for lethal poisoning of about 40 % can be derived. This level is supported by experimental studies performed in healthy human subjects. Studies by Chiodi et al. (1941), Henderson et al. (1921), and Haldane (1895) suggest that a COHb of about 34-56 % does not cause lethal effects in healthy individuals. Further support come from the studies by Kizakevich et al. (1994), Stewart et al. (1970), and Nielsen (1971) that reported headache as the only symptom when subjects were exposed to 20-33 % COHb. A level of 40 % COHb was used as the basis for AEGL-3 derivation. This point of departure is supported by studies in animals reporting minimum lethal COHb levels in rats and mice of about 50-70 % (E.I. du Pont de Nemours and Co., 1981; Rose et al., 1970). A mathematical model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a COHb of 40 % at the end of exposure periods of 10 and 30 minutes and 1, 4 and 8 hours. A total uncertainty factor of 3 was used. A total uncertainty factor of 3 for intraspecies variability was considered adequate based on supporting evidence for susceptible subpopulations: 1) Exposure to the derived AEGL-3 concentrations will result in COHb values of about 14-17 % in adults, which, based on case reports, was considered to protect heart patients against CO-induced myocardial infarction. It should be noted, however, that a clear threshold for this endpoint cannot be defined because myocardial infarction might be triggered at lower COHb in hypersusceptible individuals. 2) This COHb level was considered protective of lethal effects in the unborn, because in the case studies available, stillbirths were found only after measured maternal COHb of about 22-25 % or higher (Caravati et al., 1988; Koren et al., 1991) and the level was supported by animal studies.

The AEGL values are listed in the table below.

SUMMARY TABLE OF AEGL VALUES FOR CARBON MONOXIDE						
Classification	**10-Minute**	**30-Minute**	**1-Hour**	**4-Hour**	**8-Hour**	**Endpoint (Reference)**
AEGL-1 (Nondisabling)	N.R.[a]	N.R.	N.R.	N.R.	N.R.	-
AEGL-2 [b] (Disabling)	420 ppm (480 mg/m³)	150 ppm (170 mg/m³)	83 ppm (95 mg/m³)	33 ppm (38 mg/m³)	27 ppm (31 mg/m³)	Cardiac effects in humans with coronary artery disease (Allred et al., 1989; 1991)
AEGL-3 [c] (Lethal)	1700 ppm (1900 mg/m³)	600 ppm (690 mg/m³)	330 ppm (380 mg/m³)	150 ppm (170 mg/m³)	130 ppm (150 mg/m³)	Lethal poisoning was associated with a COHb ≥40 % in 98 % of cases (Pach et al., 1978; 1979); no severe or life-threatening effects in healthy humans at COHb of 34-56 % (Chiodi et al., 1941; Henderson et al., 1921; Haldane, 1895)

[a] N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population.

[b] It was estimated that exposure to the AEGL-2 concentration-time combinations result in COHb levels of 5.3-5.6 % in newborns, 4.9-5.2 % in 5-year-old children, 4.0 % in adults and 6.2-11.5 % in adult smokers.

[C] It was estimated that exposure to the AEGL-3 concentration-time combinations result in COHb levels of 19.5-20.1 % in newborns, 18.1-18-7 % in 5-year-old children, 13.8-17.2 % in adults and 16.1-23.0 % in adult smokers.

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1. INTRODUCTION

Carbon monoxide (CO) is a tasteless, odorless and colorless gaseous substance (WHO, 1999a). CO is produced by both natural and anthropogenic processes. The main source of CO production is the combustion of fuels. The burning of any carbonaceous fuel produces CO and carbon dioxide as the primary products. The production of carbon dioxide predominates when the air or oxygen supply is in excess of the stoichiometric needs for complete combustion. If burning occurs under fuel-rich conditions, with less air or oxygen than is needed, CO will be produced in abundance (WHO, 1999a). Emission sources include gasoline- and diesel-powered motor vehicles, stationary combustion equipment, such as heating and power generating plants, industrial processes, such as blast furnace operation in steel industry, indoor sources, such as gas ovens, unvented kerosene and gas space heaters and coal and wood stoves, as well as wildfires and tobacco smoking. Exposure at the workplace occurs in blast furnace operations in the steel industry and when gasoline- or propane-powered forklifts, chain-saws or other machines are used in confined spaces, such as companies, tunnels and mines. Low concentrations are produced in the atmosphere by reactions of hydroxyl radicals with methane and other hydrocarbons as well as by the reactions of alkenes with ozone.

In addition to exogenous sources, humans are also exposed to small amounts of CO produced endogenously. In the process of natural degradation of hemoglobin to bile pigments, oxidation of the tetrapyrrol ring of heme leads to opening of the ring and formation of biliverdin and CO (WHO, 1999a). The endogenous CO formation leads to a background carboxyhemoglobin concentration in blood (COHb) of about 0.5 to 0.8 % (NIOSH, 1972).

Increased destruction of red blood cells, e.g. caused by hematomas, blood transfusion or intravascular hemolysis, and accelerated breakdown of other heme proteins will lead to increased production of CO. In patients with hemolytic anemia, the CO production rate was 2-8 times higher and blood COHb was 2-3 times higher than in healthy individuals (Coburn et al., 1966).

Smokers are exposed to considerable CO concentrations leading to an average COHb of 4 %, with a usual range of 3-8 % (Radford and Drizd, 1982).

Exposure to CO can also be caused indirectly by exposure to certain halomethanes, particularly dichloromethane (synonym: methylene chloride), because these solvents are at least partly metabolized oxidatively to CO by cytochrome P450 (Gargas et al., 1986; see ATSDR, 1998 for review).

Environmental exposure to CO can occur while traveling in motor vehicles, working, visiting urban locations associated with combustion sources, or cooking and heating with domestic gas, charcoal or wood fires, as well as by environmental tobacco smoke. WHO (1999a) summarized environmental concentrations as follows: CO concentrations in ambient air monitored from fixed-site stations are generally below 9 ppm (8-hour average). However, short-term peak concentrations up to 50 ppm are reported on heavily traveled roads. The CO levels in homes are usually lower than 9 ppm; however, the peak value in homes could be up to 18 ppm with gas stoves, 30 ppm with wood combustion and 7 ppm with kerosene heaters. The CO concentrations inside motor vehicles are generally around 9-25 ppm and occasionally over 35 ppm. Similar exposure levels were reported by EPA (2000).

335 **TABLE 1: CHEMICAL AND PHYSICAL DATA**

Parameter	Value	Reference
Molecular formula	CO	WHO, 1999a
Molecular weight	28.01	WHO, 1999a
CAS Registry Number	630-08-0	WHO, 1999a
Physical state	gaseous	WHO, 1999a
Color	colorless	WHO, 1999a
Synonyms	none	
Density	1.250 g/l at 0 °C 1.145 g/l at 25 °C	WHO, 1999a
Melting point	-199 °C	WHO, 1999a
Boiling point	-191.5 °C	WHO, 1999a
Solubility	35.4 ml/l at 0 °C 21.4 ml/l at 25 °C	WHO, 1999a
Odor	odorless	WHO, 1999a
Explosive limits in air	12.5 % (LEL) to 74.2 % (UEL)	WHO, 1999a
Conversion factors	1 ppm = 1.145 mg/m³ 1 mg/m³ = 0.873 ppm	WHO, 1999a

2. HUMAN TOXICITY DATA

Based on older literature the COHb in the blood has been correlated with symptoms in healthy adults, shown in the left half of Table 2 (WHO, 1999a). Very similar tables are found in different publications (e.g. AIHA, 1999; Winter and Miller, 1976, Holmes, 1985, Stewart, 1975). However, with respect to both lethal and nonlethal effects of CO, susceptible subpopulations have been identified and effects on these are depicted in the right half of Table 2 for comparison (see subsequent sections for references). The unborn fetus and adults with coronary artery disease are considerably more susceptible for lethal effects of CO than healthy adults. For nonlethal effects of CO, subjects with coronary artery disease (increased frequency of arrhythmias and reduced time to onset of angina and to changes in the electrocardiogram and children (syncopes, long-lasting neurotoxic effects) constitute susceptible subpopulations.

TABLE 2: SYMPTOMS ASSOCIATED WITH COHb IN HEALTHY ADULT HUMANS AND SUSCEPTIBLE SUBPOPULATIONS

Healthy Adults; adopted from WHO, 1999a		Susceptible Subpopulations	
COHb (%)	**Symptoms**	**COHb (%)**	**Symptoms**
≈1	physiologic background concentration	2	during physical exertion reduced time to onset of angina and electrocardiogram signs of myocardial ischemia in subjects with coronary artery disease
3-8	background concentration in smokers	5-6	increase in cardiac arrhythmias in subjects with coronary artery disease
		7	headache, nausea in children
10	no appreciable effect, except shortness of breath on vigorous exertion, possible tightness across the forehead, dilation of cutaneous blood vessels	13	cognitive development deficits in children
		15	myocardial infarction in subjects with coronary artery disease
20	shortness of breath on moderate exertion, occasional headache with throbbing in temples	25	syncopes in children
		25	stillbirths
30	decided headache, irritable, easily fatigued, judgment disturbed, possible dizziness, dimness of vision		
40-50	headache, confusion, collapse, fainting on exertion		
60-70	unconsciousness, intermittent convulsion, respiratory failure, death if exposure is long continued		
80	rapidly fatal		

2.1. Acute Lethality

Mortality from CO poisoning is high: for England and Wales, 1365 deaths due to CO exposure were reported in 1985. In the USA, more than 3800 people annually die from accidental or intentional CO exposure (WHO, 1999a).

Immediate death from CO is most likely caused by effects on the heart, because the myocardial tissue is most sensitive to hypoxic effects of CO. Severe poisoning results in marked hypotension and lethal arrhythmias, which have been considered responsible for a large number of pre-hospital deaths. Rhythm disturbances include sinus tachycardia, atrial flutter and fibrillation, premature ventricular contractions, ventricular tachycardia and fibrillation (WHO, 1999a).

The susceptible subpopulations for lethal effects are subjects with coronary artery disease and the unborn fetus (see Section 2.3). The review on death causes by Balraj (1984) shows an association between coronary artery disease and relatively low COHb. A number of case studies is presented in which CO exposure contributed to myocardial infarction (all cases of infarction are presented in this section irrespective of whether the patients were rescued from death by intensive medical care or not).

The British Standards Institution (BSI, 1989) has published the following concentration-time combinations as lethal exposures to CO (used for hazard estimation in fires): 40000 ppm x 2 minutes, 16000 ppm x 5 minutes, 8000 ppm x 10 minutes, 3000 ppm x 30 minutes and 1500 ppm x 60 minutes. The International Standard Organization has published lethal exposure concentrations of 12000-16000 ppm for 5 minutes and 2500-4000 ppm for 30 minutes (for an adult engaged in light activity) (ISO, 1989). From the documents it was concluded that the published values are for normal, healthy adults and that the values were based on animal data (especially monkeys; Purser and Berrill, 1983); the documents did not discuss the issue of subpopulations at higher risk for lethal effects.

2.1.1 Case Studies

Pach et al. (1978; 1979) reviewed a cases of carbon monoxide in the Toxicological Clinic, Cracow, Poland in the years 1975-1976. Excluded from this study were mixed intoxications, e.g., by CO and medicaments. Group A were 101 persons (60 men and 41 women, mean age 48 ±15 years) that had died from CO poisoning before arrival at the clinic. Measurement of COHb and autopsy was done on these subjects. Group B comprised 220 subjects (95 men and 125 women, mean age 38 ±18 years) that were treated for CO poisoning. COHb was determined upon arrival at the clinic. Patients for which the time between the end of exposure and blood drawing at the clinic was longer than 120 minutes (N = 62) were excluded from further analysis. For the patients, the COHb at the end of exposure was recalculated. Mean COHb values for Groups A and B were 62 ±10 % and 28 ±14 %, respectively. In Group A, the percentages of subjects with COHb between 30-40, 40-50, 50-60, 60-70, 70-80 and 80-90 % were 2, 6, 26, 44, 21 and 2, respectively, while 3, 25, 32, 24, 12, 3, 0.6 and 0.6 % of the patients in the corrected Group B had COHb values between 0-10,10-20, 20-30, 30-40, 40-50, 50-60, 60-70 and 70-80 %, respectively. Within each group no correlation between COHb and either sex, blood alcohol above 0.1% or poisoning circumstances (accidental or suicidal) were found. Group A showed a higher percentage (34 %) of subjects that were 60 years or older than Group B (13 %), while Group B had a higher percentage of subjects younger than 30.

Grace and Platt (1981) reported two cases of myocardial infarction due to CO poisoning. In the first case, a 67-year-old man was exposed to increased CO concentrations for about a few weeks in his home due to a rusted-out flue of a gas-furnace. The man presented to the emergency room after three days of persistent light-headedness with vertigo, brief stabbing anterior chest pain that worsened with deep inspiration, a dry cough, chills and a mild headache. His wife experienced similar malaise and dizziness that had been resolving over the past week. At the hospital, his symptoms were explained with a diagnosis of viral syndrome, hypokalemia of unclear origin and diabetes mellitus with diabetic peripheral and autonomic neuropathy. Ten days after discharge he was seen in the emergency room with true vertigo, palpitations and nausea, but was sent home to be followed up as an outpatient. Four days later he returned to the emergency room after development of rectal urgency and an explosive incontinent diarrheal stool, followed by a severe crushing anterior chest pain. With the pain he collapsed on the floor. The electrocardiogram showed an acute myocardial infarction. His COHb (measured on arterial blood gases) was 15.6 %, the level of the patient‘s wife was 18.1 %. The patient survived and recovered completely.

In the second case, a 69-year-old man came to the emergency room after awakening two days earlier with confusion, nausea and vomiting. He then passed out and awoke the next day in the bathroom. He crawled to the living room, where he again passed out for an undetermined amount of time, awoke to open his door for fresh air, and then went to bed. He later experienced auditory and visual hallucinations and phoned his neighbor for help. An acute inferior myocardial infarction with secondary mild congestive heart failure and chronic obstructive pulmonary disease was diagnosed. During his hospitalization, his sister and daughter-in-law spent a night in his mobile home. They arrived at the emergency room early the next morning with throbbing headaches, vomiting and vertigo. Their COHb values were 28 and 32 %. A faulty gas water heater had caused CO exposure. The patient survived and recovered completely.

Atkins and Baker (1985) described two fatal cases of workers with severe atherosclerotic coronary artery disease. The first worker (age not stated) was a shipping employee in a plant that reconditioned steel dyes. A gas-fired furnace was used for tempering the dyes, but also for heating the plant. One day the worker was found unconscious and resuscitation efforts at a nearby hospital were unsuccessful. Autopsy showed a severe two-vessel coronary artery disease and old scarring, and a COHb of 30 %. Four other workers of the plant complaining of nausea were seen in the emergency room, but COHb was not obtained. The second worker (age not stated) was operating a bale press in a used-clothing company. As well as gas- and oil-fired heaters, there were a number of propane-fueled forklifts used to transport bales of clothing and ventilation was poor. Resuscitation was unsuccessful after his collapse. Autopsy revealed three-vessel coronary artery disease and global subendocardial ischemia. Two blood samples showed COHb of 24.1 and 21.5 %. Five other workers from the same company were also seen, complaining of light nausea, lightheadedness and headache. One was hospitalized with a COHb of 35 %; the others had levels from 4.1 to 12.8 %. CO measurement was performed in the company the next day and revealed concentrations of 135-310 ppm. Concentrations were highest near forklifts (250-310 ppm) and near the bale press (120-230 ppm), which was where the patient had been working at the time of his death.

Ebisuno et al. (1972) reported a case of myocardial infarction after acute CO poisoning in a healthy young man. A 28-year-old male ironworker was admitted to the emergency room complaining of precordial pain. Two hours before admission the patient had been exposed accidentally to CO for about one hour while working at a blast furnace. After the exposure he experienced a sense of fullness of the head and precordial pain following transient unconsciousness. Blood samples two hours after the exposure contained COHb of 21 %. The electrocardiogram was interpreted as an acute anterior myocardial infarction. The coronary arteriogram one month after onset of infarction showed no significant narrowing on both left and right

coronary arteries. The left ventriculogram showed a giant aneurysm in the apical portion. At operation from the ventricular aneurysmectomy, a massive transmural myocardial necrosis was observed. After surgical treatment, the patient is free of symptoms.

Marius-Nunez (1990) reported the case of a 46-year-old man, who suffered an acute myocardial infarction after CO exposure. He was found unconscious in a doorway of a burning apartment. Artificial respiration was initiated until arrival at the emergency room. The electrocardiogram showed sings of myocardial infarction, which was confirmed by high levels of cardiac enzymes in the patient‘s serum. Blood gas analysis revealed a COHb of 52.2 %. After 3 hours treatment with 100 % oxygen, the patient became alert and oriented, COHb was 23 %. After 7 hours, he was extubated and a COHb of 13.4 % was measured. The patient‘s medical profile was negative for coronary heart disease risk factors, such as smoking, hypertension, diabetes mellitus or coronary artery disease. A coronary angiogram performed one week later failed to reveal evidence of coronary obstructive lesions.

Balraj (1984) reviewed all deaths that were certified by the Cuyahoga County Coroner‘s Office from the years 1958-1980, wherein asphyxia by CO was the primary caused of death and a natural disease was the „other“ diagnosis or vice versa. During the 23-year period, 38 deaths were certified. These were divided into two groups: Group 1 consisted of 28 cases where all diagnosis including the abnormal COHb was documented by complete postmortem examination. Group 2 consisted of 10 cases where the diagnosis of the "other" condition was based on review of medical records, including results of coronary angiogram, serum enzymes, and clinical history; autopsy was not performed on these 10 cases. The Group 3 served for comparison and comprised all deaths that occurred in individuals 35 to 86 years of age in whom the COHb was 60 % and more (n = 100). A complete autopsy had been performed in each of these cases.

Of the 28 cases in Group 1, the primary cause of death was asphyxia by CO in 21 cases. The "other" condition in 19 of these cases was atherosclerotic coronary artery disease. Of these, 8 persons had hypertensive cardiovascular disease and 2 had pulmonary emphysema in addition. In the remaining 7 cases of this group, the primary cause of death was atherosclerotic coronary artery disease and the "other" condition was asphyxia by CO. In Group 2 atherosclerotic coronary artery disease was the primary cause of death and asphyxia by CO was the "other" condition in 3 cases. In the remaining 7 cases asphyxia by CO was the primary cause of death and in all but one of these cases, the "other" condition was atherosclerotic coronary artery disease, two of the individuals had hypertensive cardiovascular disease in addition. The results are presented in Table 3.

TABLE 3: INCIDENCE OF ATHEROSCLEROTIC CORONARY ARTERY DISEASE AND COHb IN FATALITIES THAT INVOLVED CO EXPOSURE; adopted from Balraj, 1984

		Number of cases		
		Group 1	**Group 2**	**Group 3**
Total		28	10	100
Age (years)	30-40	1	0	22
	41-50	1	0	31
	51-60	7	2	28
	61-70	10	4	10
	71-80	5	2	6
	81-90	4	2	3
COHb (%)	10-30	14	5	0
	40-50	4	3	0
	60 and more	0	0	100
Delayed deaths		10	2	0
Coronary atherosclerosis	mild	2	unknown	89
	moderate	2	unknown	5
	severe	24	5	6
Myocardial infarct	recent	1	0	0
	old	4	1	2
Heart weight (g)	415 and more	20	unknown	13

2.2. Nonlethal Toxicity

Nonlethal effects of CO on humans have been reported in experimental studies in both healthy individuals and in patients with coronary artery disease (see Section 2.2.1). Case studies (see Section 2.2.2) are presented for children and adults and identify children as another susceptible subgroup for nonlethal CO effects.

2.2.1 Experimental Studies

2.2.1.1 Subjects with Coronary Disease

A large number of studies investigated the effects of low CO exposure (COHb <10 %) on healthy individuals and high-risk groups. These experiments have been reviewed extensively by WHO (1999a) and EPA (2000). In healthy individuals, symptoms, such as decreases in work capacity and decrements of neurobehavioral function, start at COHb of 5 % (WHO, 1999a; EPA, 2000; Hazucha, 2000). With respect

to high-risk groups, studies evaluating ST-segment changes in the electrocardiogram and cardiac arrhythmogenic effects in patients with coronary artery disease will be presented here, because these gave the most consistent results and also were considered most relevant for AEGL derivation (for review see WHO 1999a; EPA, 2000).

Caracteristic points of an electrocardiogramm are the P wave, reflecting atrial depolarization, the QRS-complex, representing the ventricular muscle depolarization, and the T-wave, reflecting ventricular muscle repolarization. In the normal electrocardiogramm, the ST-segment is isoelectric, resting at the same potential as the interval between the T-wave and the next P wave. Horizontal depression or a downsloping ST-segment merging into the T-wave occurs as a result of ischemia, ventricular strain, changes in the pattern of ventricular depolarization or drug effects. In chronic ischemic heart disease, there may be moderate degrees of horizontal ST-segment depression or a downward sloping ST-segment, flattening or inversion of T-waves and prominent U-waves. It is difficult to define an abnormal ST-segment depression in precise quantitative terms. However, a myocardia ischemia has to be considered if the beginning of the ST-segment is more than 0.5 mm (corresponding to 0.05 mV) below the isoelectric line and there is an associated T-wave abnormality (Wilson et al., 1991).

Allred et al. (1989a; b; 1991) conducted a multicenter study of effects of low COHb on 63 individuals with coronary artery disease. Male subjects aged 41-75 (mean = 62.1 years) with stable exertional angina pectoris (diagnosis established for >3 months; no at rest symptoms) and a positive stress test (measured by a greater than 1-mm change in the ST-segment of the electrocardiogram and occurrence of angina symptoms), were studied in three different test centers using standardized test protocols. Only patients showing reproducible effects before and after a test stay in the exposure chamber on the qualifying visit were included. On the subsequent exposure days, the stress test was repeated before the exposure and if the result was not reproducible compared to the qualifying visit, the visit was repeated on another date and at the second failure in the pretest the subject was dropped from the study. Further evidence that these subjects had coronary artery disease was provided by the presence of at least one of the following criteria: angiographic evidence of narrowing (~70 %) of at least one coronary artery, documented prior myocardial infarction or a positive stress thallium test demonstrating an unequivocal perfusion defect.

All patients were tested three times on separate days in a double-blind fashion. On each of the 3 exposure days, the subject performed a symptom-limited exercise test on a treadmill (pretest), he was then exposed for 50-70 minutes randomly to air and to CO (subjects were exposed to CO concentrations that were experimentally determined to produce end-exposure COHb of 2.2 % or 4.4 %; these COHb values were 10 % higher than the targeted concentrations to compensate for the CO loss during exercise) and afterwards he performed a second symptom-limited exercise test. The mean exposure levels and ranges for the test environment were clean air (0 ppm), 117 ppm (range 42-202 ppm) for COHb of 2 % and 253 ppm (range 143-357 ppm) for COHb of 4 %. Gas chromatographic measurements of COHb were performed 1 minute after the pretest, after 30 and 40 minutes into exposure, at the end of exposure and 1 minute after the second stress test and revealed postexercise COHb of 2.0±0.1 and 3.9±0.1 %, respectively. The time to onset of angina and the time to 1-mm ST-segment change were determined for each test. The percent changes following exposure at both 2 % and 4 % COHb were then compared with the same subject's response to the randomized exposure to room air.

When potential exacerbation of the exercise-induced ischemia by exposure to CO was tested using the objective measure of time to 1-mm ST-segment change, exposure to CO levels producing COHb of 2 % resulted in a overall statistically significant 5.1 % decrease in the time to attain this level of ischemia. For individual centers, results were significant in one, borderline significant in one and nonsignificant in one

center. At 4 % COHb, the decrease in time to the ST criterion was 12.1% (statistically significant for all patients, the effect was found in 49/62 subjects) relative to the air-day results. Significant effects were found in all three test centers. The maximal amplitude of the ST-segment change was also significantly affected by the carbon monoxide exposures: at 2 % COHb the maximal increase was 11 % and at 4 % COHb the increase was 17 % relative to the air day.

At 2 % COHb, the time to angina was reduced by 4.2 % in all patients (effects were significant in two test centers and nonsignificant in one center). At 4 % COHb, the time was reduced by 7.1 % in all patients (effects were significant in one, borderline significant in one and nonsignificant in one center). The two endpoints (time to angina and time to ST change) were also significantly correlated.

Only at 4 % COHb a significant reduction in the total exercise time and in the heart rate-blood pressure product was found (this double product provides a clinical index of the work of the heart and myocardial oxygen consumption).

A number of other studies also evaluated the same endpoints. A reduced time to onset of exercise-induced chest pain was reported at COHb of 2.5-3.0 % (Aronow et al., 1972), 3 % (Kleinman et al., 1989), 2.9 % and 4.5 % (Anderson et al., 1973) and at 3.9 % (Kleinman et al., 1998). No significant depression of the ST-segment was found at COHb of 3.8 % (Sheps et al., 1987) and 3.9 % (Kleinman et al., 1998). WHO (1999a) has tried to explain the differences between these studies by differences in experimental methodology and analysis of data and by differences in subject populations and sample size.

Sheps et al. (1990; 1991) assessed the effect of CO exposure on ventricular arrhythmias. 41 subjects with established coronary artery disease (36 men and 5 women) with a mean age of 62.8±1.1 years were analyzed. Patients were categorized based on arrhythmia frequency on the training day before, during and 6 hours after exercise: 10 had no arrhythmias (0-2 ventricular premature depolarizations (VPD)/h), 11 had low-level arrhythmias (3-50 VPD/h), 11 had intermediate-level arrhythmias (51-200 VPD/h) and 9 had high-level arrhythmias (>200 VPD/h). The protocol was performed over 4 consecutive days. Day 1 was the familiarization session and instructions were given how to use the 24-hour ambulatory electrocardiogram recorder; a symptom-limited maximal bicycle exercise test was done. Days 2 to 4 were exposure days with either pure room air or CO (100 or 200 ppm) administered in a randomized double-blind fashion. COHb measurements were performed before exposure, after 30 and 60 minutes into the exposure, at the end of the exposure and before and after exercise using an IL-282 CO-oximeter. Exposures were stopped when the target levels of 4 or 6 % COHb was reached. Exposure durations were 94.2 ± 4.2 (SE) minutes (range 40 to 170 min) for the 4 % level and 82.3 ± 2.9 (SE) minutes (range 39 to 135 min) for the 6 % level. On all three test days, the mean pre-exposure COHb was 1.8 %. The post-exposure and post-exercise COHb measured were 1.46 and 1.36 % for air exposure, 4.01 and 3.93 % for the 4-% group and 5.91 and 5.02 % for the 6-% group. Comparisons of arrhythmia data were done at COHb of 1.41, 3.71 and 5.33 %, respectively.

During the exposure period, the mean number of single VPD/h on the room air day was significantly higher than on the 4 % COHb day, while no significant difference in the mean number of VPD/h was noted between room air and 6 % COHb exposure. When the baseline level of VPD frequency was controlled for by calculating the difference between the VPD frequency during exposure and the VPD frequency before exposure, there was no significant difference between the room air and 4 % COHb exposure.

During exercise period, the frequency of single VPD/h was greater in the 6-% day than on room-air day (167±38 vs. 127±28 VPD/h; p=0.03). This effect was still significant, when the baseline VPD level was controlled for (117±34 vs. 74±26, p=0.04). For this analysis, data from subjects in the low, medium and high VPD frequency groups were pooled. The difference remained significant when all subjects, including those

categorized in the "no arrhythmia" group were included in the analysis. The VPD frequency was not significantly increased at 4 % COHb.

The initial findings (essentially negative) of this study in 10 patients with ischemic heart disease and no ectopy during baseline monitoring were also published separately (Hinderliter et al., 1989).

Dahms et al. (1993) studied 28 men and 5 women with documented coronary artery disease and a minimum of 30 ventricular ectopic beats per hour over a 20-h period studied. On three testing days, the subjects were exposed in a randomized double-blind fashion to either room air or sufficient CO to elevate their COHb to 3 or 5 % in 1 hour. The mean exposure concentrations during this hour were 159±25 ppm and 292±31 ppm, respectively. This was followed by a maintenance exposure to mean concentrations of 19.3 and 31 ppm, respectively, for an additional 90 minutes, which included the exercise test (after 60 minutes of equilibrium exposure) and immediate postexercise phase. The subjects then left the laboratory and resumed their normal daily activity to determine changes in ventricular ectopic beats after CO exposure. To this end, continuous 20-h ambulatory electrocardiograms were obtained with the recorder placed on the patients 2 hours before CO exposure. There was no significant change in the frequency of single ventricular ectopic beats at rest from 115±28 (in room air) to 121±31 at 3 % and 94±23 at 5 % COHb. Exercise itself increased the frequency of ventricular ectopic beats (from a baseline of 116 to 206 during exercise and 375 during exercise recovery for the room air exposure), but there was no additional effect of CO exposure. Analysis of the data based on grouping of the subjects by the severity of disease (ventricular ectopic beat frequency, ejection fraction, presence of exercise-induced ischemia) indicated no proarrhythmic effect of CO.

2.2.1.2 Healthy Adults

Chiodi et al. (1941) exposed each of 4 male subjects (aged 21-33 years) repeatedly to CO concentrations of 0.15-0.35 % (1500-3500 ppm) for 70 minutes or longer. During 1 hour before exposure, basal oxygen consumption, ventilation, pulse rate and blood pressure were recorded and arterial blood for pH determination was obtained. The subject, remaining in rest during exposure, then breathed CO-containing air from a 600-liter gasometer. The measurement of the above mentioned parameters was continued during exposure. In one set of experiments the test subjects reached COHb between 3.4 and 10.4 % (8 experiments in total with the following COHb at the end of exposure: 4.6, 6.3, 7.2, 9.2 and 9.8 % in subject H.C. and 3.4, 9.5 and 10.4 % in subject F.C.). In another set of experiments , three subjects reached COHb of 27-52% at the end of exposure (in 11 of a total of 22 experiments COHb between 40 and 52 % were measured). The following COHb values were measured at the end of exposure: 0, 31, 32, 32, 33, 39, 41, 42, 43, 45 and 52 % in subject H.C., 0, 27, 35, 41, 43 and 48 % in subject F.C. and 0, 0, 41, 42 and 44 % in subject S.H. No statement was made on whether any symptoms were observed. The cardiac output increased 20-50 % at COHb >40 %, while the changes were negligible at COHb of <30 %. No effects on the other parameters measured were found.

Henderson et al. (1921) exposed volunteers in a 6.4-m^3 gas-tight, steel-walled exposure chamber. CO was generated by dripping formic acid into strong sulfuric acid. A defined volume of CO was led into the chamber and mixed with an electric fan. Analysis of the exposure concentration in the chamber was done using the iodine pentoxide method. Subjects (9 men and 1 woman; number of subjects at each concentration given in brackets) were exposed for 1 hour at 200 ppm (2), 300 ppm (3), 400 ppm (11), 500 ppm (1), 600 ppm (9), 800 ppm (4), 900 ppm (1) or 1000 ppm (1) CO. Blood samples were taken before exposure, at 30 minutes into the exposure, at the end of the exposure (60 minutes) and once or twice during the next three hours after

end of the exposure. The COHb was determined using the carmine method. Directly after leaving the exposure chamber, subjects breathed several times into a bladder bag and CO was determined in the exhaled air using the iodine pentoxide method. CO concentrations in alveolar air after 60 minutes was 130-136 ppm at an exposure concentration of 400 ppm, 120-230 ppm at 600 ppm and 140-230 ppm at 800 ppm. The COHb percentage ranged from 11-12 % at 200 ppm, 10-14 % at 300 ppm, 14-22 % at 400 ppm, 16-26 % at 600 ppm, 26-34 % at 800 ppm, 34 % at 900 ppm and 38 % at 1000 ppm. After exposure to up to 500 ppm for 60 minutes, no symptoms were observed. At 600 ppm, 2/9 subjects reported slight frontal headache. At 800 ppm all subjects reported decided frontal headache during 4-8 hours. At 900 ppm insomnia and irritability occurred in addition to headache. At 1000 ppm, irritability, throbbing frontal headache and at times Cheyne-Stokes breathing were observed. The Romberg test (ability to stand erect with eyes closed) showed a marked loss of equilibrium after a 60-minute exposure to 800 ppm or higher.

Haldane (1895) reported on a series of 11 studies in which the author exposed himself to different CO concentrations for different exposure times. The exposure conditions and effects are summarized in the following Table 4. The subject breathed the CO atmosphere from a mouthpiece. No mentioning of an analytical measurement of the exposure concentrations used was made. At the end or one or more times during the exposure, the exposure was interrupted and the subject walked in the room or ran up a flight of stairs (once or a few times) to investigate the effect of physical exertion at different COHb levels. The COHb was determined colorimetrically by measuring the amounts of carmine solution that had to be added to the diluted blood sample or to an equal dilution of normal, oxygenated blood to adopt the color of a CO-saturated blood dilution. For COHb <70 %, the author found his COHb determinations accurate within a 5 % error. Although the exposure measurement of this study does not meet today‘s standards, the reported COHb values are in fairly well agreement with the values calculated from the given exposure concentration and exposure time using the mathematical model of Coburn, Forster and Kane (see Section 4.3.4) when assuming a resting ventilation rate (see Table 21 in Appendix B).

TABLE 4: EFFECTS OF ACUTE CO EXPOSURE IN A HUMAN SUBJECT; adopted from Haldane, 1895

No.	Exp. conc. (vol. %) [ppm]	Total exposure time (min)	Observations	at time (min) / COHb (%)
1	0.50 [5000]	11.5	no symptoms; hyperpnea after running upstairs	
2	0.39 [3900]	30.5	no symptoms	15 min / 23 %
			slight feeling of palpitation, pulse 102	22 min
			palpitation, respiration 18, pulse 120, feeling abnormal	29 min
			after running upstairs became giddy, much out of breath, palpitations, slightly impaired vision	30.5 min / 39 %
3	0.40 [4000]	24	no symptoms except unusual hyperpnea and giddiness after running upstairs	24 min / 27 %
4	0.36 [3600]	29	-	18 min / 26 %
			on walking throbbing in the head and palpitations, on running giddy, short of breath	29 min / 37 %
5	0.41 [4100]	29	-	15 min / 13 %
			very slight hyperpnea and palpitations	28 min
			after running marked giddiness and impairment of vision and hearing (for 1-2 min)	29 min / 35 %
6	0.12 [1200]	120	-	15 min / 8 %
			slight tendency to palpitations, pulse 96	33 min
			no symptoms	46 min / 18 %
			slight palpitations, sleepy	67 min
			after running (no exposure) distinct dimness of vision and hearing, slight tendency to stagger, abnormal hyperpnea	90 min / 27 %
			slight hyperpnea while sitting	104 min
			distinct hyperpnea, feeling uneasy, dull and abnormal; after running: weak in the legs, markedly impaired vision and hearing, confusion	120 min / 37 %
7	0.21 [2100]	71.5	-	20 min / 17 %
			very slight feeling of fullness, throbbing in the head	34 min
			-	40 min / 39 %
			feeling decidedly abnormal, slight hyperpnea, marked throbbing	43 min
			breathing decidedly deeper, pulse 104	45 min

No.	Exp. conc. (vol. %) [ppm]	Total exposure time (min)	Observations	at time (min) / COHb (%)
			feeling decidedly abnormal, impaired vision, slight feeling of giddiness	54 min
			hyperpnea more distinct, beginning to look pale/yellowish	59 min
			-	61 min / 44.5 %
			feeling worse shortly after any movement in the chair	63 min
			hyperpnea marked, slight confusion of mind	65 min
			vision dim, limbs weak, difficulty in getting up and walking without assistance; at 6 min after exposure stop very unsteady walking, nearly falling, very indistinct vision	71 min / 49 %
8	irregular due to disconnected tubing, 0.43 % for last 10 min	35	hardly able to stand, no walking alone without falling down	35 min, 56 %
9	0.027 [270]	210	-	60 min / 7 %
			-	120 min / 11 %
			-	180 min / 15 %
			no symptoms; after running: very slight unusual shortness of breath and palpitations	210 min / 14 %
10	0.021 [210]	240	-	60 min / 8 %
			-	120 min / 13 %
			-	180 min / 13 %
			no symptoms	240 min / 13 %
11	0.046 [460]	240	-	60 min / 17 %
			-	120 min / 28 %
			-	180 min / 28 %
			no symptoms; after running: unusual hyperpnea, slight palpitations	240 min / 23 %

Stewart et al. (1970) performed 25 inhalation exposure experiments on a total of 18 healthy men (age 24-42). These were exposed sedentary in an exposure chamber at <1, 25, 50, 100, 200, 500 or 1000 ppm for periods of 30 minutes to 24 hours. The chamber atmosphere was monitored continuously by infrared spectroscopy and periodically by gas chromatography. The subjects performed the following psychoneurological tests: hand and foot reaction time in a driving simulator, Crawford collar and pin test, Crawford screw test, hand steadiness test, Flanagan coordination test, othorator visual test, complete audiogram, resting 12-lead electrocardiogram, standard electroencephalogram, visual evoked response and time estimation-hand reaction time test. No subjective symptoms or objective signs of illness were noted

during or in the 24-hour period following exposure to 25 ppm for 8 hours, 50 ppm for 1, 3 or 8 hours, or 100 ppm for 1, 3 or 8 hours. There was no detectable change from control values in the clinical tests. A significant relationship between the Crawford collar and pin test and CO concentration was considered a chance finding by the authors. Of 11 subjects exposed to 200 ppm for 4 hours, 3 subjects reported they had developed a „mild sinus“ headache in the final hour. In the clinical tests, no detectable statistical change from control values was observed. In the first exposure to 500 ppm for 1.8 hours, one of the two subjects reported light-headedness after 20 minutes of exposure, which was believed to be due to his hyperventilation. After 1 hour of exposure, both subjects were aware of a 10 % increase in heart rate with the minimal exertion of walking to the blood port. After 90 minutes of exposure the second subject noted the onset of mild frontal headache. During the second exposure to 500 ppm for 2.3 hours, the same subjects both developed mild frontal headaches after 1 hour of exposure. Minimal exertion caused a transient intensification of the pain. Both headaches remained mild during the first postexposure hour, then they intensified into excruciatingly severe occipitofrontal headaches, reaching a pain peak 3.5 hours after exposure, and persisted for 7 hours. During the third exposure to 500 ppm, the occurrence of mild frontal headaches was noted after 1 hour of exposure. Immediately after exposure, both subjects were placed in a hyperbaric chamber and administered oxygen and the mild headaches were gone within minutes. The mean COHb reached after 2.3-h exposure to 500 ppm was about 25.5%, after 4-h exposure to 200 ppm about 16.0 % and after 8-h exposure to 100 ppm about 12.5 %.

In another experiment (Kizakevich et al., 1994) evaluating cardiovascular responses of exercising individuals, 16 health young men performed a sequence of brief (5 minutes) multi-level treadmill and hand-crank exercises at <2 % COHb and after attaining 5, 10, 15 or 20 % COHb on different days . Non-invasive impedance cardiography was used to estimate cardiac output, stroke volume, heart rate, cardiac contractility and time-to-peak ejection time. The electrocardiogram was used to assess myocardial irritability and ischemia and changes in cardiac rhythm. The results showed that compensatory cardiovascular responses to submaximal upper- and lower-body exercise (e.g., increased heart rate, cardiac contractility, cardiac output) occur after CO exposures. These changes were highly significant for exposures attaining 20% COHb. The authors concluded that healthy young men can perform submaximal exercise without overt impairment of cardiovascular function after CO exposures attaining 20 % COHb.

Nielsen (1971) investigated the effect of CO exposure on thermoregulation. Experiments were performed repeatedly on two subjects. Subject JHB reached COHb levels of 25 % (mean of 8 experiments) and 33 % (4 experiments) and subject PJC reached 30 % (4 experiments). After reaching the desired COHb level, the subjects exercised on a chair-ergometer for 1 hour at a medium to high workload (mean heart rate 120-170 beats per minute). The subjects were not exposed continuously to CO during exercise, but the COHb level was maintained by breathing a calculated volume of CO from an anesthesia bag for 1-1.5 minutes every 15 minutes during exercise. CO exposure led to an increase in the plateau level of the deep body temperature during exercise of 0.3-0.5 °C. The lactic acid concentration was not increased after exercise at air exposure (120 mg/l in JHB and 79 mg/l in PJC), but increased during CO exposures (309-660 mg/l in both subjects). The authors stated neither the absence nor the presence of any symptoms of CO exposure.

720 ### 2.2.2 Case Studies

721 #### 2.2.2.1 Children

722 Klasner et al. (1998) published a retrospective chart review on a mass poisoning at an elementary
723 school. The CO leak was discovered at noon, about 4 hours after school started. Of the 564 people at school,
724 504 were children. Any child who showed evidence or complained of symptoms was sent to a hospital by
725 ambulance or school bus. 177 children (mean age 8.7±1.8 years, range 4-12 years) were taken to one of three
726 hospitals. All children were given 100 % oxygen by face mask in the hospital (the authors stated that only
727 few of these received simple face mask oxygen en route to the hospital). The level of poisoning was assessed
728 according to standardized poison center data sheets (TESS, toxic exposure surveillance sheets) and was
729 recorded as unknown (n=6), no effect (n=16), minor effect (n=124) or moderate effect (n=30). One child, for
730 whom the data sheet classification was that of a major effect, was considered miscoded by the authors because
731 the medical record showed that this child was sent home from the hospital without further treatment.
732 Symptoms were present in 155 children and a mean COHb of 7.0 % (95 %-C.I. 6.6-7.5 %) was measured in
733 a total of 147 children (blood was drawn at the same time oxygen therapy began). The authors estimated that
734 the children were exposed at least 60 minutes (in some cases 90 to 120 minutes) to fresh air prior to obtaining
735 their initial COHb. In the 177 children the following symptoms (number of mentionings) were observed
736 (some children reported more than one symptom): headache (139), nausea (69), dizziness (30), dyspnea (19),
737 vomiting (13), abdominal pain (11), drowsiness (9), other symptoms (0). The authors found a correlation
738 between the total number of symptoms reported and the COHb, such that children with higher COHb were
739 slightly more likely to report more symptoms. The authors did not mention how many of the 60 adults
740 experienced symptoms, but stated that symptomatic adults were taken adult hospital facilities.

741 Crocker and Walker (1985) analyzed 28 patients with CO poisoning that were 14 years old or
742 younger. 25/28 CO exposures were secondary to faulty venting or faulty combustion of gas furnaces, 2/28
743 were secondary to faulty combustion of a gas stove and 1/28 to motor vehicle exhaust. 12 patients had COHb
744 of less than 15 % and were completely asymptomatic. These patients were considered to have nontoxic
745 exposures, and they were not studied further. Of the 16 patients (mean age 7.0±3.8 years, 3 children were
746 younger than 5 years) with COHb of 15 % or higher, 16/16 experienced nausea, 12/16 experienced associated
747 vomiting, 13/14 (no information on 2) complained of headache and 11/16 patients were reported to be
748 lethargic.3/14 patients reported visual problems, such as blurred or double vision. 9/16 reported at least one
749 syncopal episode with an average COHb of 31.6 % and a threshold level of 24.3 %. Every patient with a
750 COHb of 24.5 % or higher experienced syncope. Lethargy was reported in 11/16 patients at a mean COHb
751 of 25.9 % and a threshold of 18.6 %. Symptoms and COHb are presented in Table 5. All patients were
752 successfully treated with hyperbaric oxygen. The authors provided the COHb measured after hospital
753 admission, but did not give any information on the delay between the end of exposure and measurement and
754 on (probable) oxygen administration before hospital admission, e.g. oxygen by face mask during ambulance
755 transport.
756 Patient follow-up utilizing parental telephone interview and medical record review 3-12 months after
757 the poisoning was used to screen for neurologic sequelae. Three patients had developed problems: a 12-year-
758 old boy with 36.1 % COHb had developed chronic headaches, a 6-year-old girl with 36.9 % COHb had
759 developed memory difficulties after suffering a major motor seizure during the poisoning episode and an 8-
760 year-old girl with 24.5 % COHb developed poor school performance, which were attributed to her long-
761 standing poor reading ability; psychological evaluation revealed no cognitive deficits. The former two
762 children reported complete resolution of their symptoms by 9 months post exposure.

TABLE 5: SYMPTOM THRESHOLD VALUES FOR PEDIATRIC CO TOXICITY; adopted from Crocker and Walker, 1985

Symptom	Threshold COHb (%)	Average COHb (%)	Percentage of patients * (%)
none	<15	<15	100
Nausea	16.7	27.1	100
Vomiting	19.8	29.4	78.6
Headache	16.7	28.3	91.6
Lethargy	18.6	25.9	78.6
Visual symptoms	24.5	32.5	25.0
Syncope	24.5	31.6	64.3
Seizures	36.9	36.9	6.3

* The percentage of patients showing the respective symptom refers to the 16 patients with COHb >15 %, except for asymptomatic patients ("none"), which refers to the 12 patients with COHb <15 %.

Klees et al. (1985) investigated the neurotoxic sequelae of CO poisoning in children that had been brought to the emergency department of St. Pierre Hospital, Brussels following CO poisoning (irrespective of whether they were subsequently hospitalized or not). Cases were only studied when follow-up was possible: in a short-term follow-up of 20 children that were submitted to psychological tests at the time of the intoxication and who were re-examined again about 3 months later, and in a long-term follow-up of 14 children that were re-examined between 2-11 years after the intoxication. The authors listed the COHb measured after hospital admission, but did not give any information on the delay between the end of exposure and measurement neither did they indicate a (probable) oxygen administration before hospital admission, e.g. oxygen by face mask during ambulance transport.

In the long-term follow-up, 6 of the 14 children (age 2.8-12.1 years at the time of intoxication; mean age 7.8 years) exhibited serious disorders (spatial organization problems, constructive apraxia, deterioration of lexical activity, as well as spelling and arithmetic); two of them had a previous history of psychological difficulties, but displayed additional difficulties after the poisoning. COHb between 13 and 32 % (mean 21 %) have been reported for 4/6 children (no data on the other 2 children were available). Seven of the 14 children (age >6 years, except for one 3.5-year old child; mean age 9.8 years) exhibited slight impairment of visual memory and concentration; these children had COHb between 16 and 26 % (mean 22 %). One child of this group did not display any sequelae.

In the short-term follow-up, the authors grouped the 20 children according to age. In children below 3 years of age (n=6, 2.0-2.9 years), medium intoxications (n=5, symptoms included loss of consciousness, but no coma; reported COHb 16-27 %) did not produce manifest sequelae except for a momentary standstill in the child‘s progress of about 2 months, but their negative behavior was found to be amplified (children were more nervous, more irritable, more anxious); however it was not possible to determine if these behavioral disturbances were a direct effect of the CO intoxication of whether they were due to neurophysiological causes or to the stressful psychological conditions surrounding the intoxication. In one case of severe intoxication (symptoms included coma; COHb 37 %) developmental level regression (motricity and language), violent anger and nervosity were observed.

In children from 4 to 9 years old (n=8), the intoxication did not alter the intellectual capacities, but in 6 cases (reported COHb of 4, 6, 25 and 27 %; missing data for two children) the mnestic and instrumental

aspects of the cognitive development were modified (the other two were difficult to evaluate due to intellectual retardation and language retardation). Visuo-spatial perceptions and topographical memory were particularly perturbed, as was auditory memory.

In children over 10 years of age (n=10), difficulty in perceiving and organizing the material to be memorized either auditory or visually was found in the three children less than 12 years (COHb of 26, 27 and 36 %). With the three children over 14 years, one case (30 % COHb) of serious balance impairment was observed and only some slowness and instability with the other two (COHb of 26 and 30 %).

Meert et al. (1998) evaluated clinical characteristics and neurologic outcome of all children with CO poisoning admitted to the Children's Hospital of Michigan, Detroit between January 1987 and December 1996. Exposures were categorized as 1) severely toxic when COHb was >25 %, 2) toxic when COHb was between 10.1 and 25 %, 3) suspected toxic when COHb was ≤10 % with acute neurologic manifestations, or 4) nontoxic when COHb was ≤10 % without acute neurologic manifestations. Of 106 cases (median age 3.5 years, range 0.1 to 14.9 years) were investigated, 37 with severe toxic, 37 with toxic, 13 with suspected toxic and 19 with nontoxic exposures. The most common presenting symptoms included altered level of consciousness (lethargy, unresponsiveness), metabolic acidosis, tachycardia and hypertension. All exposures were accidental, occurring as a result of smoke inhalation during house fires in 95, motor vehicle exhaust in 6 and defective heating system in 5 cases. Forty-three children had an associated cutaneous burn injury. All patients received normobaric oxygen for a median period of 5.5 hours (range 0.6 to 44 hours). Fifteen patients died, 8 from hypoxic-ischemic encephalopathy after cardiopulmonary arrest at presentation, 3 from massive burn injury and 4 from late complications of burn injury. Nine survivors suffered neurologic sequelae: 1) 6 had persistent deficits, such as cognitive and motor deficits or developmental delay (of these 4 had presented with respiratory or cardiorespiratory arrest with COHb between 31.5 and 45 % and the other two; COHb 14.8 and 5.9 %; had severe burns with 40 and 75 %, respectively, of the body surface area affected) and 2) 3 patients developed delayed neurologic syndromes (2 children; COHb 33.3 and 34.8 %; with transient tremors, cognitive deficits and hallucinations starting after 4 and 14 days, that resolved spontaneously after about 2 months, and 1 child; COHb 3.1 %; that developed deficits in cognitive and interpersonal skills after 51 days and in whom brain imaging revealed bilateral occipital lobe infarcts).

Further information on pediatric CO poisoning can be found in the review of White (2000).

2.2.2.2 Adults

Burney et al. (1982) reported an epidemiologic and clinical investigation of 184 persons exposed to CO in a public school. CO release was from a furnace and was caused because of a door to the exhaust chamber had been inadvertently left ajar. The CO was distributed throughout the school building by a forced air heating system. Exposure began at 7.30 a.m. and ended at 10.00 a.m. Of the 184 exposed persons (146 students and 38 teachers, mean age for all exposed was 20 years) 160 became ill and 96 were transported to four hospitals for treatment. COHb levels were measured on 66 persons and showed a mean of 18.2±6.4 %, with almost half falling between 21 and 25 %. Persons in whom COHb levels were drawn had a mean exposure time of 107±33 minutes. Of the 160 persons who became ill, the following symptoms were reported for 159 persons: headache (90 %), dizziness (82 %), weakness (53 %), nausea (46 %), trouble thinking (46 %), shortness of breath (40 %), trouble with vision (26 %), and loss of consciousness (6 %). For headache, dizziness, muscle weakness, trouble with vision and trouble with thinking, a strong correlation between symptom and duration of exposure was found, while nausea, shortness of breath and loss of consciousness

did not show this correlation. The authors corrected the measured COHb level for the delay between exposure and the drawing of blood samples and reported a corrected mean COHb of 20.7±7.0 %.

Ely et al. (1995) reported a poisoning incident in a warehouse of a small sewing company. A propane-fueled forklift was in use in the warehouse, in which a total of 30 people worked. The forklift was parked in a position where its exhaust focused directly into an air intake duct, that communicated with a vent opening above a table in the inspection and packing area, where 5 people worked. On the day of the incident, one man reported pronounced nausea, vomiting, dizziness and had a tonic-clonic seizure. Simultaneous, other coworkers developed chest pain and dyspnea. The warehouse was evacuated immediately. Air CO measurements were 386 ppm in the sewing area and 370 ppm in an unrelated work area. Thirty persons with complaints of severe headaches (93 %), dizziness (63 %), weakness (63 %), nausea (60 %), chest pain or tightness (57 %), shortness of breath (50 %), vomiting (37 %), abdominal pains (33 %), muscle cramping (30 %), difficulty concentrating (23 %), visual changes (20 %) and confusion (17 %) were treated for CO exposure. Twenty-six patients had expiratory CO analyses after being treated with 100 % oxygen for over 2 hours. Expiratory CO was higher in those from the inspection and packing area (21.1±0.7 % versus 8.4±4.8 %). These persons were among the most severely ill. The authors extrapolated the mean expiratory CO concentration of 21.1 % back to a COHb of about 35 % at the end of exposure. Two years after the incident, follow-up was obtained for 25 (83 %) of the patients: 11 (44 % of those reached) reported seeing physicians for persisting symptoms (numbness in arms or legs, 36 %; restlessness, 36 %; persistent headaches, 32 %; irritable or violent behavior, 16 %; confusion, 16 %; incontinence, 16 %; difficulty walking or moving arms/legs, 16 %; memory loss, 16 %; difficulty speaking, 4 %).

Sokal and Kralkowska (1985) analyzed 39 patients (18 men, 21 women) that were hospitalized for acute CO poisoning. 25 patients were intoxicated by household gas and 14 patients by coal-stove gas. The patient‘s ages ranged from 13 to 78 years. The duration of the poisoning varied between 1 and 14 hours and was established on the basis of an epidemiological review of the circumstances of poisoning. The severity of poisoning evaluated on admission to hospital according to the clinical criteria presented in Table 6. On basis of the clinical criteria, 16 cases were classified as degree I, 12 as degree II, 8 as degree III and 4 as degree IV. For statistical analysis the mild and moderate cases (I and II) were pooled into one group and the severe and very severe cases (III and IV) into another. Results presented in Table 7 show that mean COHb in severe and very severe poisonings were only slightly higher (not statistically significant) than those in the mild and moderate group. On the other hand, the average duration of exposure which induced severe or very severe poisonings was about twice as long as that associated with mild and moderate poisonings. In the severe and very severe poisonings, the lactic acid concentration in blood, as an indicator of metabolic acidosis, was significantly higher. For pyruvate and glucose concentrations no significant differences were found (not shown).

TABLE 6: SEVERITY OF CO POISONING; from Sokal and Kralkowska, 1985

Grade I (mild)	headache, vomiting, tachycardia, no disturbances of consciousness
Grade II (moderate)	disturbances or loss of consciousness without other neurological symptoms, tachycardia, pain-induced reflexes still intact
Grade III (severe)	loss of consciousness, intense muscular tonus, neurological symptoms, tachycardia and tachypnea, circulatory and respiratory disturbances not observed
Grade IV (very severe)	loss of consciousness, clinical signs of central nervous system damage, circulatory

TABLE 7: COHb, EXPOSURE DURATION AND LACTATE CONCENTRATIONS IN RELATION TO SEVERITY OF CO POISONING; from Sokal and Kralkowska, 1985

	Mild and moderate poisonings (I and II) (n)		Severe and very severe poisonings (III and IV) (n)		Very severe poisonings (IV) (n)	
COHb (%)	27 ± 12	(27)	34 ± 13	(11)	31 ± 14	(3)
Exposure duration (h)	4.6 ± 3.3	(27)	9.1 ± 3.5	(12)	10.3 ± 1.3	(4)
Blood lactate concentration (µmol/ml)[a]	4.1 ± 3.6	(27)	8.8 ± 3.1	(11)	11.0 ± 2.2	(3)

[a] Blood lactate concentrations in 12 control individuals was 1.4 ± 0.3 µmol/ml.

Deschamps et al. (2003), in a prospective study, measured effects on memory one month after an acute CO intoxication. Of all patients examined in the hospital for suspicion of acute CO intoxication over 4 years (N=944), 230 patients fulfilled the inclusion criterion of a COHb level of 11 % or higher in the first blood sample measured at the hospital. After applying further inclusion criteria, i.e., age between 18 and 60, fluent in French language, no disease or risk factor which might impair memory, e.g., excessive alcohol consumption, treatment with psychotropic drugs, drug abuse, neurological or psychiatric diseases and exposure to solvents or heavy metals, 38 patients were suitable for inclusion, of which 32 were examined. The median COHb in the first blood sample was 23 %. Median blood CO at the end of exposure was calculated as 30 %. The median number of days between intoxication and psychometric testing was 31. Each patient was paired with a control with respect to gender, age and educational level. Tests were selected to study several types of memory, i.e., long term and working memory (verbal Buschke's test) and short term memory (digit span (verbal) and Corsi's test (visual)). Other tests addressed disturbances of attention (simple reaction time test, verbal fluence test) and divided attention (reaction time test with double task and color/word decoding test). The only tests indicating a lower performance of patients were for number recall and fatagability (mean reaction time was higher for the second part of the trial than for the first part. The results did not correlate with the end-of-exposure COHb. In several other tests, patients showed a better performance than controls, some of these tests showed a positive correlation between result and the end-of-exposure COHb. The authors concluded that one month after the incident, the memory of the patients was not lower than in paired controls, and was even higher for learning and word recall.

2.3. Developmental/Reproductive Toxicity

Koren et al. (1991) described a prospective, multicenter study of acute CO poisoning during pregnancy. Between December 1985 and March 1989, a total of 40 cases of CO poisoning during pregnancy were collected. All pregnant women were in good health prior to the CO poisoning and had not suffered from a known chronic illness. The 40 pregnancies included 3 twin births, 1 termination of pregnancy at 16 weeks of gestation, and 4 births that were pending. The CO poisoning was caused by malfunctioning furnaces (n = 23), malfunctioning water heaters (n = 7), car fumes (n = 6), methylene chloride exposure (n = 3) and yacht engine fumes (n = 1). The exposure occurred during the first trimester (n = 12), second trimester (n = 14) or third trimester (n = 14). The clinical grade of poisoning was based on clinical signs and symptoms as shown in Table 8. Cases in which COHb values were available or could be estimated from the known ambient CO concentrations are presented in Table 9. Adverse fetal outcome occurred only after Grade 4 or 5 poisoning.

TABLE 8: SEVERITY OF CO POISONING; adopted from Koren et al., 1991	
Grade 1	Alert, oriented, headache, dizziness, nausea
Grade 1+	As Grade 1, but another person exposed in the same incidence was unconscious
Grade 2	Alert, alterations of mental state, more pronounced headache, dizziness, nausea
Grade 3	Not alert, disorientation, loss of recent memory, muscle weakness, incoordination
Grade 4	Disoriented, depressed sensorium, limited and inappropriate response to simple commands
Grade 5	Comatose, responding only to pain or not responding to any stimulus

TABLE 9: OVERVIEW OF CLINICAL SCORING, COHb AND FETAL OUTCOME; adopted from Koren et al., 1991

Grade	COHb (%)	Time of exam after exposure (h)	Treatment [a]	Outcome
5	40-50	2	HfO, 2 h	Elective termination (in the text the authors state: fetal death at term followed by maternal demise)
5	26	1	HfO, 3 h	Stillborn
4	39	2	HybO, 2 h	Normal
4	25	2	HfO, 2 h	Cerebral palsy compatible with postanoxic encephalopathy
4	21	2	HybO, 2 h	Normal
2	13.8	1	HfO, 7 h and HybO, 2 h	Normal
1	18	unknown	HfO, 12 h	Normal
1	14	unknown	none	Normal
1	6.2	1.5	none	Normal
1	2.4	unknown	none	Normal
1	0.8	1	none	Normal
1	2	unknown	none	Normal
Cases with indirect measures of exposure				
1+	32, measured in affected son	2	HfO, 12 h	Normal
1+	32	-	none	Fetal bradycardia
1	32	-	none	Normal
1	14	-	none	Normal
1	14	-	none	36-week gestation
1	5	-	none	Normal

[a] HfO = high-flow oxygen; HybO = hyperbaric oxygen

952 Caravati et al. (1988) reported on six cases of acute CO poisoning during pregnancy (all cases of
953 patients with CO poisoning during pregnancy admitted to two teaching hospitals in Salt Lake City during a
954 two-year period). Results of COHb measurements and outcomes are given in Table 10. Cases 5 and 6 were
955 treated with 100 % oxygen for 5 hours before the COHb measurement, which is between 3 and 4 half-life
956 times of CO under this condition, using a half-life time of 80 minutes for treatment with 100 % oxygen
957 (Peterson and Stewart, 1970). It can be concluded that the end-of-exposure COHb values were about 8-16
958 fold higher and thus were about 40-80 % in Case 5 and 22-44 % in Case 6. In conclusion, the three cases of
959 stillbirths were associated with maternal COHb concentrations of 22 % or higher.

TABLE 10: OVERVIEW OF MATERNAL CLINICAL EFFECTS, COHb AND FETAL OUTCOME; adopted from Caravati et al., 1988

Case	COHb (%)	Time between end of exposure and blood sampling (h)	Treatment	Maternal Effects and Fetal Outcome
1 28-year-old, pregnancy week 20	9.6	8	100 % oxygen by face mask for 10 h; then COHb had reduced to 1.7 %	Poisoning was caused by a gas-leak in the restaurant where the woman worked; during a 6-hour working period, she developed severe headache, nausea and dizziness; she visited hospital 6 hours later with persisting headache, lethargy and dizziness; she was discharged in good health and delivered a normal female infant weighing 2900 g four months later.
2 32-year-old, pregnancy week 16	23	not stated	100 % oxygen by face mask for 10 h; after 2.5 and 9.5 h COHb was 8.9 and 1.8 %, respectively.	Poisoning was caused by clogged furnace; she complained of headache, nausea and dizziness of 48 hours duration; she was discharged 36 hours later in good health and delivered a term healthy male infant weighing 2920 g.
3 19-year-old, pregnancy week 30	39	not stated	100 % oxygen by face mask for 8 h; after 5 h COHb had reduced to 4 %	Poisoning was caused by a malfunctioning heater; after 18 hours exposure she complained of severe headache and nausea; she was discharged after 8 hours of oxygen therapy and delivered a healthy 3940-g male infant.
4 18-year-old, pregnancy week 41	32	not stated	oxygen treatment using iron lung	The woman was found unconscious and was combative on arrival in the emergency department; her mental status rapidly improved an she recalled having nausea, vomiting and headache earlier that day; fetal heart tones were absent and the woman delivered a stillborn female infant the next day.
5 20-year-old, pregnancy week 38	5	5 hours with oxygen treatment	100 % oxygen by face mask during ambulance and helicopter transport to the hospital	The woman was found awake outside her home together with case 6; they had occluded the furnace the evening before to improve heating; she delivered a stillborn 3380-g male fetus 36 hours later.

Case	COHb (%)	Time between end of exposure and blood sampling (h)	Treatment	Maternal Effects and Fetal Outcome
6 18-year-old, pregnancy week 13	2.8	5 hours with oxygen treatment	100 % oxygen by face mask during ambulance and helicopter transport to the hospital	The woman was found unconscious together with case 5; fetal heart rate was 136 per min at the scene and 190-200 per min 5 hours after the exposure; after 5 hours, she was somnolent but oriented and regained full mental alertness during the next 2 hours; fetal heart rate decreased to 150-160 per min the next day and the woman was discharged; she delivered a nonviable 1210-g fetus at 33 weeks of gestation; autopsy revealed brachycephaly, craniosynostosis, multiple organ cavity anomalies, multiple contractures of extremities, hypoplastic lungs and a small brain with hydrocephalus.

Farrow et al. (1990) reported a case of fetal death in a 20-year-old woman, who was exposed to CO due to use of a portable propane heater in her unventilated mobile home. She arrived by ambulance at the hospital approximately 60 minutes after being found unconscious at her mobile home. En route to hospital she had been intubated and had received 100 % supplemental oxygen. Her measured COHb at the time of admission was 7 %. On the second day in hospital, the patient delivered a 1050-g stillborn female fetus. On gross autopsy, bright red discoloration of the skin and visceral organs was noted. A fetal COHb of 61 % was measured. The authors assumed that the mother had reached a minimal COHb of 40 to 50 % since she was found unconscious.

2.4. Genotoxicity

No studies documenting genotoxic effects of CO in humans were located in the available literature.

2.5. Carcinogenicity

No studies documenting carcinogenic effects of CO in humans were located in the available literature.

2.6. Summary

In healthy adults, death from CO poisoning occurs at COHb larger than 50 % (AIHA, 1999; WHO, 1999a; Steward, 1971; Steward et al, 1970). At COHb of about 16 % headaches can develop (Steward et al., 1970). Subtle (non-adverse) effects, such as decrements in neurobehavioral function start at about 5 % COHb (WHO, 1999a; EPA, 2000).

Analysis of clinical case reports of CO poisoning revealed that only about 2 % of subjects that had died had COHb levels below 40 %. Of the patients that survived about 16 % had a COHb above 40 % (Pach et al., 1978; 1979). Persons with coronary artery disease constitute a subpopulation that is much more susceptible to the effects of CO. Case reports indicate that death through myocardial infarction can occur at COHb around 20-30 % and as low as about 15 % in this group (Balraj, 1984; Atkins and Baker, 1985; Ebisuno et al., 1986; Grace and Platt, 1981). In individuals with coronary artery disease, a COHb of 2.0 or 4.0 % can significantly reduce the time to onset of angina and the time to 1-mm ST-segment change in the electrocardiogram during physical exercise (Allred et al., 1989a; b; 1991). At 5.3 %, but not at 3.7 % COHb an increased arrhythmia frequency was observed in subjects with coronary artery disease (Sheps et al., 1990; 1991).

Children and the unborn also constitute susceptible subpopulations: Measured COHb of higher than 22-25 % in the mothers‘ blood may lead to stillbirths (Koren et al., 1991; Caravati et al., 1988). After CO poisonings associated with mean COHb of 21 % (range 13-32 %) irreversible neurotoxic effects resulting in defects in the cognitive development and in behavioral alterations were observed in a long-term follow-up study, especially in young children (mean COHb 21 %) (Klees et al., 1985). Acute symptoms of CO poisoning in children include effects, such as nausea, vomiting, headache and lethargy. These symptoms were reported to occur already at a COHb of 7 % in one study (Klasner et al., 1998), while in another study a threshold of 16.7-19.8 % COHb was found (Crocker and Walker, 1985). Visual symptoms and syncopes occurred at a threshold of 24.5 % COHb, at higher COHb every child experienced at least one syncope (Crocker and Walker, 1985).

3. ANIMAL TOXICITY DATA

3.1. Acute Lethality

Lethality data for acute inhalation exposure have been reported for rats, mice and guinea pigs. The lethality data are summarized in Table 12 and graphically presented in Figure 1.

3.1.1. Rats

E.I. du Pont de Nemours and Co. (1981) determined LC_{50} values for male Crl:CD rats (weight 250±25 g) at exposure times of 5, 15, 30, and 60 minutes. The experiment was performed in duplicate with one set of animals exposed head only to the test gas while the other set was unrestrained inside a 175-liter rectangular exposure chamber. In restrained rats, respiration rate was monitored by recording pressure fluctuations due to breathing in a body plethysmograph. During CO exposures the chamber atmosphere was monitored continuously for oxygen (BioMarine Industries model 225 oxygen meter), carbon dioxide and CO (InfraRed Industries model 702-D non-dispersive analyzer) using infrared analyzers. Blood from CO exposed rats that died during or within 30 minutes post-exposure was collected by cardiac puncture. The blood was measured for hemoglobin, COHb and oxyhemoglobin by an Instrumentation Laboratories model 282 CO-Oximeter. The post-exposure observation period was 14 days during which time body weights were monitored.

Nearly all of the deaths occurred during the exposure period; of all animals that died only 2 of 216 restrained and 3 of 148 unrestrained rats died after the end of the exposure period. The authors reported LC_{50} values for the 5-, 15-, 30-, and 60-minute exposure periods for the unrestrained rats of 10151 ppm (95% C.I., 9580-10953 ppm), 5664 ppm (95% C.I., 5218-6078 ppm), 4710 ppm (95% C.I., 4278-5254 ppm), and 3954 ppm (95% C.I., 3736-4233 ppm), respectively. The LC_{50} values were lower (higher toxicity) for restrained rats. For the respective exposure durations values of 10754, 4318, 2890 and 1888 ppm were obtained. The RD_{50} for rats exposed to CO was 15000 ppm. The COHb values were 60 % or higher in rats that had died after unrestrained exposure and 50 % or higher in rats that had died after restrained exposure.

Darmer et al. (1972) reported a LC_{50} of 14200 ppm for 5 minutes exposure. Haskell Laboratory (1978) obtained a LC_{50} of 4070 ppm for 30 minutes exposure. Hartzell et al. (1985) reported a LC_{50} of 8636 ppm for 15 minutes exposure and 5207 ppm for 30 minutes exposure. Kimmerle (1974) reported a LC_{50} of 5500 ppm for 30 minutes and 4670 ppm for 60 minutes exposure.

Rose et al. (1970) reported a LC_{50} of 2070 mg/m³ (95 % C.I. 1831-2241 mg/m³) (1807, 1598-1956 ppm) for 4 hours exposure in male Sprague-Dawley rats. The COHb in animals that had died was between 50 and 80 %.

3.1.2. Mice

Pesce et al. (1987) exposed groups of about 100 OF_1-strain mice/age group/sex to 5.5 Torr (about 7200 ppm; final analytical concentration) for 76 minutes or to 4.4 Torr (about 5800 ppm) for 146 minutes. For the 76-minute exposure, survival rates for males were 36 % for 31-day-old males and 22 % for 184-day-old males. Of the exposed females, 57 % of 31-day-old females and 63 % of 184-day-old females survived. After exposure for 146 minutes, survival rates were 40 % for 34-day-old males, 27 % for 85-day-old males, 24 % for 230-day-old males and 27 % for 387-day-old males and 48 % for 34-day-old females, 67 % for 85-

day-old females and 56 % for 387-day-old females. Except for the about 1-month-old mice, male mice showed a significantly lower survival than females. Survival was not significantly influenced by age.

Winston and Roberts (1978) investigated the influence of age on lethal effects of CO on mice (strain not stated; male mice were used in all groups, except for the two youngest groups that comprised both males and females). Animals of different age were exposed to 2000 ppm CO for up to 6 hours in stainless steel exposure chambers. The analytical concentration was determined by an automated gas chromatograph. Mortality occurred in 3/37 two-day old mice, 21/32 17-day-old mice, 16/20 30-day-old mice, 11/17 54-day-old mice, 10/20 108-day-old mice and 6/18 150-day-old mice. The animals of the youngest and that of the oldest age group were found to be more resistant to CO. These two groups were also found less susceptible to lethal effects from hypoxic hypoxia when mice were exposed to a reduced oxygen concentration of 7.5 %.

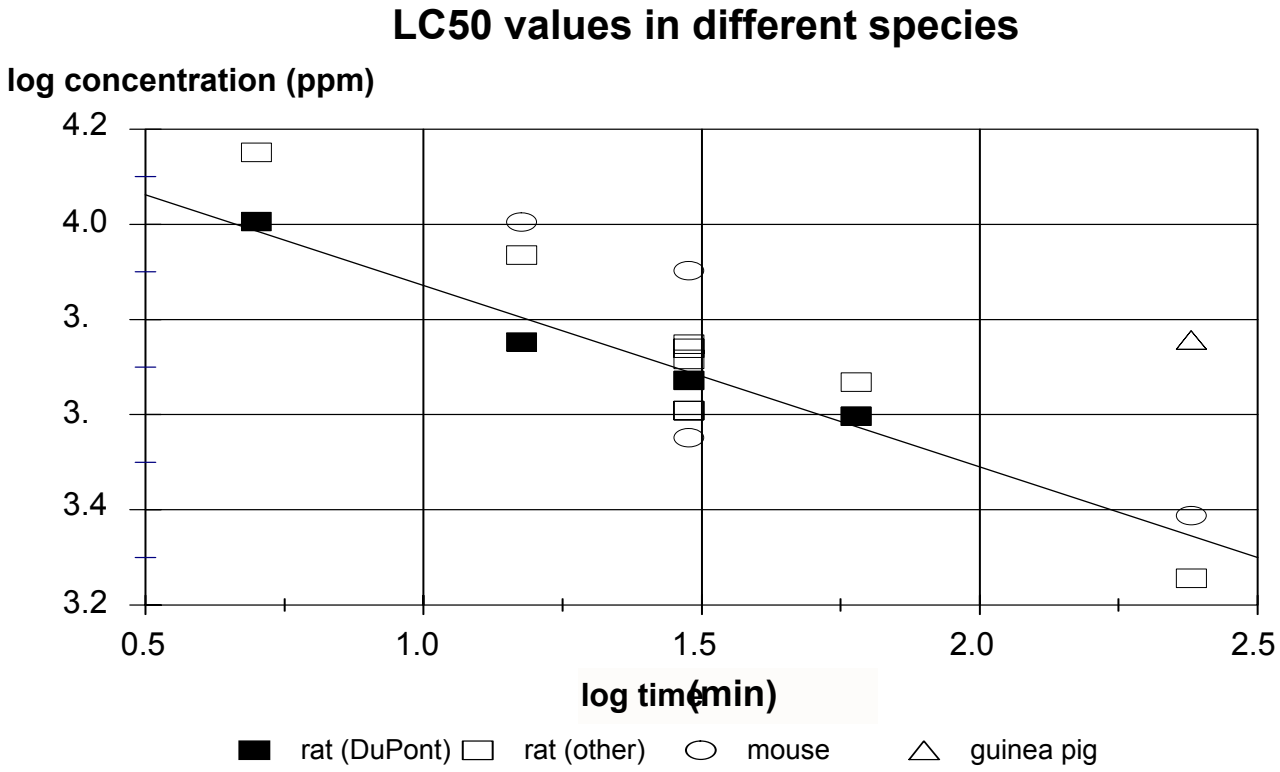
Hilado et al. (1978) reported 30-minutes LC_{50} values of 3570 ppm for Swiss-Webster mice and 8000 ppm for ICR mice. Respiratory distress was the only sign observed during the exposures.

Rose et al. (1970) reported a LC_{50} of 2800 mg/m³ (95 % C.I. 2679-2926 mg/m³) (2444, 2339-2554 ppm) for 4 hours exposure in male Swiss albino mice. COHb was not determined.

3.1.3. Guinea Pigs

Rose et al. (1970) reported a LC_{50} of 6550 mg/m³ (95 % C.I. 5509-7788 mg/m³) (5718, 4809-6799 ppm) for 4 hours exposure in Hartley guinea pigs. The COHb in animals that had died was between 57 and 90 %.

TABLE 11: SUMMARY OF LC_{50} DATA IN LABORATORY ANIMALS				
Species	**Concentration (ppm)**	**Exposure time (min)**	**Remark**	**Reference**
Rat	14200	5		Darmer et al., 1972
Rat	10151	5	Crl:Cd strain, male	E.I. du Pont de Nemours and Co., 1981
Rat	8636	15		Hartzell et al., 1985
Rat	5664	15	Crl:Cd strain, male	E.I. du Pont de Nemours and Co., 1981
Rat	5607	30		Herpol et al., 1976
Rat	5500	30		Kimerle, 1974
Rat	5207	30		Hartzell et al., 1985
Rat	4710	30	Crl:Cd strain, male	E.I. du Pont de Nemours and Co., 1981
Rat	4070	30		Haskell Laboratories, 1978
Rat	4670	60		Kimerle, 1974
Rat	3954	60	Crl:Cd strain, male	E.I. du Pont de Nemours and Co., 1981
Rat	1807	240	Sprague-Dawley strain, male	Rose et al., 1970
Mouse	10127	15		Kishitani et al., 1979
Mouse	3570	30	Swiss-Webster strain	Hilado et al., 1978
Mouse	8000	30	ICR strain	Hilado et al., 1978
Mouse	2444	240	Swiss albino strain, male	Rose et al., 1970
Guinea pig	5718	240	Hartley strain, male	Rose et al., 1970



1100 **FIGURE 1: LC_{50} VALUES FOR CO IN DIFFERENT SPECIES**
1101 The solid line was calculated by Probit analysis from the data in E.I. du Pont de Nemours and Co. (1981).
1102 The slope of this line indicates a time scaling exponent of n=2.6. Analysis of all data yielded a value of n=2.8.
1103 The LC_{50} values are taken from Table 11.

3.2. Nonlethal Toxicity

A large number of studies investigated nonlethal effects of single and repeated CO exposures in animals (see WHO, 1999a for review). Reported here are only studies that support or add information to the effects seen in humans, because these studies were considered most relevant. These include syncope-like observations and behavioral effects in monkeys, effects on heart function in dogs as well as developmental/reproductive toxic effects in different species.

3.2.1 Monkeys

Purser and Berrill (1983) studied the behavioral effects of CO exposure on cynomolgus monkeys (3 male animals, 4-5 years old). The basic behavioral model consisted of an individual monkey placed in a chamber with a lever press at one end a reward (chocolate candy) dispenser at the other. At 5-minute intervals throughout the test session a buzzer was sounded and a light flashed over the lever. If the monkey pressed the lever within a 1-minute period, a candy was presented in the dispenser. The monkey then moved the length of the chamber to pick up the candy. The major performance parameter measured was the time from the animal releasing the lever to its first touch of the dispenser, i.e., the time taken to traverse the chamber. Each session consisted of the following stages: 1) a 25-minute preexposure period during which baseline carbon dioxide production and behavioral task performance times were established, 2) 2.5 % CO was introduced into the chamber at a sufficiently high flow rate to increase the concentration to 900 ppm within 1 minute, 3) 900 ppm CO were maintained for 30 minutes, during which the effects on clinical condition, carbon dioxide production and behavioral task performance were examined, 4) the chamber was flushed of CO, decreasing the concentration to less than 100 ppm within 4 minutes, 5) animals were maintained for anther 45 minutes in the chamber while their clinical condition, carbon dioxide production and behavioral task performance were monitored. Carbon dioxide and CO concentrations were monitored continuously using infrared analyzers. Five preliminary experiments were conducted at a 1000 ppm CO, followed by the main experimental series that consisted of 10 exposures at 900 ppm, 3 for each animal, and 1 preliminary run. For 3 exposures (one for each animal) the animals were removed from the chamber 5 minutes after the end of the exposure period so that venous blood samples could be taken for COHb analysis.

During the 4 preliminary exposures to 1000 ppm CO, there was generally no visible effect of the animals until 18-20 minutes of exposure had elapsed, at which time they generally became less active, occasionally sitting down for short periods. At approximately 25 minutes a dramatic change occurred over a period of 1-2 minutes and the animals went from an apparently normal state to one of severe intoxication. This change was preceded by one or more warning signs at approximately 23 minutes, which consisted of momentary closure of eyes, yawning and shaking of the head. Immediately prior to collapse the animals sometimes paced around in a mechanical fashion, often swaying as they walked. As few as 20 seconds later the animals were lying or rolling on the floor, sometimes attempting to rise before sitting on the floor or lying down again. During recovery, the animals remained in a state of severe intoxication for approximately 30 minutes, lying down with their eyes closed. On three occasions animals vomited during this period. After 25-30 minutes the animals were usually sufficiently recovered to get up and move around the chamber, in response to the buzzer they would sometimes move towards or even press the lever although they made no attempt to fetch the candy. The performance of the behavioral task was unaffected during the first 15 minutes of exposure, but before the first minor clinical signs there was generally a slowing of response.

During exposures to 900 ppm, the first signs generally occurred after 20-25 minutes when the animals became less active, followed by the minor warning signs at approximately 26 minutes. Although in most cases the animals were lying down at the end of the exposure period, they did not appear to be severely intoxicated and in 6 of 9 exposures the signs were mild and the animals did not reach a state of collapse. During the

recovery period the animals remained in a state of intoxication for approximately 16 minutes. Recovery was more rapid than that following exposure to 1000 ppm, as all animals performed the behavioral task within 25 minutes of the end of exposure. The first effects upon the chamber traverse time occurred at 15 minutes into the exposure as a slight, statistically significant decrement in performance. The decrement at 20 minutes was not statistically significant while at 25 minutes it was highly significant, as the mean response time was twice the preexposure response time (1.10 sec vs. 0.62 sec). The first time that the test was conducted successfully on all occasions was after 25 minutes of recovery when the mean chamber traverse time was 3 times as long as the mean preexposure time. From 30 to 45 minutes the animals were more active and response times gradually improved but did not reach the preexposure level.

The mean COHb measured at the end of the exposure was 32.9 % (range 31.7-34.8 %). Carbon dioxide production, indicating the metabolism in the animals, decreased gradually throughout the exposure (statistically significant at 25 and 30 minutes of exposure) and then increased gradually towards preexposure levels during the recovery period (significantly lower until 15 minutes into the recovery period).

From earlier experiments, the authors estimated COHb of 16-21 % for the period of 15-20 minutes when deficits in behavioral task performance were started during the exposure period. In the state of severe intoxication, the animals were capable of performing some coordinated behavioral actions when they were sufficiently stimulated, e.g. by loud noise or removing them from the chamber. The authors report that in unpublished experiments using higher CO concentrations the animals passed rapidly from this stage to one of deep coma.

DeBias et al. (1979) reported that CO exposure (100 ppm for 16 h; resulting in a COHb of 9.3 %) reduced the threshold for ventricular fibrillation induced by an electrical shock applied to the myocardium of monkeys during the final stage of ventricular repolarization. The voltage required to induce fibrillation was highest in normal animals breathing air and lowest in infarcted animals breathing CO. Additivity was found for the effects of infarction alone and CO exposure alone each of which required significantly less voltage for fibrillation.

3.2.2 Dogs

Aronow et al. (1979) reported that CO exposure increased the vulnerability of the heart to induced ventricular fibrillation in normal dogs breathing 100 ppm CO for 2 hours (resulting COHb was 6.3-6.5 %). The ventricular fibrillation was induced by an electrical stimulus applied to the myocardium.

Sekiya et al. (1983) reported that exposure to CO concentrations of 3000 ppm for 15 minutes followed by 130 ppm for 1 hour (resulting COHb was 13-15 %) increased the severity and extent of ischemic injury and the magnitude of ST-segment elevation which was induced in anaesthetized dogs by coronary artery ligation more than did ligation alone.

3.3. Developmental/Reproductive Toxicity

3.3.1 Pigs

Dominick and Carson (1983) exposed pregnant sows to CO concentrations between 150 and 400 ppm for 48-96 hours between gestational days 108-110 (average gestation was 114 days). They showed a significant linear increase in the number of stillbirths as a function of increasing CO concentration. Stillbirths were significantly elevated above control levels when the maternal COHb exceeded 23 % saturation. These saturation levels were obtained at approximately 250 ppm.

Morris et al. (1985) exposed 16 pigs to 0, 200 or 250 ppm from gestational day 109 until birth (maternal COHb at 24 hours into the exposure was 0, 13.6 and 17.1 %, respectively). Stillbirth rate for the 3 groups (total of 123 piglets) were2.3, 2.4 and 4.8 %, respectively. The study authors stated that the stillbirth rate was not affected because the observed rates were lower than the industrial norm of 5-10 %. The COHb in neonatal piglets at birth were 0, 19.8 and 22.4 %, respectively. The authors found impairment of negative geotaxis behavior and open field activity 24 hours after birth in the 250-ppm group. Activity in open field was significantly reduced at 48 hours after birth in piglets from both exposure groups.

3.3.2 Rabbits

Astrup et al. (1972) reported an increase in fetal mortality and malformations in rabbits exposed to 180 ppm CO continuously throughout gestation. Maternal COHb was 16-18 %.

Rosenkrantz et al. (1986) exposed rabbits to high concentrations of CO-containing cigarette smoke (12 puffs of 2700-5400 ppm CO; exposure to puffs of cigarette smoke by face mask; each puff sequence consisted of 30 seconds cigarette smoke and 30 seconds fresh air) for 12 minutes daily from gestational days 6-18. The COHb level reached at the end of each exposure was 16 %. A large number of fetal deaths, but no malformations were observed in exposed animals.

3.3.3 Rats

Choi and Oh (1975) exposed rats to 750 ppm CO for 3 h/d on gestational days 7, 8 or 9. An excess of fetal absorptions and stillbirths as well as a decrease in body length and an increase in skeletal anomalies were observed. COHb was not determined.

Penney et al. (1980) exposed pregnant COBS rats for the last 18 days of gestation to 200 ppm CO. The mean maternal COHb was about 27.8 % and the mean fetal level was 27.0 %. The body weight of the pups was significantly lower than that of controls. The heart weight of both exposed females and pups was significantly increased.

Mactutus and Fechter (1985) exposed Long-Evans rats continuously throughout gestation to 0 or 150 ppm CO. Mean COHb was 15.6 % vs. 1 % in control subjects. At 120 days of age, CO-exposed rats acquired a conditioned avoidance response equally well as control animals. However, following a 24-h interval the CO-exposed rats failed to demonstrate significant retention. In a second experiment, in which animals received 50 training trials per day until a criterion of ten consecutive avoidance responses was met, the prenatal CO-exposed rats again acquired the task as well as control animals. When tested for retention 28 days later, a significant memory impairment was again observed in terms of trials required to retain the avoidance

criterion as well as in total percent avoidance. At one year of age, the CO-exposed rats showed impairment relative to air-exposed controls in both the original learning and retention of the two-way avoidance response.

3.3.4 Mice

Singh and Scott (1984) exposed groups of 17 pregnant CD-1 mice to CO concentrations of 0, 65, 125, 250 or 500 ppm for 24 h/d on gestational days 6 to 17. Mice were sacrificed and examined on day 18. No signs of maternal toxicity were observed at any dose. The mean percent fetal mortality per litter was 4.52, 5.89, 12.50, 15.50 and 55.30 %, respectively. Besides a dose-dependent increase in embryolethality, fetus weights were significantly reduced at exposure levels of 125 ppm or higher. No fetal malformations were detected. COHb was not determined.

Singh (1986) exposed CD-1 mice to 0, 65 or 125 ppm CO continuously during gestational days 7 to 18 (COHb not determined). No signs of maternal toxicity were observed. Exposure did not affect the number of live pups born per litter or their birth weight. Prenatal exposure to 125 ppm significantly increased the time required by pups for righting reflex on day 1 of birth and negative geotaxis on day 10. Prenatal exposure at both concentrations significantly decreased the mean aerial righting score of pups on day 14.

3.4. Genotoxicity

No information regarding the carcinogenicity of CO in animals was located in the available literature.

3.5. Carcinogenicity

No information regarding the carcinogenicity of CO in animals was located in the available literature.

3.6. Summary

Several studies reported LC_{50} values in rats, mice and guinea pigs. In the study of E.I. du Pont de Nemours and Co. (1981), the following LC_{50} values were calculated by Probit analysis: 10151 ppm for 5 minutes, 5664 ppm for 15 minutes, 4710 ppm for 30 minutes and 3954 ppm for 60 minutes.

In a study in cynomolgus monkeys, at exposure to 900 ppm no signs of intoxication occurred during the first 20-25 minutes (corresponding to COHb of about 16-21 %), at 25 minutes the animals‘ performance in a behavioral test significantly decreased and at the end of the exposure period (30 min) animals became less active and were lying down. After about 25 minutes at a 1000 ppm, within 1- 2 minutes the animals went into a state of severe intoxication, virtually unable to perform coordinated movements (Purser and Berrill, 1983).

In developmental toxicity tests, CO caused an increase in the rate of stillbirths or fetal mortality in pigs after a 2-3 day-exposure to COHb above 23 % (Dominick and Carson, 1983), in rabbits after continuous exposure to 16-18 % COHb throughout gestation (Astrup et al., 1972) as well as after daily exposure to high CO concentrations in cigarette smoke (exposure for 12 minutes/day on gestational days 6-18, resulting in COHb of 16 %) (Rosenkrantz et al., 1986), in rats after 3 exposures to 750 ppm for 3 h/d (Choi and Oh, 1975) and in mice after exposure to 125 ppm for 11 d (Singh and Scott, 1984). Significant memory impairment in behavioral tests were found in young rats after continuous CO exposure throughout gestation (mean maternal COHb was 15.6 %) (Mactutus and Fechter, 1985).

In monkeys, a COHb of 9.3 % resulted in reduced threshold for electric shock-induced ventricular fibrillation (DeBias et al., 1979). A similar effect was found in dogs at 6.3-6.5 % COHb (Aronow et al., 1979). A COHb of 13-15 % increased the severity and extent of ischemic injury and the magnitude of ST-segment elevation in a myocardial infarction model in dogs (Sekiya et al., 1983).

4. SPECIAL CONSIDERATIONS

4.1. Stability, Metabolism and Disposition

CO is produced endogenously in normal metabolism: when an α-methylene bridge in the heme group of hemoglobin is broken during the catabolic process, one molecule of CO is released. It has been estimated that this production amounts to approximately 0.3 to 1.0 ml/h with an additional 0.1 ml/h resulting from a similar catabolic process involving other heme-containing compounds (e.g., myoglobin as well as cytochrome and catalase enzymes). This endogenous production of CO gives rise to an baseline or back ground level approximately of 0.5-0.8 % COHb (NIOSH, 1972).

Almost all of the CO that has been inhaled is eliminated through the lungs when the previously exposed person enters an atmosphere free of CO. Carbon monoxide not only binds to hemoglobin forming COHb, but 10-50 % of the total body store of CO is also distributed to extravascular sites such as skeletal muscle, where it can bind to myoglobin. Extravascular CO can be slowly metabolized to carbon dioxide (Fenn, 1970). Inside the cells, CO can bind to all heme proteins capable of binding oxygen, such as myoglobin, cytochrome c oxidase, cytochrome P450 enzymes and tryptophan oxygenase (WHO, 1999a). However, the exact extent of this binding in vivo as well as the physiological consequences in terms of inhibition of protein and enzyme function and the existence and relevance of possible toxic effects has not been clearly shown up until now (cf. extensive discussion in WHO, 1999a).

The time required to eliminate half of the gas is 3 to 5 hours (Landaw, 1973), depending on the amount of respiration, which acts to wash it out of the body. Peterson and Stewart (1970) reported a range for the elimination half-time from 128 to 409 minutes from 39 experiments, with an average of 320 minutes in human subjects that breathed normal air after CO exposure. Increased oxygen pressure helps to dislodge it from the hemoglobin. One hundred percent oxygen given at atmospheric pressure reduces the half-elimination rate to about 80 minutes (Peterson and Stewart, 1970). Weaver et al. (2000) reported a half-life of 74±25 minutes for COHb in CO-poisoned patients receiving 100 % oxygen. Klasner et al. (1998) reported a half-time of 44 minutes for children (n=26, 4-12 years old) when given 100 % oxygen via face mask. Hyperbaric oxygen at 3 bar pressure reduces the half time to about 20-25 minutes (Beard, 1982; Landaw, 1973).

4.2. Mechanism of Toxicity

If not stated otherwise, the information on the mechanism of toxicity is taken from the extensive recent reviews of WHO (1999a) and EPA (2000). The best understood biologic effect of CO is its combination with hemoglobin (Hb) to form COHb, thereby rendering the hemoglobin molecule less able to bind with oxygen. Although the rate of CO binding with hemoglobin is about one-fifth slower and the rate of dissociation from hemoglobin is an order of magnitude slower than the respective rates for oxygen, the CO chemical affinity for hemoglobin (represented by the Haldane coefficient M) is about 245 times greater than that for oxygen. One part of CO and 245 parts of oxygen would form equal parts of oxyhemoglobin and COHb (50 % each), which would be achieved by breathing air containing 21 % oxygen and 570 ppm CO. The steady-state ratio of COHb/oxyhemoglobin is proportional to the ratio of their respective partial pressures:

$$COHb / O_2Hb = M (P_{CO} / P_{O2})$$

Under dynamic conditions, competitive binding of oxygen and CO to hemoglobin is complex: the greater the number of heme groups bound to CO, the greater the affinity of free heme groups for oxygen. CO not only occupies oxygen binding sites, molecule for molecule, thus reducing the amount of available oxygen, but also alters the characteristic relationship between oxyhemoglobin and the partial pressure of oxygen, which in normal blood is S-shaped. The difference in the partial pressure of oxygen between freshly oxygenated arterial blood ($P(O_2)$ = 100 mm Hg) and mixed venous blood ($P(O_2)$ = 40 mm Hg) represents a release to the tissues of approximately 5 ml O_2/100 ml blood (NIOSH, 1972). With increasing COHb in blood, the dissociation curve is shifted gradually to the left, and its shape is transformed into that of a rectangular hyperbola. This changes the release of oxygen to the tissues appreciably: the oxygen content of the blood is not only lowered during exposure to CO, but the shift of the oxyhemoglobin dissociation curve to the left decreases the amount of remaining oxygen that is made available to the tissues. Both mechanisms serve to effectively lower the tissue partial pressure of oxygen and hence can create a generalized tissue hypoxia. Because the shift occurs over a critical saturation range for release of oxygen to tissues, a reduction in oxyhemoglobin by CO poisoning will have more severe effects on the release of oxygen than the equivalent reduction of hemoglobin due to anemia.

While the brain has a higher requirement for oxygen than the heart, in contrast to the cerebral circulation the coronary circulation must supply an even increased amount of oxygen during periods of generalized tissue hypoxia; since under these circumstances the heart is forced to increase both its rate and its output in order to meet the normal oxygen demands of the body. This increase in myocardial activity demands an increased oxygen supply to the myocardium, which must be met by the coronary circulation. Under hypoxic conditions increased oxygen supply to the peripheral tissues can be accommodated by increased blood flow (via vascular dilatation) and/or increased oxygen extraction by the tissues. The myocardium under these circumstances appears only to increase the flow of blood rather than to extract an additional amount of oxygen from the coronary circulation. While the peripheral tissues normally extract only 25 percent of the oxygen content of the perfusing arterial blood during resting conditions, the myocardium extracts 75 percent, thus leaving the mixed venous blood only 25 percent saturated. This mechanism has the overall effect of maintaining the myocardial oxygen tension at a higher level than would be present in other muscle tissue and thus insures a continual aerobic metabolism, even under hypoxic duress. In terms of oxygen partial pressure, the mixed venous blood of the peripheral tissues is approximately 40 mm Hg while the mixed venous blood of the coronary circulation is only 20 mm Hg. In the presence of COHb (and the shift to the left of the oxyhemoglobin dissociation curve), however, the arterio-venous difference can only be maintained by an increased flow in the coronary circulation. In an individual with diminished coronary circulation because of coronary heart disease, however, this situation may result in a decrease in the venous oxygen partial pressure of the myocardium precipitated by an inability to maintain the normal arterio-venous gradient. Studies in dogs suggest that exercise plus an increased COHb, in addition to the global myocardial hypoxia, leads especially to areas of relative hypoxia in the left ventricle secondary to redistributive changes in subendocardial blood flow (Einzig, 1980). This hypoxic effect is further enhanced, as mentioned above, by an increase in cardiac rate and output as a general response to peripheral tissue hypoxemia. A person with diminished coronary circulation caused by coronary heart disease, consequently, may be constantly near the point of myocardial tissue hypoxia, which can ultimately lead to myocardial infarction.

4.3. Other Relevant Information

4.3.1. Species Variability

With regard to lethal effects, COHb of 50-80 % have been reported as lethal level in rats and guinea pigs (Rose et al., 1970; E.I. du Pont de Nemours and Co., 1981). In apparently healthy people that died from CO poisoning, usually COHb of 60 % or higher are found (Balraj, 1984; AIHA, 1999; Winter and Miller, 1976, Holmes, 1985, Stewart, 1975).

Syncopes have been reported to occur in children at a threshold of 24.5 % COHb (Crocker and Walker, 1985). In monkeys, at COHb little higher than 16-21 % syncope-like effects occurred (Purser and Berrill, 1983). The lowest COHb that resulted in cognitive development defects in children in a long-term follow-up study was 13 % (Klees et al., 1985). In mice, memory impairment was found in the offspring of rats exposed continuously at 15.6 % COHb during gestation (Mactutus and Fechter, 1985).

Taken together, these studies imply a limited species variability for different effects with regard to the COHb at which these effects occur. However, the exposure conditions necessary to reach a certain COHb differ between species due to different affinities of their hemoglobin for CO.

The equilibrium COHb of different species is determined by the species-specific Haldane (affinity) constant M. Reported values are 228 for dogs (Sendroy and O'Neal, 1955), 195 for monkeys (Sendroy and O'Neal, 1955), 170 for rats (Rodkey and O'Neal, 1970) and 117 for guinea pigs (Rodkey and O'Neal, 1970). Jones et al. (1971) reported equilibrium COHb in different species after 48-hour continuous exposure as shown in Table 12. Using the mathematical model described in Appendix B, corresponding COHb values for a 70-kg man can be calculated as 7.9, 13.8 and 25.0 % for 51, 96 and 200 ppm, respectively.

TABLE 12: COHb AFTER 48 HOURS CONTINUOUS EXPOSURE TO CO; adopted from Jones et al., 1971

CO concentration (ppm)	species	COHb in blood (%) (n)	
51	dog	5.7	(2)
51	monkey	5.3	(3)
51	rat	5.1	(15)
51	guinea pig	3.2	(15)
96	dog	12.5	(2)
96	monkey	10.3	(3)
96	rat	7.5	(15)
96	guinea pig	4.9	(15)
200	dog	20.8	(2)
200	monkey	20.0	(3)
200	rat	16.4	(15)
200	guinea pig	9.4	(15)

4.3.2. Intraspecies Variability

Experiments in mice did not indicate that very young or very old animals were more susceptible to lethal effects of CO exposure (Pesce et al., 1987; Winston and Roberts, 1978). However, there is considerable variability within human subpopulations: a COHb of about 15 % only leads to very slight symptoms, such as headache, in healthy adults (Stewart et al., 1970; WHO, 1999a). In contrast, the same COHb was reported to cause long-lasting defects in the cognitive development and behavioral alterations in children (Klees et al., 1985) or even to contribute to death from myocardial infarction in individuals with coronary artery disease (Grace and Platt, 1981; Balraj, 1984). In case reports of myocardial infarction, other subjects that were exposed under the same conditions (and sometimes had higher COHb) did not experience effects above the AEGL-2 level (Atkins and Baker, 1985; Grace and Platt, 1981).

Subpopulations at higher risk for toxic effects of CO include the following groups:

a) fetuses because of higher CO affinity and slower CO elimination (see Sections 2.3 and 4.3.4);

b) children because they develop acute neurotoxic effects (e.g. headaches, nausea), long-lasting neurotoxic effects (e.g. memory deficits) and impaired ability to escape (i.e. syncopes) at lower COHb than adults (see Section 2.2.2.1);

c) people with pre-existing diseases, either known or unknown, that already decrease the availability of oxygen to critical tissues, including subjects with coronary artery disease (see Sections 2.2.1 and 2.2.1.1), chronic obstructive lung disease, chronic anemia and hemoglobinopathies, such as sickle cell anemia. For example, in sickle-cell disease, the average lifespan of red blood cells with abnormal hemoglobin is 12 days compared to an average of 120 days in healthy individuals with normal hemoglobin. “As a result, baseline COHb levels can be as high as 4%. Presumably, exogenous exposure to CO, in conjunction with higher endogenous CO levels, could result in critical levels of COHb. However, it is not known how ambient or near-ambient levels of CO would affect individuals with these disorders” (EPA, 2000; see also WHO, 1999a). Due to the physiologic adaptation in these subpopulations, they are not considered more susceptible than patients with coronary artery disease.

d) people at high altitude, especially those not living there long enough for physiological adaptation. “It is important to distinguish between the long-term resident of high altitude and the newly arrived visitor from low altitude. Specifically, the visitor will be more hypoxemic than the fully adapted resident. One would postulate that the combination of high altitude with carbon monoxide would pose the greatest risk to persons newly arrived at high altitude who have underlying cardiopulmonary disease, particularly because they are usually older individuals. Surprisingly, this hypothesis has never been tested adequately” (WHO, 1999a). Due to physiologic adaptation, people living at high altitude are not considered generally more susceptible than patients with coronary artery disease. Since it is generally not advisable for patients with severe coronary artery disease to travel to places at high altitude, it is not considered necessary to especially take that part of the identified susceptible subpopulation (i.e. patients with coronary artery disease; see below) into account when deriving AEGL values.

An estimated 62 million people in the United States (about 20 % of the population) have one or more types of cardiovascular disease (American Heart Association, 2003). For the major diseases within the category of total cardiovascular disease, about 50 million Americans have high blood pressure, 13 million

have coronary heart disease, 4.9 million have heart failure, 4.7 million have cerebrovascular disease (stroke), and 1 million have congenital cardiovascular defects.

The prevalence of cardiovascular diseases increases with age. It is 10 % for males and 4 % for females at age 25-34, 51 % for males and 48 % for females at age 55-64 and 71 % for males and 79 % for females at age 75 or older (American Heart Association, 2003).

Coronary heart disease caused more than 1 of every 5 deaths in the USA in 2000. Coronary heart disease was mentioned as cause of death in 681,000 cases and myocardial infarction in 239,000 deaths. Fifty percent of men and 63 % of women who died suddenly of coronary heart disease had no previous symptoms of this disease (American Heart Association, 2003).

Within the group of people with coronary heart disease, 7.6 million had myocardial infarction (heart attack) and 6.6 million of angina pectoris (chest pain) (American Heart Association, 2003). The prevalence of angina pectoris in the British adult population is about 4 % (Williams and Stevens, 2002).

Angina pectoris is a symptom of coronary heart disease. Common features of an attack are central chest pain, pain radiating to the lower jaw, or arms, and shortness of breath. The pain occurs when there is insufficient oxygen delivery to the heart, leading to ischemia. This is usually, although not exclusively, a result of an atheromatous narrowing (stenosis) in one or more of the coronary arteries. Angina can classified broadly as stable or unstable, depending on its severity and pattern of occurrence. Stable angina is typically provoked by exercise (e.g., hurrying across a street or climbing a long flight of stairs), stress or extremes of temperature and is relieved by either rest or sublingual nitrates or both. Unstable angina is understood as anginal pain that occurs with lesser degrees of exertion, with increasing frequency, or at rest (i.e., without exertion). The pain may be more severe, last longer, and requires more intensive intervention (usually hospitalization for initiation of medication under cardiac monitoring). If left untreated, unstable angina may result in a heart attack and irreversible damage to the heart. The diagnosis of angina is generally based on clinical history, electrocardiograph stress testing (where patients are exercised on a treadmill to look at the effect on their electrocardiogram), and coronary angiography (looking for narrowings in the coronary arteries) (Williams and Stevens, 2002).

4.3.3. Time Scaling

The LC_{50} values for different exposure periods are shown in Figure 1. Overall the distribution does not seem to argue against a linear relationship between log(concentration) and log(time) and from the data from E.I. du Pont de Nemours and Co. (1981) a value of 2.6 can be calculated for the exponent n from the slope. Regression analysis of all data yielded a value of n=2.8. However, taking a closer look at the data from this study suggests that the data might be distributed non-linearly and that the slope decreases with increasing exposure time.

The AEGL-2 and AEGL-3 exposure concentrations were derived from a mathematical model based on the same COHb at the end of the respective exposure periods. These values are also distributed non-linearly in a log-log plot: the slope between the two shortest exposure periods (10 and 30 min) is equivalent to n=1.0-1.1 and the slope between the two longest exposure periods (4 and 8 h) is equivalent to n=2.9-3.4. This non-linearity is probably caused by the fact that the COHb depends strongly on the ventilation rate and lung blood flow for short exposure rates, while for long exposure rates the COHb becomes independent of

these parameters and exclusively depends on the affinity of hemoglobin for CO (represented by the Haldane constant M). Since rats have a higher ventilation rate per kg body weight than humans, their COHb reaches the steady state faster and therefore for the same exposure time the slope for rats is smaller than the corresponding slope for humans, i.e., COHb depends stronger on the ventilation rate in humans compared to rats.

4.3.4. Mathematical models of COHb formation

In 1965, Coburn, Forster and Kane developed a differential equation (CFK model) to describe the major physiological variables that determine the COHb in blood using data from patients with increased endogenous production of CO due to anemia (Coburn et al., 1965). The CFK model is represented by the following equation:

$$\frac{d(COHb)_t}{dt} = \frac{V_{CO}}{Vb} - \frac{COHb_t * P_{O2}}{M * B * Vb * OHb} + \frac{P_{CO}}{B * Vb}$$

where:
$B = 1 / D_L + P_L / V_A$
M = Ratio of affinity of blood for CO to that for O_2; M = 218
OHb = ml of O_2 per ml blood; OHb = 0,2
$COHb_t$ = ml of CO per ml blood at time
P_{O2} = average partial pressure of oxygen in the lung capillaries; P_{O2} = 100 mm Hg
V_{CO} = rate of endogenous CO production; V_{CO} = 0.007 ml/min
D_L = diffusivity of the lung for CO; D_L == 30 ml / min mm Hg
P_L = barometric pressure minus the vapor pressure of water at body temperature,
P_L = 713 mm Hg
Vb = blood volume; Vb = 5500 ml
P_{CO} = partial pressure of CO in the air inhaled (mm Hg)
V_A = alveolar ventilation rate; V_A = 6000 ml/min (awake), 4000 ml (sleeping)
t = exposure duration (min)

Peterson and Stewart (1970) reported that the CFK model well predicted COHb measured in 18 healthy male students, aged between 24 and 42 years, that were exposed to the following combinations of CO concentrations and exposure times: about 50 ppm for 30 minutes to 24 hours, about 100 ppm for 15-480 minutes, about 200 ppm for 15-120 minutes and about 500 ppm for 15-114 minutes. They used the following integrated form of the CFK equation and parameters:

$$\frac{A * COHb_t - B * V_{CO} - P_{CO}}{A * COHb_0 - B * V_{CO} - P_{CO}} = \exp(-t\ A / B * Vb)$$

where
$A = P_{O2} / M\ OHb$
$B = 1 / D_L + P_L / V_A$
M = Ratio of affinity of blood for CO to that for O_2; M = 218
OHb = ml of O_2 per ml blood; OHb = 0,2
$COHb_t$ = ml of CO per ml blood at time
$COHb_0$ = ml of CO per ml blood at beginning of the exposure

P_{O2} = average partial pressure of oxygen in the lung capillaries; P_{O2} = 100 mm Hg
V_{CO} = rate of endogenous CO production; V_{CO} = 0.007 ml/min
D_L = diffusivity of the lung for CO; D_L == 30 ml / min mm Hg
P_L = the vapor pressure of water at body temperature, P_L = 713 mm Hg
Vb = blood volume; Vb = 5500 ml
P_{CO} = partial pressure of CO in the air inhaled (mm Hg)
V_A = alveolar ventilation rate; V_A = 6000 ml/min (awake), 4000 ml (sleeping)
t = exposure duration (min)

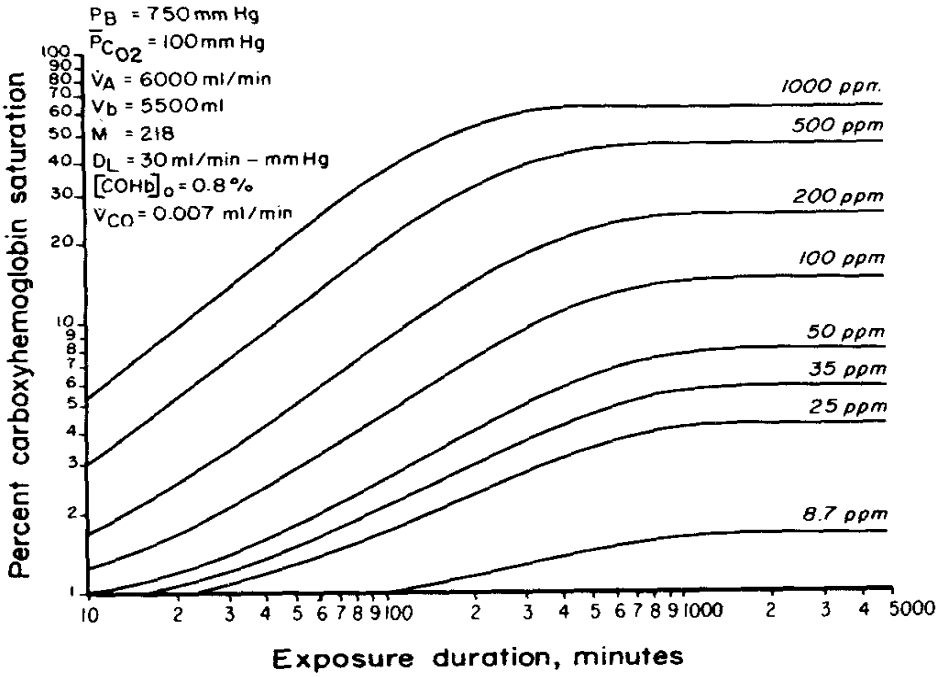


FIGURE 2: COHb FOR DIFFERENT EXPOSURE CONCENTRATION-TIME COMBINATIONS
(from Peterson and Stewart, 1975)

In another study by Peterson and Stewart (1975), data from a series of human exposures to CO were analyzed to determine the fit to the theoretical CFK equation. 19 men and 3 women were exposed to concentrations of 50, 100 or 200 ppm for 0.33-5.25 hours. Three exercise levels from sedentary to 0, 150 or 300 kpm/min on an ergometer were used (15 subjects in total). These resulted in mean ventilation rates of 10.1 (9.1 for women), 14.0, 24.0 (19.7 for women) and 29.7 l/min, respectively. The CFK model predicted COHb for both men and women as well as for resting and exercising subjects within a standard error of about 2 %. In contrast to the original model, which assumes all variables to be constant except t, P_L, $COHb_t$ and P_{CO}, the following parameter alterations were introduced:

P_{O2}: When the partial pressure of oxygen in inspired air (Pi_{O2}) is less than the 149 mm Hg found under normal conditions, the partial pressure of oxygen in the lung capillaries will be less than the value of 100 mm Hg assumed by Coburn and coworkers. From measurements of oxygen partial pressure in arterial blood, which is assumed to be the same as the oxygen

partial pressure in lung capillaries, the following equation was derived: $P_{O2} = 1 / (0.072 - 0.00079\ Pi_{O2} + 0.000002515\ (Pi_{O2})^2)$ and
$Pi_{O2} = Fi_{O2}\ (P_B - 47 - Pi_{CO})$ with Fi_{O2} = fraction of oxygen in inspired air, P_B = barometric pressure (mm Hg), Pi_{CO} = partial pressure of CO in inspired air

D_L: Body size effects on diffusivity at rest were was calculated from published data as:
$D_L = 1 / (-0.0287 + 0.1188/A)$ with A = body surface in m^2

Vb: the published blood volume relationship of 74 mg/kg of body weight for men and 73 ml/kg for women was used.

V_A: The alveolar ventilation rate was expressed as: $V_A = V_E - f\ V_D$; with V_E = total rate of ventilation (ml/min), f = respiration rate (min^{-1}) and V_D = dead space (ml)

OHb_t: At standard concentrations, 1 g of hemoglobin will hold 1.38 ml of oxygen and thus OHb_{max} = 1.38 [Hb]/100, with [Hb] being the hemoglobin concentration in blood (g/100 ml). During and after CO exposure, the value of OHb_t that must be used is actually $OHb_t = OHb_{max} - COHb_t$. In this case, the CFK equation can only be solved by iterative procedures.

COHb: This value can be converted to the more conventional „percentage saturation“ by:
% carboxyhemoglobin = $COHb\ 100/OHb_{max}$

Tikuisis et al. (1992) studied the rate of formation of COHb in healthy young males at a low (45 W) and moderate (90 W) exercise load. Ten nonsmoking subjects were exposed to CO on two separate occasions distinguished by the activity level. Each experiment began with an exposure to 3000 ppm for 3 minutes during a rest period followed by 3 intermittent exposures ranging from 3000 ppm for 1 minute at low exercise to 667 ppm for 3 minutes at moderate exercise. The net increase in COHb after all exposures (about 10 %) deviated by <1 % between the measured and values predicted from the CFK model. Within this deviation, there was a general tendency of the CFK equation to underpredict the increase in COHb for the exposures at rest and the first exercise exposure and to overpredict levels for the latter two exposures at exercise.

Benignus et al. (1994) exposed 15 men to 7652 mg/m³ (6683 ppm) CO for 3.1-6.7 minutes at rest. Except for the Haldane constant M, which was assumed to be 245, all other physiological parameters of the CFK equation were measured for each individual from the very beginning of exposure. Arterial COHb was considerably higher than the venous COHb. The rate of increase in blood COHb and the arterial-venous COHb differences varied widely among individuals. The peak arterial COHb at the end of exposure ranged from 13.9 to 20.9 %. The peak venous levels reached during the recovery period ranged from 12.4 to 18.1 %. The arterial-venous difference ranged from 2.3 to 12.1 % COHb. The CFK equation overestimated venous blood COHb, whereas arterial blood levels were significantly and consistently underestimated.

Hill et al. (1977) developed a mathematical model to predict values of blood COHb in mother and fetus for prolonged exposures to 30-300 ppm CO. During CO exposure, fetal COHb lag behind maternal COHb by several hours. During prolonged uptake, fetal levels eventually overtake maternal levels and approach equilibrium values as much as 10 % higher than the mother‘s, due to the higher affinity of CO for fetal hemoglobin compared to adult hemoglobin. During CO washout the fetal levels again lag behind the mothers.

5. DATA ANALYSIS FOR AEGL-1

5.1. Human Data Relevant to AEGL-1

CO has no odor and does not cause irritative effects. A large number of studies investigated the effects of low CO exposure (COHb <10 %) on healthy individuals and high-risk groups. In these, effects on healthy persons, such as decreases in work capacity and decrements of neurobehavioral function, start at COHb of 5 % (WHO, 1999a; EPA, 2000).

In patients with coronary artery disease, which constitute the most susceptible subpopulation, the time to onset of angina and the time to 1-mm ST-segment change in the electrocardiogram during physical exercise were significantly reduced at COHb of 2.0 or 4.0 % (Allred et al. 1989a; b; 1991).

5.2. Animal Data Relevant to AEGL-1

No studies in experimental animals were located that were considered relevant for the derivation of AEGL-1 values. The studies describing effects of CO on cardiac function, such as Sekiya et al. (1983), DeBias et al. (1979) and Aronow et al. (1979), normally employ models in which the heart was damaged additionally by an electric stimulus or by coronary artery ligation. Effects of CO exposure found in these systems can hardly be extrapolated quantitatively to humans.

5.3. Derivation of AEGL-1

CO is an imperceptible toxic gas. Until very severe symptoms occur (inability to walk) none or only nonspecific symptoms were noted in healthy humans and monkeys (Haldane, 1895; Purser and Berrill, 1983).

In patients with coronary artery disease, which constitute the most susceptible subpopulation, effects, such as significant electrocardiogram changes, reduced time to the onset of angina and increased cardiac arrhythmia, start occurring at exposure concentrations little higher than current ambient air quality guidelines, e.g. the U.S. National Air Quality Guideline of 9 ppm for 8 hours (National Air Pollution Control Administration, 1970; FR , 2000; EPA, 2000; Raub, 2000), the WHO Air Quality Guideline of 10 mg/m³ (9 ppm) for 8 hours (based on 2.5 % COHb) (WHO, 1999a) and the designated European Union Limit Value of 10 mg/m³ (9 ppm) for 8 hours (EC, 1999). These cardiac effects were considered above the AEGL-1 level and thus would not constitute a suitable basis for the derivation of AEGL-1 values.

AEGL-1 values are not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population.

In addition, CO exposures encountered frequently in everyday life are at or above the concentration range, in which AEGL-1 level would have to be set: smokers have COHb in the range of 3-8 % (Radford and Drizd, 1982) and CO concentrations of about 10-50 ppm, which can be found on heavily traveled roads, inside motor vehicles and in homes with gas-, coal-, wood- or kerosene-fired heaters and stoves, correspond to an equilibrium COHb of 1.8-7.5 % (see Figures 2 and 4).

TABLE 13: AEGL-1 VALUES FOR CARBON MONOXIDE					
AEGL Level	**10 minutes**	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	N.R.[a]	N.R.	N.R.	N.R.	N.R.

[a] N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population

6. DATA ANALYSIS FOR AEGL-2

6.1. Human Data Relevant to AEGL-2

In patients with coronary artery disease, COHb of 2 or 4 % significantly reduced the time to angina and the time to 1-mm change in the ST-segment of the electrocardiogram upon physical exercise; at 4 % the total exercise time and the heart rate-blood pressure product were also significantly reduced (Allred et al., 1989a; b; 1991). A reduced time to onset of exercise-induced chest pain at COHb between 2.5 and 4.5 % was also reported by several other studies (Aronow et al., 1972; Anderson et al., 1973; Sheps et al., 1987; Kleinman et al., 1989; 1998).

Sheps et al. (1990; 1991) reported that in patients with coronary artery disease the frequency of ventricular premature depolarizations was significantly increased at an COHb of 5.3 %, but not at 3.7 %, compared to room air exposure. Dahms et al. (1993) found no increased frequency of ventricular ectopic beats at COHb of 3 or 5 %.

Klasner et al. (1998) analyzed a mass poisoning of 504 school children. In 147 of 155 children that showed symptoms, the mean COHb measured about 1 hour (up to 2 hours) after removal from the CO atmosphere was 7.0 % COHb. Of all children that were examined in hospital (177) (mean age 8.7 years) the following symptoms were observed: headache (139), nausea (69), dizziness (30), dyspnea (19), vomiting (13), abdominal pain (11) and drowsiness (9).

In an analysis of CO poisonings in 16 children (up to 14 years of age) with COHb of 15 % or higher, Crocker and Walker (1985) reported thresholds for effects, such as nausea, vomiting, headache and lethargy between 16.7 and 19.8 % COHb (average concentrations in children displaying these symptoms were 25.9-29.4 %). Visual symptoms and syncopes occurred at a threshold of 24.5 % COHb (average 31.6-32.5 %). All 9 children with a COHb of 24.5 % or higher experienced at least one syncope.

In an investigation on long-term effects of CO poisoning in children, evaluated 2-11 years after the poisoning, Klees et al. (1985) reported that 6 of the 14 children exhibited serious disorders (spatial organization problems, constructive apraxia, deterioration of lexical activity, as well as spelling and arithmetic). Compared to the other 7 children, that exhibited only slight impairment of visual memory and concentration, the first group of more severely affected children were younger (mean age 7.8 years; range 2.8-12.1 years) than the latter group (mean age 9.8 years; range 3.5-14.5); there was no difference in measured COHb (mean 21 (range 13-32) % in the first vs. 22 (16-26) % in the latter group). A short-term follow-up (3 months after the poisoning) suggested that medium intoxications (reported COHb 16-27 %) did not produce manifest sequelae except for a momentary standstill in the child‘s progress of about 2 months.

Kizakevich et al. (1994) reported that healthy young men can perform submaximal exercise without overt impairment of cardiovascular function after CO exposures attaining 20 % COHb. Stewart et al. (1970) found that a CO exposure of healthy subjects resulting in 12.5 to 25.5 % COHb did not affect the results of several neurophysiological tests. Nielsen (1971) did not report on severe effects in three subjects that were repeatedly exposed to CO resulting in concentrations of 25-33 % COHb. In a poisoning incident at the workplace, severe headaches, dizziness, weakness, nausea, chest pain, shortness of breath and other symptoms were reported for a COHb of about 35 % (Ely et al., 1995).

6.2. Animal Data Relevant to AEGL-2

In a study in cynomolgus monkeys, Purser and Berrill (1983) reported that during exposure to 900 ppm CO for a total of 30 minutes, no signs of intoxication occurred until 20-25 minutes (corresponding to COHb of about 16-21 %). At 25 minutes into the exposure, the animals‘ performance in a behavioral test significantly decreased. At the end of the exposure period, the animals became less active, most of them were lying down, but animals did not collapse. At a 1000 ppm, no effects were observed during the first 16-20 minutes. At this time the animals became less active and sat down for short periods. At about 25 minutes, the animals went into a state of severe intoxication within 1-2 minutes, in which animals were lying down with eyes closed, they sometimes vomited and were virtually unable to perform coordinated movements.

Significant memory impairment in behavioral tests were found in young rats after continuous CO exposure throughout gestation (mean maternal COHb was 15.6 %) (Mactutus and Fechter, 1985).

In monkeys, a COHb of 9.3 % resulted in reduced threshold for electric shock-induced ventricular fibrillation (DeBias et al., 1979). Aronow et al. (1979) reported that CO exposure increased the vulnerability of the heart to induced ventricular fibrillation in normal dogs breathing 100 ppm CO for 2 hours (resulting COHb was 6.3-6.5 %). The ventricular fibrillation was induced by an electrical stimulus applied to the myocardium. A COHb of 13-15 % increased the severity and extent of ischemic injury and the magnitude of ST-segment elevation in a myocardial infarction model in dogs (Sekiya et al., 1983).

6.3. Derivation of AEGL-2

The derivation of AEGL-2 values was based on effects in patients with coronary artery disease. An estimated 62 million people in the United States (about 20 % of the population) have one or more types of cardiovascular disease (American Heart Association, 2003). For the major diseases within the category of total cardiovascular disease, about 50 million Americans have high blood pressure, 13 million have ischemic (coronary) heart disease, 5 million have heart failure, 4 million have cerebrovascular disease (stroke), and 2 million have rheumatic fever or heart disease.

For the derivation of AEGL-2 values a level of 4 % COHb was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion (Allred et al., 1989a; b; 1991).

Caracteristic points of an electrocardiogramm are the P wave, reflecting atrial depolarization, the QRS complex, representing the ventricular muscle depolarization, and the T wave, reflecting ventricular muscle repolarization. In the normal electrocardiogramm, the ST segment is isoelectric, resting at the same potential as the interval between the T wave and the next P wave. Horizontal depression or a downsloping ST segment merging into the T wave occurs as a result of ischemia, ventricular strain, changes in the pattern of ventricular depolarization or drug effects. In chronic ischemic heart disease, there may be moderate degrees of horizontal ST segment depression or a downward sloping ST segment, flattening or inversion of T waves and prominent U waves. It is difficult to define an abnormal ST segment depression in precise quantitative terms. However, a myocardia ischemia has to be considered if the beginning of the ST segment is more than 0.5 mm (corresponding to 0.05 mV) below the isoelectric line and there is an associated T wave abnormality (Wilson et al., 1991).

According to the practice guidelines for chronic stable angina (Gibbons et al., 1999), a ST-segment depression at rest is a marker for adverse cardiac events in patients with and without known coronary artery disease. Additional exercise-induced ST-segment depression in the patient with >=1 mm rest ST-segment depression is a reasonably sensitive indicator of coronary artery disease. The ST-segment depression is indicative of clinically relevant myocardial ischemia requiring medical treatment. From the ST-segment depression, the Duke treadmill score can be calculated. It equals the exercise time in minutes minus (5x the ST-segment deviation, during or after exercise, in millimeters) minus (4x the angina index, which has a value of "0" if there is no angina, "1" if angina occurs, and "2" if angina is the reason for stopping the test). Among outpatients with suspected coronary artery disease, the two thirds of patients with scores indicating low risk (score >=5) had a four-year survival rate of 99% (average annual mortality rate 0.25%), and the 4% who had scores indicating high risk (score <-10) had a four-year survival rate of 79% (average annual mortality rate 5%) (Gibbons et al., 1999).

In the available experimental studies, the CO exposure alone (i.e. with subjects at rest) did not cause angina, while exercise alone did so. Moreover, the changes in the electrocardiogram (ST-segment depression of 1 mm or greater) as well as the angina symptoms can be considered fully reversible after a single incident. This effect level was considered to be below that defined for AEGL-2. It should be noted that all experimental studies used patients with stable exertional angina, who did not experience angina while at rest. Thus, it is considered likely that in more susceptible individuals (a part of the patients with unstable angina pectoris might belong to this group) CO exposure alone could increase angina symptoms. In hypersusceptible patients more severe effects, even including myocardial infarction cannot be ruled out.

It should be noted that in contrast to the anecdotal case reports on myocardial infarction discussed in the derivation of AEGL-3, the studies investigating electrocardiogram changes and angina symptoms in patients with coronary artery disease, used here for the derivation of AEGL-2 values, are high-quality, well-conducted experimental studies with well-characterized exposure conditions and information on interindividual variability.

An exposure level of 4 % COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. This effect has been observed at COHb of 5.3 %, but not at 3.7 % (Sheps et al., 1990; 1991), while in another study no effect of CO exposure on ventricular arrhythmia was found at 3 or 5 % COHb (Dahms et al., 1993). No experimental studies in heart patients are available that used significantly higher levels of COHb.

Use of a level of 4 % COHb as a point of departure for the derivation of AEGL-2 values is supported by the studies in animals: a COHb of 9.3 % resulted in a reduced threshold for electric shock-induced ventricular fibrillation in monkeys (DeBias et al., 1979) and a COHb of 6.3-6.5 % increased the vulnerability of the heart to electrically induced ventricular fibrillation in healthy dogs (Aronow et al., 1979). These animal studies suggest that a level below 6-9 % COHb should be selected for AEGL-2 derivation in order to protect individuals with compromised cardiac function.

A total uncertainty factor of 1 for intraspecies variability was considered adequate based on supporting evidence in other susceptible subpopulations (children, pregnant women, elderly people and smokers):

1) The derived AEGL-2 values would result in a COHb of 4.9-5.2 % in 5-year-old children (see Table 19 in Appendix B). This level is considered protective of neurotoxic effects in children: 1) in the study by Klasner et al. (1998) acute neurotoxic effects, such as headache, nausea, dizziness, dyspnea and vomiting were found at a mean COHb of 7.0 % (measured after a mean time of 1 hour (up to 2 hours) after removal of the children from the CO atmosphere). This suggests that the end of exposure COHb had been between 10 and 14 % (these values were estimated using the mathematical model of Coburn et al. (1965) and Peterson and Stewart (1975). 2) In the study by Crocker and Walker (1985) a threshold of 24.5 % COHb for syncopes in children, an effect that was considered to impair the ability to escape, was reported. 3) In the study by Klees et al. (1985), that investigated long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children, the lowest concentration resulting in cognitive development defects was 13 % COHb in the long-term follow-up study. The COHb reported in the Crocker and Walker (1985) as well as in the Klees et al. (1985) studies were measured after hospital admission and may have been considerably lower than levels at the time of the end of the CO exposure, as has also been described in the Klasner et al. (1998) study. Also the percentage of children that received oxygen before hospital admission was probably considerably higher in these two studies since after acute exposure to high CO concentrations (e.g. by fires in homes) severe poisoning symptoms occurred. Oxygen administration reduces the elimination half time in children to about 44 minutes (Klasner et al., 1998).

The observations in children are supported by observations in experimental animals. In the study by Purser and Berrill (1983) at COHb little higher than 16-21 % syncope-like effects occurred in monkeys and in mice memory impairment was found in the offspring of rats exposed continuously at COHb of 15.6 % during gestation (Mactutus and Fechter, 1985).

2) Caravati et al. (1988) and Koren et al. (1991) described cases of stillbirth after CO exposure of pregnant women. In these cases, the COHb measured in the maternal blood were higher than 22-25 %. There are no studies reporting effects on the unborn after a single acute exposure resulting in lower COHb levels (EPA, 2000). Cigarette smoking of pregnant women is associated with a lower birth weight, however, these effects cannot be clearly attributed to CO only because cigarette smoke is a complex mixture of chemicals (EPA, 2000). There is no evidence that a single elevation of COHb has any negative effects on pregnancy.

3) There is no evidence that elderly people without cardiovascular disease are more susceptible to an acute CO exposure than younger adults (EPA, 2000; WHO, 1999a). Therefore, AEGL-2 values derived on effects in coronary artery disease patients are likely to protect other elderly people.

4) In smokers with a background COHb of 3-8 % from smoking, exposure to the AEGL-3 concentration-time combinations will result in 6.2. and 11.5 % COHb (see Table 19 in Appendix B). Smokers may show an adaptive response to their chronically elevated COHb levels, as evidenced by increased red blood cell volumes or reduced plasma volumes (EPA, 2000). This adaptive response is likely to reduce the effect level in smokers compared to non-smokers exposed to the same total COHb level. The estimated COHb exposure level in smokers who are healthy adults is unlikely to lead to significant health effects (Kizakevich et al., 1994; Stewart et al., 1970; Nielsen, 1971). For pregnant women, cigarette smoking alone may cause effects on the unborn (EPA, 2000). A single additional exposure to COHb levels of 6.2-11.5 % over the “smoking background” of 3-8 % COHb is considered unlikely to significantly contribute to the effects of smoking during pregnancy. No study is available that compared the effects on the cardiovascular system of a 4 % elevation of the background COHb level in non-smoking and smoking patients with coronary artery disease.

However, a single exposure to COHb levels of 6.2-11.5 % over the "smoking background" of 3-8 % COHb is considered unlikely to significantly contribute to the effects of smoking on the cardiovascular system.

In conclusion, patients with coronary artery disease must be considered more susceptible to the effects of CO than other subpopulations that may be more susceptible than healthy adults, i.e., children, elderly people and pregnant women. A level of 4 % COHb was the NOEL for AEGL-2 effects in patients with coronary artery disease, while the LOEL was estimated at 6-9 %. In comparison, the LOEL was about 10-15 % in children and 22-25 % in pregnant women. Since AEGL-2 values were based on experimental data on the most susceptible subpopulation, they were considered protective also for other subpopulations and a total uncertainty factor of 1 was used.

Using the CFK model (Coburn et al., 1965; Peterson and Stewart, 1975), exposure concentrations were calculated for 10 minutes, 30 minutes, 1 hour, 4 hours and 8 hours, that would result in a end-of-exposure COHb of 4 % in adults (see Appendix B). It should be noted that calculations were performed for a 70-kg man with a starting COHb of 0.75 % due to endogenous CO production and using a ventilation rate of 23 m^3/day. Somewhat higher end-of-exposure COHb would result for children. For a 5-kg child with an alveolar ventilation rate of 3580 mg/min, COHb values between 4.9 to 5.2 % were calculated for the different AEGL time points. For a 3.5-kg newborn with an alveolar ventilation rate of 1250 ml/min, COHb values between 5.3 and 5.6 % were calculated. Higher COHb value will also be obtained in people having a higher starting COHb as a result from other exposures. For smokers having typical starting COHb levels between 3 and 8 %, COHb values between 6.2 and 11.5 % will result from exposure to AEGL-2 concentration-time combinations.

A total uncertainty factor of 1 was used. An intraspecies uncertainty factor of 1 was considered adequate because the values are based on observations in the most susceptible human subpopulation (patients with coronary artery disease).

It is acknowledged that apart from emergency situations, certain scenarios could lead to CO concentrations which may cause serious effects in persons with cardiovascular diseases. These scenarios include e.g. extended exposure to traffic fume emissions (e.g., in tunnels or inside cars with defect car exhaust systems), charcoal or wood fire furnaces, and indoor air pollution by tobacco smoking.

The values are listed in Table 14 below.

TABLE 14: AEGL-2 VALUES FOR CARBON MONOXIDE

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-2	420 ppm (480 mg/m^3)	150 ppm (170 mg/m^3)	83 ppm (95 mg/m^3)	33 ppm (38 mg/m^3)	27 ppm (31 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Human Data Relevant to AEGL-3

A large number of deaths occur annually due to acute poisonings in fires and in closed locations (e.g. in private homes and workplaces). In the latter instance, poisoning usually occurs because gas-, oil- or coal-fired furnaces or stoves are operated without sufficient ventilation. In apparently healthy people that died from CO poisoning, usually COHb of 60 % or higher are found (Balraj, 1984; AIHA, 1999; AIHA, 1999; Winter and Miller, 1976, Holmes, 1985, Stewart, 1975). In early experimental studies, healthy subjects were exposed to sufficient concentration-time combinations to reach levels of about 40 to 55 % COHb (Haldane, 1895; Chiodi et al., 1941). Effects described at this level of CO exposure included hyperpnea, confusion of mind, dim vision and unsteady/inability to walk (Haldane, 1895). Henderson et al. (1921) exposed subjects for 1 hour to 34-38 % COHb. Subjects showed a marked loss of equilibrium in the Romberg test, irritability, throbbing frontal headache and at times Cheyne-Stokes breathing was observed. Analysis of 101 cases of lethal CO poisoning and 158 surviving patients revealed that only about 2 % of deceased subjects had COHb levels below 40 %. Of the patients that survived about 16 % had a COHb above 40 % (Pach et al., 1978; 1979).

Kizakevich et al. (1994) reported that healthy young men can perform submaximal exercise without overt impairment of cardiovascular function after CO exposures attaining 20 % COHb. Stewart et al. (1970) found that a CO exposure of healthy subjects resulting in 12.5 to 25.5 % COHb did not affect the results of several neurophysiological tests. Nielsen (1971) did not report on severe effects in three subjects that were repeatedly exposed to CO resulting in concentrations of 25-33 % COHb.

In susceptible groups of the population, deaths may be caused by considerable lower exposure to CO: Caravati et al. (1988) and Koren et al. (1991) described cases of stillbirth after CO exposure of pregnant women. In these cases, the COHb measured in the maternal blood were higher than 22-25 %.

Persons with coronary artery disease constitute another susceptible subpopulation (Balraj, 1984). Several case reports indicate that death through myocardial infarction can occur after repeated or prolonged exposure, the corresponding COHb levels measured after transport to the hospital (and thus not representing the end-of-exposure concentrations) were around 20-30 % and as low as about 15 % (Atkins and Baker, 1985; Ebisuno et al., 1986; Grace and Platt, 1981).

7.2. Animal Data Relevant to AEGL-3

Several studies reported LC_{50} values for rats, mice and guinea pigs for exposure durations between 5 minutes and 4 hours. The values are given in Table 11 and are shown in Figure 1. Similar to humans, the minimum lethal COHb in rats and mice were about 50-70 % (E.I. du Pont de Nemours and Co., 1981; Rose et al., 1970).

An increase in the rate of stillbirths was reported in pigs after a 2-3 day-exposure to CO resulting in maternal COHb above 23 % (Dominick and Carson, 1983). Increased rates in fetal mortality were also observed in rabbits after continuous exposure maternal COHb of 16-18 % throughout gestation (Astrup et al., 1972) as well as after daily exposure to high CO concentrations in cigarette smoke (exposure for 12 minutes/day on gestational days 6-18, resulting in COHb of 16 %) (Rosenkrantz et al., 1986).

7.3. Derivation of AEGL-3

The derivation of AEGL-3 values was based on observations in humans. Several case reports indicate that in patients with coronary artery disease, CO exposure can contribute to myocardial infarction (which was considered an AEGL-3 endpoint). In the published cases of myocardial infarction, the following COHb values were measured after transport to the hospital: 52.2 % (Marius-Nunez, 1990), 30 %, 22.8 % (Atkins and Baker, 1985), 21 % (Ebisuno et al., 1986), 15.6 % (Grace and Platt, 1981). These anecdotal reports on cases affecting susceptible subpopulations were considered as important supporting information, but not as an adequate basis for the derivation of AEGL-3 values because of uncertainties about the end of exposure COHb levels, and whether repeated and/or prolonged exposures caused the infarction.

The analysis of 101 cases of lethal poisoning and 158 cases of non-lethal poisoning by Pach et al. (1878; 1979) was used as the basis for derivation of AEGL-3 values. In the group of surviving patients only those were included from which blood for COHb analysis had been obtained within 2 hours from cessation of exposure. The COHb at the end of exposure was calculated by the authors of the report. Analysis revealed that only about 2 % of deceased subjects had COHb levels below 40 %. Of the patients that survived about 16 % had a COHb above 40 %. From this study a threshold for lethal poisoning of about 40 % can be derived. This level is supported by experimental studies performed in healthy human subjects. Studies by Chiodi et al. (1941), Henderson et al. (1921), and Haldane (1895) suggest that a COHb of about 34-56 % does not cause lethal effects in healthy individuals. Further support comes from the studies by Kizakevich et al. (1994), Stewart et al. (1970), and Nielsen (1971) that reported headache as the only symptom when subjects were exposed to 20-33 % COHb. A level of 40 % COHb was used as the basis for AEGL-3 derivation. This point of departure is supported by studies in animals reporting minimum lethal COHb levels in rats and mice of about 50-70 % (E.I. du Pont de Nemours and Co., 1981; Rose et al., 1970).

Using the CFK model (Coburn et al., 1965; Peterson and Stewart, 1975), exposure concentrations were calculated that would result in a COHb of 40 % at the end of exposure periods for 10 and 30 minutes as well as for 1, 4 and 8 hours (see Appendix B).

A total uncertainty factor of 3 for intraspecies variability was considered adequate based on supporting evidence in susceptible subpopulations:

1) Exposure to the derived AEGL-3 concentrations will result in COHb values of about 14-17 % in adults (see Table 21 in Appendix B). In the reported cases of myocardial infarction, the measured COHb was normally above 20 %, except in one case in which the measured COHb was about 15 %. In this case (Grace and Platt, 1981), the man was exposed during several weeks to (presumably) the same high CO concentration in his home and presented two times to the emergency room with signs of CO intoxication (which were misdiagnosed) until the infarction occurred. Therefore, the derived AEGL-3 values are considered to protect heart patients against CO-induced myocardial infarction. It should be noted, however, that a clear threshold for this endpoint cannot be defined because myocardial infarction might be triggered at lower COHb in hypersusceptible individuals and myocardial infarction can also occur spontaneously or by trigger effects (e.g. psychological stress, physical exertion) which have no relevant effects on the health of normal subjects.

2) With regard to stillbirths, a COHb of 14-17 % was considered protective of lethal effects on the unborn, because in the case studies available, stillbirths were found only after measured maternal COHb of about 22-25 % or higher (Caravati et al., 1988; Koren et al., 1991). In the clinic, a measured COHb of about 15-20 %

in pregnant women (implicating a higher end-of-exposure level) is considered a severe CO intoxication that could require hyperbaric oxygen treatment (Ellenhorn, 1997; Tomaszewski, 1998). Available animal studies reported increased rates of stillbirths after a 2-3 day exposure at maternal COHb above 23 % (Dominick and Carson, 1983), after continuous exposure at maternal COHb of 16-18 % (Astrup et al., 1972), and repeated short-term exposures at 16 % maternal COHb (Rosenkrantz et al., 1986). Taken together, the animal data support the conclusion that pregnant women should not be exposed to COHb levels higher than about 14-17 % in order to prevent lethal effects on the unborn.

3) In smokers with a background COHb of 3-8 % from smoking, exposure to the AEGL-3 concentration-time combinations will result in COHb levels between 16.1 and 23.0 % (see Table 21 in Appendix B). Smokers may show an adaptive response to their chronically elevated COHb levels, as evidenced by increased red blood cell volumes or reduced plasma volumes (EPA, 2000). This adaptive response is likely to reduce the effect level in smokers compared to non-smokers exposed to the same total COHb level. The estimated COHb exposure level in smokers is considered protective of lethal effects if they are healthy adults. Also, from the discussion above, it is considered unlikely that smoking pregnant women will have an increase risk of stillbirths at the AEGL-3 exposure level. As discussed above, a threshold for the induction of myocardial infarction by CO exposure cannot be defined. Therefore, heavy smokers with coronary artery disease, which have a higher risk for myocardial infarction already from smoking (American Heart Association, 2003) , may be at somewhat higher risk compared to non-smoking patients.

The values are listed in Table 15 below.

TABLE 15: AEGL-3 VALUES FOR CARBON MONOXIDE

AEGL Level	10 minutes	30 minutes	1 hour	4 hours	8 hours
AEGL-3	1700 ppm (1900 mg/m³)	600 ppm (690 mg/m³)	330 ppm (380 mg/m³)	150 ppm (170 mg/m³)	130 ppm (150 mg/m³)

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

The AEGL values for various levels of effects and various time periods are summarized in Table 16. They were derived using the following key studies and methods.

AEGL-1 values are not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population.

The AEGL-2 was based on cardiovascular effects in patients with coronary artery disease, which constitute the most susceptible subpopulation. For the derivation of AEGL-2 values a level of 4 % COHb was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion. The changes in the electrocardiogram (ST-segment depression of 1 mm or greater) associated with angina symptoms were fully reversible. An exposure level of 4 % COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. A mathematical model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations resulting in a COHb of 4 % at the end of exposure periods of 10 and 30 minutes and 1, 4 and 8 hours. An intraspecies uncertainty factor of 1 was used. A total uncertainty factor of 1 was used. An intraspecies uncertainty factor of 1 was considered adequate because the values are based on observations in the most susceptible human subpopulation (patients with coronary artery disease).

The AEGL-3 was based on the study by Pach et al. (1978; 1979) that analyzed 101 cases of lethal and 158 cases of non-lethal poisoning and revealed that only about 2 % of subjects that had died had COHb levels below 40 %. Of the patients that survived about 16 % had a COHb above 40 %. A threshold for lethality of 40 % is supported by experimental studies by Chiodi et al. (1941), Henderson et al. (1921), and Haldane (1895), in which exposures resulting in COHb of 34-56 % did not cause lethal effects in healthy individuals. Further support comes from the studies of Kizakevich et al. (1994), Stewart et al. (1970), and Nielsen (1971) that reported headache as the only symptom when health adults were exposed to 20-33 % COHb. A level of 40 % COHb was used as the basis for AEGL-3 derivation. A mathematical model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations resulting in a COHb of 40 % at the end of exposure periods of 10 and 30 minutes and 1, 4 and 8 hours. An intraspecies uncertainty factor of 3 was used. The derived values (corresponding to a COHb value of about 15%) are supported by information on effects, such as myocardial infarction and stillbirths, reported in more susceptible subpopulations.

TABLE 16: SUMMARY/RELATIONSHIP OF AEGL VALUES FOR CARBON MONOXIDE

Classification	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1 (Nondisabling)	N.R. [a]	N.R.	N.R.	N.R.	N.R.
AEGL-2 (Disabling)	420 ppm (480 mg/m³)	150 ppm (170 mg/m³)	83 ppm (95 mg/m³)	33 ppm (38 mg/m³)	27 ppm (31 mg/m³)
AEGL-3 (Lethal)	1700 ppm (1900 mg/m³)	600 ppm (690 mg/m³)	330 ppm (380 mg/m³)	150 ppm (170 mg/m³)	130 ppm (150 mg/m³)

[a] N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population

All inhalation data are summarized in Figure 3 below. The data were classified into severity categories chosen to fit into definitions of the AEGL level health effects. The category severity definitions are "No effect"; "Discomfort"; "Disabling"; "Some Lethality"; "Lethal" and "AEGL". In the figure depicting the COHb levels, the AEGL lines are drawn at the COHb levels for adults. The grey boxes above the lines indicate the range of COHb levels in neonates, children and smokers (with 8 % COHb from smoking).

The single exposure animal data point in the AEGL-2 COHb box represents the study by Aronow et al. (1979) using dogs with electrically damaged hearts. The two single exposure human data points in the bos represent the study by Sheps et al. (1990; 1991) reporting increase arrhythmia in heart patients and the study by Klasner et al. (1998) reporting moderate neurotoxic effects in children.

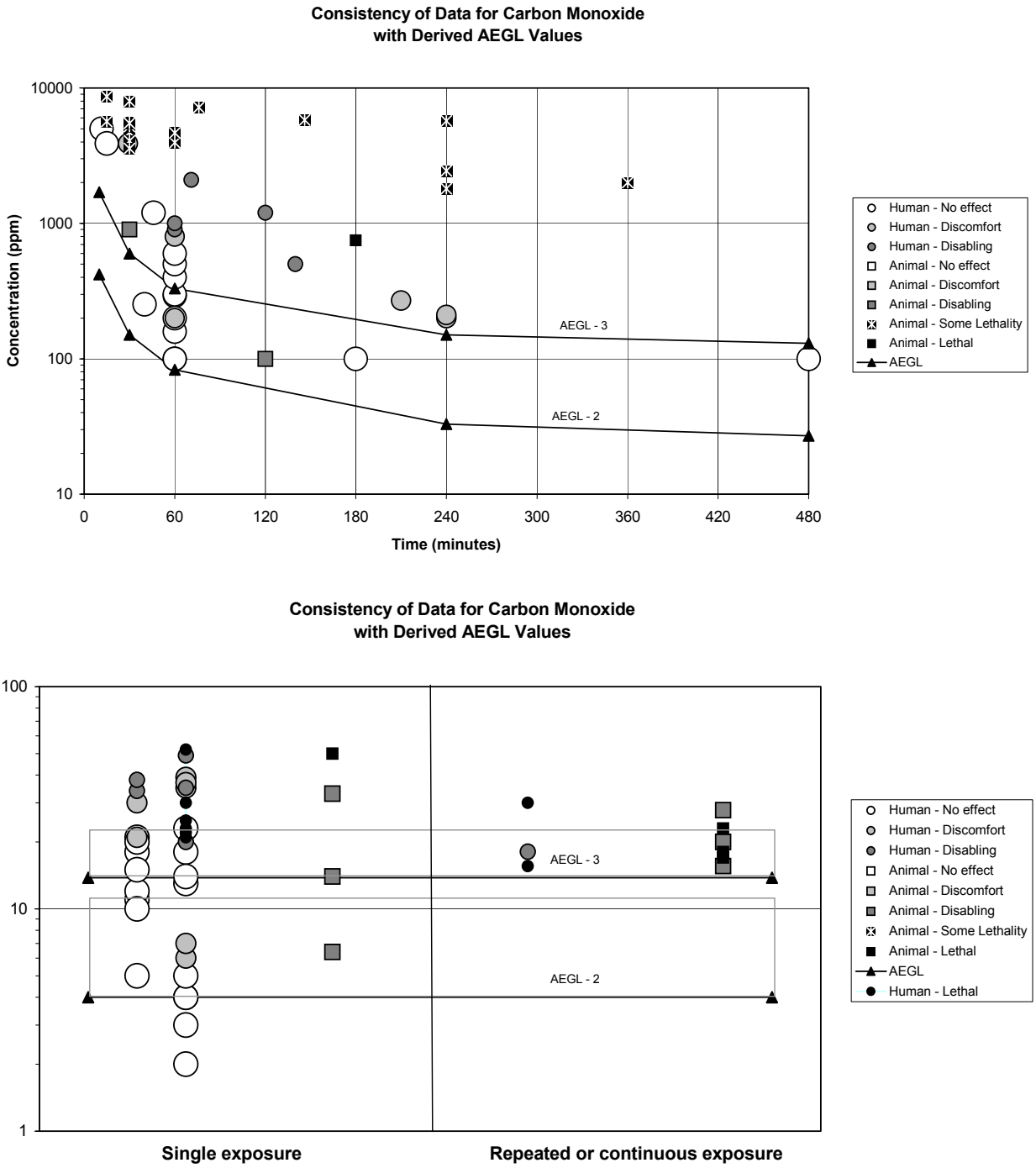


FIGURE 3: CATEGORICAL REPRESENTATION OF ALL CO INHALATION DATA

8.2. Comparison with Other Standards and Criteria

Other standards and guidance levels for workplace and community exposures are listed in Table 17. The German BAT (Biologischer Arbeitsstoff-Toleranz-Wert; biological exposure index) is 5 % COHb, equivalent to a concentration of 30 ppm CO (Greim und Lehnert, 1994). The ACGIH BEI (biological exposure index) is 3.5 % COHb at the end of shift, equivalent to a CO concentration in end exhaled air of 20 ppm (ACGIH, 1999).

TABLE 17: EXTANT STANDARDS AND GUIDELINES FOR CARBON MONOXIDE

Guideline	Exposure Duration				
	10 minutes	**30 minutes**	**1 hour**	**4 hours**	**8 hours**
AEGL-1	N.R. *	N.R.	N.R.	N.R.	N.R.
AEGL-2	420 ppm	150 ppm	83 ppm	33 ppm	27 ppm
AEGL-3	1700 ppm	600 ppm	330 ppm	150 ppm	130 ppm
ERPG-1 (AIHA) [a]			200 ppm		
ERPG-2 (AIHA)			350 ppm		
ERPG-3 (AIHA)			500 ppm		
EEGL (NRC) [b]	1500 ppm	800 ppm	400 ppm		50 ppm [24 hours]
PEL-TWA (OSHA) [c]					50 ppm
IDLH (NIOSH) [d]		1200 ppm			
REL-TWA (NIOSH) [e]					35 ppm [200 ppm ceiling]
TLV-TWA (ACGIH) [f]					25 ppm
MAK (Germany) [g]					30 ppm
MAK Spitzenbegrenzung (Germany) [h]		60 ppm			
MAC (The Netherlands) [i]					25 ppm
Einsatztoleranzwert [j]				100 ppm	
WHO Air Quality Guideline [k]	87 ppm for 15 min	52 ppm	26 ppm		9 ppm
U.S. National Ambient Air Quality Standard [l]			35 ppm		9 ppm
EU Ambient Air Limit Value [m]					9 ppm

* N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population.

[a] **ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association)** (AIHA, 1999)

The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor. The ERPG-1 value is based on a COHb of 5-6 %, which, based on the original CFK model using a ventilation rate at rest, is considered to be produced by 1-hour CO exposure to 200 ppm.. This exposure level is not expected to produce any effects during a 1-hour exposure period. While delayed transient effects, such as headache, are possible, no permanent effects in more susceptible individuals are expected.

The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual‘s ability to take protective action. The ERPG-2 value is based on a COHb of 10-12 %, which, based on the original CFK model using a ventilation rate at rest, is considered to be produced by 1-hour CO exposure to 350 to 500 ppm.. This exposure level is expected to cause slight neurological symptoms (increased threshold of visual light) in healthy individuals and chest pain at less exertion in heart patients. (Comment: The ERPG derivation does not discuss the CO effects on children. Moreover, model calculation for deriving ERPG values assumed a resting ventilation rate, while for derivation of AEGL values a ventilation rate corresponding to light to moderate activity was assumed).

The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects. The ERPG-3 is based on the believe that humans can generally tolerate COHb of 20 % for brief periods without substantial toxicity. Based on the original CFK model using a ventilation rate at rest, it was considered that exposure to 500 ppm for 1 hour will lead to a COHb of about 15 %. (Comment: The ERPG derivation does not discuss the CO effects on children. Moreover, model calculation for deriving ERPG values assumed a resting ventilation rate, while for derivation of AEGL values a ventilation rate corresponding to light to moderate activity was assumed).

[b] **EEGL (Emergency Exposure Guidance Levels, National Research Council)** (NRC, 1987)

is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury. The NRC document states that 400 ppm (460 mg/m³) was determined as the concentration of CO to which a 1-hour exposure would result in a carboxyhemoglobin (COHb) level of less than 10% in resting individuals. The committee cautions that sensitive individuals, such as persons with angina or heart disease, should not be exposed to concentrations approaching the EEGL as they may incur serious adverse health effects (Comment: The EEGL derivation excludes patients with coronary artery disease. Moreover, model calculation for deriving EEGL values assumed a resting ventilation rate, while for derivation of AEGL values a ventilation rate corresponding to light to moderate activity was assumed).

[c] **OSHA PEL-TWA (Occupational Health and Safety Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA, website)

is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d] **IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH, 1996)

represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects. The IDLH value is based on the observation by Henderson et al., 1921, that exposure of a healthy man at 1000 ppm for 1 hour caused unpleasant but no dangerous symptoms, and that more severe symptoms develop at 40 % COHb (Steward, 1975). According to the CFK model, a 30-minute exposure at 1200 ppm will produce a COHb of 10-13 %. (Comment: The IDLH derivation does not discuss patients with coronary artery disease. In the Henderson et al. (1921) study, the subject was sitting still during exposure and developed Cheyne-Stokes breathing at the end of exposure, which is considered a serious effect. Moreover, model calculation in the IDLH derivation assumed a resting ventilation rate, while for derivation of AEGL values a ventilation rate corresponding to light to moderate activity was assumed).

[e] **NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH, 1996)

is defined analogous to the ACGIH-TLV-TWA.

[f] **ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH, 2001)

is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect. “This value is intended to maintain blood COHb levels below 3.5 %, to minimize the potential for adverse neurobehavioral changes, and to maintain cardiovascular work and exercise capacities”.

[g] **MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration], Deutsche Forschungsgemeinschaft [German Research Association], Germany)** (Henschler, 1981; DFG, 1999)

is defined analogous to the ACGIH-TLV-TWA.

[h] **MAK Spitzenbegrenzung (Kategorie II,2) [Peak Limit Category II,1]** (DFG, 1999)

constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes, with no more than 4 exposure periods per workshift; total exposure may not exceed 8-hour TWA MAK.

[i] **MAC ([Maximum Workplace Concentration], Dutch Expert Committee for Occupational Standards, The Netherlands)** (MSZW, 1999)

is defined analogous to the ACGIH-TLV-TWA.

[j] **Einsatztoleranzwert [Action Tolerance Levels] (Vereinigung zur Förderung des deutschen Brandschutzes e.V. [Federation for the Advancement of German Fire Prevention])** (Greim, 1996)

constitutes a concentration to which unprotected firemen and the general population can be exposed to for up to 4 hours without any health risks.

[k] **Air Quality Guideline** (WHO, 1999a)

is based on a COHb of 2.5 %, which should not be exceeded even when a normal subject engages in light or moderate exercise.

[l] **U.S. National Ambient Air Quality Standard** (National Air Pollution Control Administration, 1970; FR , 2000; EPA, 2000)

[m] **EU Limit Value for Ambient Air** (EC, 1999)

8.3. Data Adequacy and Research Needs

A sufficient number of experimental and case studies in humans is available for the derivation of AEGL values.

CO is the classical example of an imperceptible toxic gas. Until very severe symptoms occur (inability to walk) none or only nonspecific symptoms were noted in monkeys and healthy humans. For this reason no AEGL-1 values for CO are recommended.

AEGL-2 values were based on cardiac effects in subjects with coronary artery disease. Several high quality studies are available addressing endpoints such as time to the onset of exercise-induced angina, time to the onset of exercise-induced 1-mm ST-segment changes in the electrocardiogram and frequency of exercise-induced arrhythmias. However, no experimental studies in heart patients are available that used significantly higher levels of COHb than about 5 % COHb.

AEGL-3 values were based analysis of clinical cases of lethal and non-lethal poisoning as well as on old experimental studies in which healthy subjects were exposed to COHb of up to 40-56 %. The AEGL-3 values derived using an intraspecies uncertainty factor of 3 (corresponding to an COHb of about 15 %) are supported by the available case reports of lethal effects (myocardial infarction, stillbirths) in more susceptible subpopulations. Lethal effects from myocardial infarction in hypersusceptible patients with coronary artery disease at even lower CO concentrations, which could be at the upper end of the range of CO concentrations found inside buildings and in ambient air outside, cannot be excluded.

Most studies relating COHb on health effects do not investigate whether the frequency or severity of the effects increase with exposure time (at a constant COHb). There is thus an uncertainty concerning the increase of effects with time at a constant COHb. This is true for all AEGL levels. Studies elucidating this exposure-effect-time relationship could support the derived AEGL-2 and AEGL-3 values.

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APPENDIX A

Time Scaling Calculations for AEGLs

Time Scaling Calculations for AEGL-2

Key study:	Allred et al. (1989a; b; 1991); Sheps et al. (1990; 1991)
Toxicity endpoint:	In an experimental study in 63 subjects with coronary artery disease, a significantly reduced time to ST-segment depression in the electrocardiogram and a significantly reduced time to onset of angina pectoris during physical exercise were found at 2 or 4 % COHb (Allred et al., 1989a; b; 1991). At higher COHb of 5.3, but not at 3.7 %, a significantly increased frequency of exercise-induced arrhythmias was found (Sheps et al., 1990; 1991). AEGL-2 values were derived on a COHb of 4 %.
Mathematical model:	The CFK model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations resulting in a COHb of 4 % at the end of the exposure periods. Concentrations were calculated for 10 and 30 minutes, 1, 4 and 8 hours (see Appendix B).
Scaling:	Instead of a time scaling according to $C^n \times T = const.$, a mathematical model was used to calculated exposure concentrations for the relevant time periods (see Appendix B).
Uncertainty factors:	Uncertainty factor of 1 1 for intraspecies variability
Calculations:	
10-minute AEGL-2	10-min AEGL-2 = 424 ppm/1 = 420 ppm (480 mg/m³)
30-minute AEGL-2	30-min AEGL-2 = 150 ppm/1 = 150 ppm (170 mg/m³)
1-hour AEGL-2	1-hour AEGL-2 = 83 ppm/1 = 83 ppm (95 mg/m³)
4-hour AEGL-2	4-hour AEGL-2 = 33 ppm/1 = 33 ppm (38 mg/m³)
8-hour AEGL-2	8-hour AEGL-2 = 27 ppm/1 = 27 ppm (31 mg/m³)

Time Scaling Calculations for AEGL-3

Key study:	Pach et al. (1978; 1979); Chiodi et al. (1941); Henderson et al. (1921); Haldane (1895)
Toxicity endpoint:	Exposure of healthy subjects to sufficient concentration-time combinations to reach levels of about 34 to 56 % COHb did not result in severe or lift-threatening effects. At this level of CO exposure, Haldane described symptoms including hyperpnea, confusion of mind, dim vision and unsteady/inability to walk. Analysis of clinical case reports of CO poisoning revealed that only about 2 % of subjects that had died had COHb levels below 40 %. Of the patients that survived about 16 % had a COHb above 40 % (Pach et al., 1978; 1979).
Mathematical model:	The CFK model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations resulting in a COHb of 40 % at the end of the exposure periods. Concentrations were calculated for 10 and 30 minutes and 1, 4 and 8 hours (see Appendix B).
Scaling:	Instead of a time scaling according to $C^n \times T = const.$, a mathematical model was used to calculated exposure concentrations for the relevant time periods (see Appendix B).
Uncertainty factors:	Total uncertainty factor of 3 3 for intraspecies variability
Calculations:	
10-minute AEGL-3	10-min AEGL-3 = 5120 ppm/3 = 1700 ppm (1900 mg/m³)
30-minute AEGL-3	30-min AEGL-3 = 1810 ppm/3 = 600 ppm (690 mg/m³)
1-hour AEGL-3	1-hour AEGL-3 = 998 ppm/3 = 330 ppm (380 mg/m³)
4-hour AEGL-3	4-hour AEGL-3 = 439 ppm/3 = 150 ppm (170 mg/m³)
8-hour AEGL-3	8-hour AEGL-3 = 403 ppm/3 = 130 ppm (150 mg/m³)

The COHb levels corresponding to the AEGL-3 values are given in Table 21 in Appendix B.

APPENDIX B

Mathematical Model for Calculating COHb and Exposure Concentrations

Mathematical Model for Calculating COHb and Exposure Concentrations

Study describing model: Coburn et al. (1965); Peterson and Stewart (1975)

Model: For the calculation of concentration-time combinations that result in a certain COHb, the model of Coburn, Forster and Kane (CFK model) (see Section 4.3.4) was used.

Since this model in the formulation of Peterson and Stewart (1975) calculates COHb larger than 100 % at high exposure concentrations, the following correction proposed by Peterson and Stewart (1975) was used: the amount of bound oxygen is actually not constant, but is dependent on the COHb, therefore:

$OHb_t = OHb_{max} - COHb_t$.

Since in this case, the CFK equation can only be solved iteratively, calculations were done using time steps (Δt) of 1 minute for the period of 0-10 minutes, steps of 5 minutes between 10 and 60 minutes, steps of 15 minutes between 60 and 240 minutes, and steps of 20 minutes between 240 and 480 minutes. In each step, the COHb of the step before was used to calculate OHb_t. For the first step, a background COHb of 0.75 % was assumed.

The alveolar ventilation rate was calculated as:

$V_A = V_E - f\,V_D$ (Peterson and Stewart, 1975);

with V_E = total rate of ventilation (ml/min),

f = respiration rate (min^{-1}) and

V_D = dead space (ml).

Derivations were done for a 70-kg man, assuming a blood volume of 5500 ml (Coburn et al., 1965) and a daily inhalation volume (V_E) of 23 m^3 (8 hours resting and 16 hours light/non-occupational activity; WHO, 1999b), a respiration rate (f) of 18 min^{-1} and a dead space (V_D) of 2.2 ml/kg (Numa and Newth, 1996).

Calculations using the following equation were carried out in a spreadsheet computer program:

$$\Delta(COHb)_t = \left(\frac{V_{CO}}{Vb} - \frac{COHb_{t-1} * P_{O2}}{M * B * Vb\ (OHb_{max} - COHb_{t-1})} + \frac{P_{CO}}{B * Vb} \right) \Delta t$$

where:

$COHb_t$ = ml of CO per ml blood at time t (min)

Conversion: % carboxyhemoglobin = COHb 100 / OHb_{max}

V_{CO} = rate of endogenous CO production; V_{CO} = 0.007 ml/min

Vb = blood volume; Vb (70-kg man) = 5500 ml; Vb (5-yr child, 20 kg) = 1500 ml; Vb (newborn, 3.5 kg) = 400 ml

M = Ratio of affinity of blood for CO to that for O_2; M = 218 (newborn: M = 240)

$B = 1 / D_L + P_L / V_A$

with: D_L = diffusivity of the lung for CO; D_L = 30 ml / min mm Hg

P_L = barometric pressure minus the vapor pressure of water at body temperature,

P_L = 713 mm Hg

V_A = alveolar ventilation rate;

V_A (70-kg man) = 23 m^3/d * 1 · 10^6 ml/m^3 * 1/1440 min/d - 18 /min * 2,2 ml/kg * 70 kg

V_A (70-kg man) = 13200 ml/min

V_A (5-yr child) = 3580 ml/min

V_A (newborn) = 1250 ml/min

OHb_{max} = ml of O_2 per ml blood under normal conditions; OHb = 0,2

P_{O2} = average partial pressure of oxygen in the lung capillaries; P_{O2} = 100 mm Hg

P_{CO} = partial pressure of CO in the air inhaled (mm Hg);

Conversion: P_{CO} (mm Hg) = P_{CO} (ppm) / 1316

t = exposure duration (min)

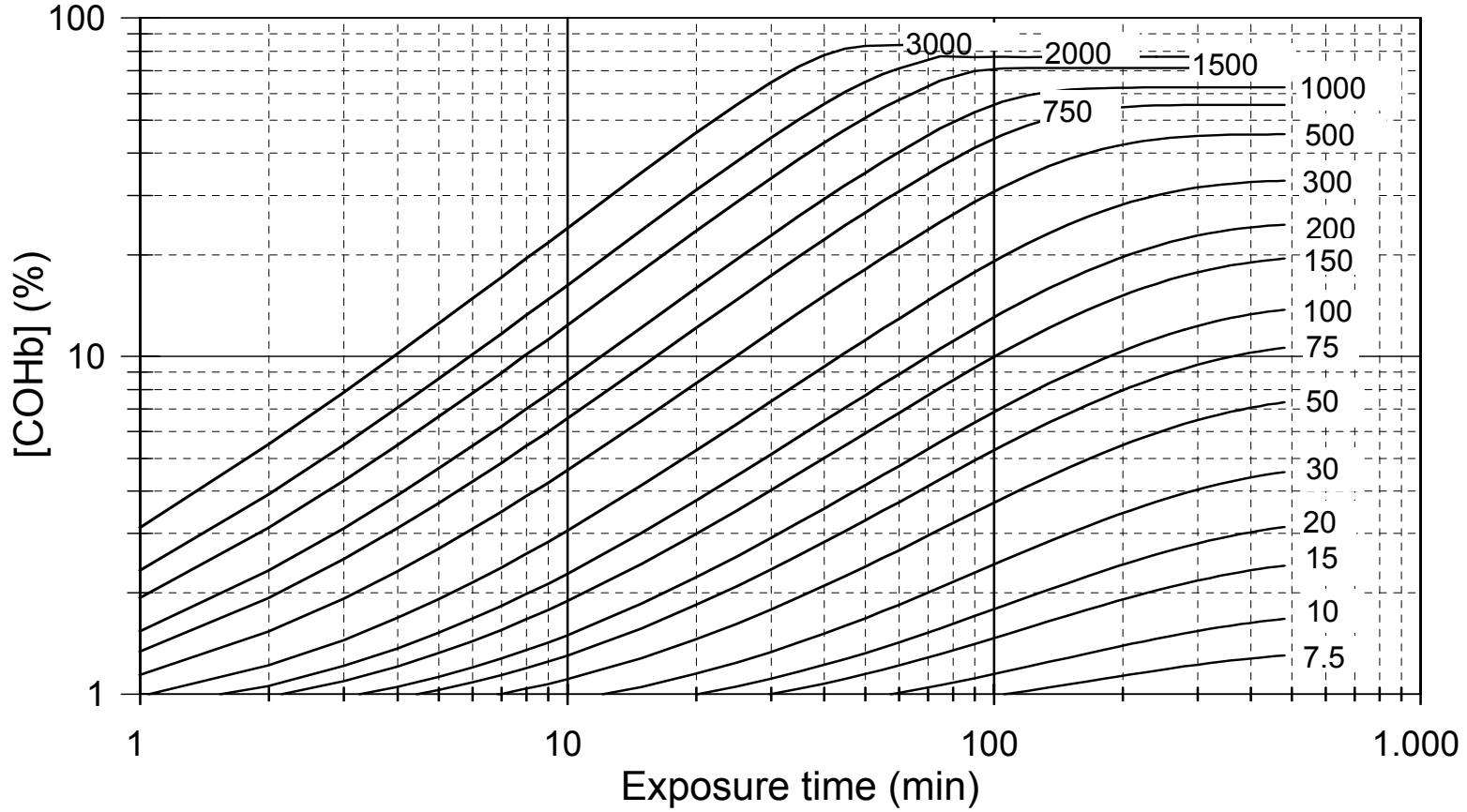

FIGURE 4: COHb VS. EXPOSURE TIME PLOTS
Data are shown for CO exposure concentrations indicated (70-kg man).

CFK Modell for Calculation of COHb

Dr. Peter Griem

Model by Coburn, Forster and Kane (1965) with corrections introduced by Peterson and Stewart (1975)

Model parameters (see TSD):

PL	713	mm Hg		
M	218			
OHb	0.2	ml/ml blood		
PO2	100	mm Hg		
Vb	5500	ml		
Vco	0.007	ml/min		
D	0.0015	ml CO/ml blood	in %:	0.75
Va	13200	ml/min		
DL	30	ml/min mm Hg		
COHbt	0.02	ml CO/ml blood	in %:	10
COHbo	0.0015	ml CO/ml blood	in %:	0.75
Exp. Time	60	min		
Exp. Conc.				
CO	83	ppm		

Physiologic parameters:

	70-kg adult	20-kg child	3.5-kg newborn
M			200
OHb			0.27
Vb	5500	1500	400
Va	13200	3580	1250

Auxiliary expressions:

A	2.293578
B	0.0873485
COHbt	0.02
COHbo	0.0015
a	0.7509257

Results for exposure to 83 ppm:

time (min)	COHb (%)
10	1.3631498
30	2.5132273
60	4.0330397
240	9.4791254
480	11.619731

Calculated COHb (according to original CFK model) after exposure to 83 ppm for 60 min:

COHb:	0.008042	ml/ml blood	4.020977	%

Calculated COHb according to model by Coburn, Forster and Kane (1965) with corrections introduced by Peterson and Stewart (1975):

time (min)	dt	dHbCO	HbCO	%
			0.0015	0.75
1	1	0.0001253	0.0016253	0.81267
2	1	0.0001247	0.0017501	0.875035
3	1	0.0001241	0.0018742	0.937098
4	1	0.0001235	0.0019977	0.998859
5	1	0.0001229	0.0021206	1.060319
6	1	0.0001223	0.002243	1.12148
7	1	0.0001217	0.0023647	1.182343
8	1	0.0001211	0.0024858	1.242908
9	1	0.0001205	0.0026064	1.303176
10	1	0.0001199	0.0027263	1.36315
15	5	0.0005968	0.0033231	1.661547
20	5	0.0005821	0.0039052	1.9526
25	5	0.0005677	0.0044729	2.236448
30	5	0.0005536	0.0050265	2.513227
35	5	0.0005397	0.0055661	2.783074
40	5	0.0005261	0.0060922	3.046124
45	5	0.0005128	0.006605	3.302513
50	5	0.0004997	0.0071047	3.552373
55	5	0.0004869	0.0075917	3.795838
60	5	0.0004744	0.0080661	4.03304

FIGURE 5: CALCULATION OF 60-MINUTE AEGL-2 FOR HEALTHY ADULT

Calculations: For the derivation of AEGL-2 values, exposure concentrations were calculated that would result in a COHb of 4 %. A representation of the spreadsheet for the 60-minute AEGL-2 is shown in Figure 5. Results are shown in the following Table 18.

TABLE 18: CONCENTRATION-TIME COMBINATIONS RESULTING IN 4 % COHb

Exposure time (min)	for a 70-kg adult man	
	exposure concentration (ppm)	exposure concentration (ppm), rounded
10	424	420
30	150	150
60	83	83
240	33	33
480	27	27

For children, newborns and adult smokers, the end-of-exposure COHb values for exposure to the concentrations calculated in Table 18 were computed using the CFK model:

TABLE 19: COHb VALUES FOR AEGL-2 CONCENTRATION-TIME COMBINATIONS IN DIFFERENT SUBPOPULATIONS

Exposure time (min)	Exposure concentration (ppm)	5-yr Child	Newborn	Healthy adult	Smoker (3 % COHb)	Smoker (8 % COHb)
10	420	5.2	5.5	4.0	6.2	11.2
30	150	5.2	5.6	4.0	6.3	11.3
60	83	5.2	5.6	4.0	6.4	11.4
240	33	5.0	5.4	4.0	6.6	11.5
480	27	4.9	5.3	4.0	6.7	11.5

For the derivation of AEGL-3 values, exposure concentrations were calculated that would result in a COHb of 40 %. A representation of the spreadsheet for the 60-minute value is shown in Figure 6. Results are shown in the following Table 20.

TABLE 20: CONCENTRATION-TIME COMBINATIONS RESULTING IN 40 % COHb		
Exposure time (min)	**for a 70-kg adult man**	
	exposure concentration (ppm)	**exposure concentration (ppm), rounded**
10	5120	5100
30	1810	1800
60	998	1000
240	439	440
480	403	400

For children, newborns, healthy non-smoking adults and smokers, the end-of-exposure COHb values for exposure to the AEGL-3 exposure concentration-time combinations were computed using the CFK model. For all subpopulations, the endogenous CO production rate was adjusted so that the starting level of 0.75 % for children and newborn and 3 and 8 % for smokers were constant without additional CO exposure.

TABLE 21: COHb VALUES FOR AEGL-3 CONCENTRATION-TIME COMBINATIONS IN DIFFERENT SUBPOPULATIONS						
Exposure time (min)	**Exposure concentration (ppm)**	**5-yr Child**	**Newborn**	**Healthy adult**	**Smoker (3 % COHb)**	**Smoker (8 % COHb)**
10	1700	18.7	19.9	13.8	16.1	21.1
30	600	18.5	19.8	14.0	16.2	21.1
60	330	18.3	19.6	14.1	16.4	21.2
240	150	18.6	20.1	16.4	18.6	22.7
480	130	18.1	19.5	17.2	19.2	23.0

CFK Modell for Calculation of COHb

Dr. Peter Griem

Model by Coburn, Forster and Kane (1965) with corrections introduced by Peterson and Stewart (1975)

Model parameters (see TSD):

					Physiologic parameters: 70-kg adult	20-kg child	3.5-kg newborn
PL	713	mm Hg					
M	218						200
OHb	0.2	ml/ml blood					0.27
PO2	100	mm Hg					
Vb	5500	ml			5500	1500	400
Vco	0.007	ml/min					
D	0.0015	ml CO/ml blood	in %:	0.75			
Va	13200	ml/min			13200	3580	1250
DL	30	ml/min mm Hg					
COHbt	0.02	ml CO/ml blood	in %:	10			
COHbo	0.0015	ml CO/ml blood	in %:	0.75			
Exp. Time	60	min					
Exp. Conc.							
CO	998	ppm					

Auxiliary expressions:

A	2.293578
B	0.0873485
COHbt	0.02
COHbo	0.0015
a	0.7509257

Results for exposure to 998 ppm:

time (min)	COHb (%)
10	8.4349598
30	22.664894
60	40.019622
240	62.314719
480	62.3289

Calculated COHb (according to original CFK model) after exposure to 998 ppm for 60 min:

COHb:	0.0835478	ml/ml blood	41.773906	%

Calculated COHb according to model by Coburn, Forster and Kane (1965) with corrections introduced by Peterson and Stewart (1975):

time (min)	dt	dHbCO	HbCO	%
			0.0015	0.75
1	1	0.0015726	0.0030726	1.536301
2	1	0.0015649	0.0046375	2.31876
3	1	0.0015572	0.0061947	3.097335
4	1	0.0015493	0.007744	3.871983
5	1	0.0015414	0.0092853	4.642662
6	1	0.0015333	0.0108187	5.409326
7	1	0.0015252	0.0123439	6.171932
8	1	0.001517	0.0138609	6.930437
9	1	0.0015087	0.0153696	7.684794
10	1	0.0015003	0.0168699	8.43496
15	5	0.0074593	0.0243292	12.1646
20	5	0.0072379	0.0315671	15.78355
25	5	0.0070043	0.0385714	19.28572
30	5	0.0067584	0.0453298	22.66489
35	5	0.0064999	0.0518297	25.91485
40	5	0.0062291	0.0580588	29.02939
45	5	0.0059463	0.0640051	32.00254
50	5	0.0056522	0.0696572	34.82862
55	5	0.0053477	0.075005	37.50248
60	5	0.0050343	0.0800392	40.01962

FIGURE 6: CALCULATION OF 60-MINUTE EXPOSURE CONCENTRATION THAT WOULD RESULT IN 40 % COHb IN A HEALTHY ADULT

The following end-of-exposure COHb values were calculated for the series of experiments reported by Haldane (1895). Since exposure occurred while the subject was sitting on a chair, a ventilation rate of 7.5 l/min was used for the calculation (WHO, 1999b). The alveolar ventilation rate was calculated as:

V_A (70-kg man) = 3600 l/8 h * 1 · 10^3 ml/l* 1/480 min/8 h - 18 /min * 2,2 ml/kg * 70 kg

V_A (70-kg man) = 4700 ml/min

TABLE 22: COMPARISON OF REPORTED AND CALCULATED COHb VALUES FOR THE DATA BY HALDANE (1895)

Experiment No.	Concentration (ppm)	Time (min)	COHb measured (%)	COHb calculated (%)
1	5000	11.5	not done	22
2	3900	30.5	39	43
3	4000	24	27	35
4	3600	29	37	38
5	4100	29	35	43
6	1200	120	37	46
7	2100	71	49	50
8	irregular	35	56	-
9	270	210	14	17
10	210	240	13	15
11	460	240	23	30

APPENDIX C

Derivation Summary for Carbon Monoxide AEGLs

ACUTE EXPOSURE GUIDELINES FOR CARBON MONOXIDE (CAS NO. 630-08-0)

AEGL-1 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
N.R.	N.R.	N.R.	N.R.	N.R.

[a] N.R., not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population

Reference: Not applicable

Test Species/Strain/Number: Not applicable / not applicable / not applicable

Exposure Route/Concentrations/Durations: Not applicable / not applicable / not applicable

Effects: Not applicable

Endpoint/Concentration/Rationale:
CO is the classical example of a tasteless, non-irritating, odorless and colorless toxic gas. Until very severe symptoms occur (inability to walk) none or only nonspecific symptoms were noted in monkeys and healthy humans (Haldane, 1895; Purser and Berrill, 1983). In patients with coronary artery disease, which constitutes the most susceptible subpopulation, effects, such as significant electrocardiogram changes, reduced time to the onset and increased cardiac arrhythmia, start occurring at exposure concentrations little higher than current ambient air quality guidelines, e.g. the U.S. National Air Quality Guideline of 9 ppm for 8 hours (National Air Pollution Control Administration, 1970; FR , 2000; EPA, 2000), the WHO Air Quality Guideline of 10 mg/m³ (9 ppm) for 8 hours (based on 2.5 % COHb) (WHO, 1999a) and the designated European Union Limit Value of 10 mg/m³ (9 ppm) for 8 hours (EC, 1999). These effects were considered above the AEGL-1 effect level and thus would not constitute a suitable basis for the derivation of AEGL-1 values. AEGL-1 values were not recommended because susceptible persons may experience more serious effects (equivalent to AEGL-2 level) at concentrations, which do not yet cause AEGL-1 effects in the general population.
In addition, CO exposures encountered frequently in everyday life are at or above the concentration range, in which AEGL-1 level would have to be set: smokers have COHb in the range of 3-8 % (Radford and Drizd, 1982) and CO concentrations between about 10 and 50 ppm, which can be found on heavily traveled roads, inside motor vehicles and in homes with gas-, coal-, wood- or kerosene-fired heaters and stoves, correspond to an equilibrium COHb of 1.8-7.5 % (see Figures 2 and 4).

Uncertainty Factors/Rationale: Not applicable

Modifying Factor: Not applicable

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: Not applicable

Data Adequacy: Not applicable

ACUTE EXPOSURE GUIDELINES FOR CARBON MONOXIDE (CAS NO. 630-08-0)

AEGL-2 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
420 ppm	150 ppm	83 ppm	33 ppm	27 ppm

Reference: Allred, E.N., E.R. Bleecker, B.R. Chaitman, T.E. Dahms, S.O. Gottlieb, J.D. Hackney, D. Hayes, M. Pagano, R.H. Selvester, S.M. Walden and J. Warren, 1989a. Acute Effects of Carbon Monoxide Exposure on Individuals with Coronary Artery Disease. Research Report No. 25, Health Effects Institute, Cambridge, Massachusetts, USA, 1989; Allred, E.N., E.R. Bleecker, B.R. Chaitman, T.E. Dahms, S.O. Gottlieb, J.D. Hackney, M. Pagano, R.H. Selvester, S.M. Walden and J. Warren, 1989b. Short-term effects of carbon monoxide exposure on the exercise performance of subjects with coronary artery disease. *New England Journal of Medicine* 321, 1426-1432; Allred, E.N., E.R. Bleecker, B.R. Chaitman, T.E. Dahms, S.O. Gottlieb, J.D. Hackney, M. Pagano, R.H. Selvester, S.M. Walden and J. Warren, 1991. Effects of carbon monoxide on myocardial ischemia. *Environmental Health Perspectives* 91, 89-132.

Test Species/Strain/Sex/Number: Humans with coronary artery disease / not applicable / male / 63

Exposure Route/Concentrations/Durations: Inhalation / mean concentrations of 0, 117 or 253 ppm for 50-70 minutes were used, adjusted individually to reach carboxyhemoglobin concentrations of 2.2 % or 4.4 % at the end of exposure (about 2 or 4 % COHb in the subsequent exercise tests)

Effects:
When potential exacerbation of the exercise-induced ischemia by exposure to CO was tested using the objective measure of time to 1-mm ST-segment change in the electrocardiogram, exposure to CO levels producing COHb of 2 % resulted in a overall statistically significant 5.1 % decrease in the time to attain this level of ischemia. For individual centers (patients were tested in one of three centers), results were significant in one, borderline significant in one and nonsignificant in one center. At 4 % COHb, the decrease in time to the ST criterion was 12.1% (statistically significant for all patients, the effect was found in 49/62 subjects) relative to the air-day results. Significant effects were found in all three test centers. The maximal amplitude of the ST-segment change was also significantly affected by the carbon monoxide exposures: at 2 % COHb the maximal increase was 11 % and at 4 % COHb the increase was 17 % relative to the air day.
At 2 % COHb, the time to exercise-induced angina was reduced by 4.2 % in all patients (effects were significant in two test centers and nonsignificant in one center). At 4 % COHb, the time was reduced by 7.1 % in all patients (effects were significant in one, borderline significant in one and nonsignificant in one center). The two end-points (time to angina and time to ST change) were also significantly correlated. Only at 4 % COHb a significant reduction in the total exercise time and in the heart rate-blood pressure product was found (this double product provides a clinical index of the work of the heart and myocardial oxygen consumption).

Endpoint/Concentration/Rationale: Patients with coronary artery disease show health effects at lower COHb levels than children, pregnant women or healthy adults and, thus, constitute the most susceptible subpopulation. For the derivation of AEGL-2 values a level of 4 % COHb was chosen. At this exposure level, patients with coronary artery disease may experience a reduced time until onset of angina (chest pain) during physical exertion (Allred et al., 1989; 1991). In the available studies, the CO exposure alone (i.e. with subjects at rest) did not cause angina, while exercise alone did so. However, it should be noted that all studies used patients with stable exertional angina, who did not experience angina while at rest. Thus, it cannot be ruled out that in more susceptible individuals (a part of the patients with unstable angina pectoris might belong to this group) CO exposure alone could increase angina symptoms. The changes in the electrocardiogram (ST-segment depression of 1 mm or greater) associated with angina symptoms were considered reversible, but is indicative of clinically relevant myocardial ischemia requiring medical treatment. An exposure level of 4 % COHb is unlikely to cause a significant increase in the frequency of exercise-induced arrhythmias. Ventricular arrhythmias have been observed at COHb of 5.3 %, but not at 3.7 % (Sheps et al., 1990; 1991), while in another study no effect of CO exposure on ventricular arrhythmia was found at 3 or 5 % COHb (Dahms et al., 1993). An exposure level of 4 % COHb was considered protective of acute neurotoxic effects in children, such as syncopes, headache, nausea, dizziness and dyspnea (Klasner et al., 1998; Crocker and Walker, 1985), and long-lasting neurotoxic effects (defects in the cognitive development and behavioral alterations) in children (Klees et al., 1985). It is acknowledged that apart from emergency situations, certain scenarios could lead to CO concentrations which may cause serious effects in persons with cardiovascular diseases. These scenarios include e.g. extended exposure to traffic fume emissions (e.g., in tunnels or inside cars with defect car exhaust systems), charcoal or wood fire furnaces, and indoor air pollution by tobacco smoking.
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies: Not applicable Intraspecies: 1 - A level of 4 % COHb was the NOEL for AEGL-2 effects in patients with coronary artery disease, while the LOEL was estimated at 6-9 %. In comparison, the LOEL was about 10-15 % in children and 22-25 % in pregnant women. Since AEGL-2 values were based on experimental data on the most susceptible subpopulation, they were considered protective also for other subpopulations and a total uncertainty factor of 1 was used.
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: A mathematical model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a COHb of 4 % at the end of exposure periods of 10 and 30 minutes and 1, 4 and 8 hours.

Data Adequacy:
AEGL-2 values were based on cardiac effects in subjects with coronary artery disease, which constitute the most susceptible subpopulation. Several high quality studies are available addressing endpoints such as time to the onset of exercise-induced angina, time to the onset of exercise-induced 1-mm ST-segment changes in the electrocardiogram and frequency of exercise-induced arrhythmias. However, no experimental studies in heart patients are available that used significantly higher levels of COHb than about 5 % COHb.

ACUTE EXPOSURE GUIDELINES FOR CARBON MONOXIDE (CAS NO. 630-08-0)

AEGL-3 VALUES				
10 minutes	30 minutes	1 hour	4 hours	8 hours
1700 ppm	600 ppm	330 ppm	150 ppm	130 ppm

Reference: Pach, J., L. Cholewa, Z. Marek, M. Bogusz and B. Groszek, 1978. Analysis of predictive factors in acute carbon monoxide poisoning. *Veterinary and Human Toxicology* 21 Suppl, 158-159; Pach, J., L. Cholewa, Z. Marek, M. Bogusz and B. Groszek, 1978. Various factors influencing the clinical picture and mortality in acute carbon monoxide poisoning [in Polish]. *Folia Medica Cracoviensia*, 20, 159-168; Chiodi, H., D.B. Dill, F. Consolazio and S.M. Horvath, 1941. Respiratory and circulatory responses to acute carbon monoxide poisoning. *American Journal of Physiology* 134, 683-693; Haldane, J., 1895. The action of carbonic acid on man. *Journal of Physiology* 18, 430-462; Henderson, Y., H.W. Haggard, M.C. Teague, A.L. Prince and R.M. Wunderlich, 1921. Physiological effects of automobile exhaust gas and standards of ventilation for brief exposures. *Journal of Industrial Hygiene* 3, 79-92.

Test Species/Strain/Sex/Number: Pach et al. (1978; 1979): Lethal cases (60 men and 41 women, mean age 48 ±15 years); non-lethal cases 220 subjects (95 men and 125 women, mean age 38 ±18 years) / not applicable / males and females / 321 (total)
Chiodi et al. (1941), Haldane (1895), Henderson et al. (1921): Humans (healthy young males) / not applicable / males / 4 (total)

Exposure Route/Concentrations/Durations: Inhalation / Pach et al. (1978; 1979) analyzed COHb in deceased subjects and in surviving patients that had been transported to hospital within 2 hours; for the latter end of exposure COHb were calculated; Chiodi et al. (1941): repeated test on three subjects that reached COHb of 27-52% at the end of exposure; individual COHb values were 31, 32, 32, 33, 39, 41, 42, 43, 45 and 52 % in subject H.C., 27, 35, 41, 43 and 48 % in subject F.C. and 41, 42 and 44 % in subject S.H.; Haldane (1895): repeated exposure of one subject reaching the following COHb at the end of exposure (time in min): 13 % (240 min), 14 % (210 min), 23 % (240 min), 27 % (24 min), 35 % (29 min), 37 % (29 min), 37 % (120 min), 39 % (30.5 min), 49 % (71 min), 56 % (35 min).

Effects: Pach et al. (1978; 1979) reported that only about 2 % of subjects that had died from CO poisoning had COHb levels below 40 %. Of the patients that survived about 16 % had a COHb above 40 %. In the experimental studies, no severe or life-threatening symptoms occurred. At a COHb of about 40-56 %, Haldane (1895) described symptoms included hyperpnea, confusion of mind, dim vision and unsteady/inability to walk. Chiodi et al. (1941) found no effect on oxygen consumption, ventilation, pulse rate, blood pressure and blood pH; the cardiac output increased 20-50 % at COHb >40 %, while the changes were negligible at COHb of <30 %.

Endpoint/Concentration/Rationale: The derivation of AEGL-3 values was based on observations in humans. Several case reports indicate that in patients with coronary artery disease, CO exposure can contribute to myocardial infarction (which was considered an AEGL-3 endpoint). In the published cases of myocardial infarction, the following COHb values were measured after transport to the hospital: 52.2 % (Marius-Nunez, 1990), 30 %, 22.8 % (Atkins and Baker, 1985), 21 % (Ebisuno et al., 1986), 15.6 % (Grace and Platt, 1981). These anecdotal reports on cases affecting susceptible subpopulations were considered as important supporting information, but not as an adequate basis for the derivation of AEGL-3 values because of uncertainties about the end of exposure COHb levels, and whether repeated and/or prolonged exposures caused the infarction. The analysis of 101 cases of lethal poisoning and 158 cases of non-lethal poisoning by Pach et al. (1878; 1979) was used as the basis for derivation of AEGL-3 values. In the group of surviving patients only those were included from which blood for COHb analysis had been obtained within 2 hours from cessation of exposure. The COHb at the end of exposure was calculated by the authors of the report. Analysis revealed that only about 2 % of deceased subjects had COHb levels below 40 %. Of the patients that survived about 16 % had a COHb above 40 %. From this study a threshold for lethal poisoning of about 40 % can be derived. This level is supported by experimental studies performed in healthy human subjects. Studies by Chiodi et al. (1941), Henderson et al. (1921), and Haldane (1895) suggest that a COHb of about 34-56 % does not cause lethal effects in healthy individuals. Further support come from the studies by Kizakevich et al. (1994), Stewart et al. (1970), and Nielsen (1971) that reported headache as the only symptom when subjects were exposed to 20-33 % COHb. A level of 40 % COHb was used as the basis for AEGL-3 derivation. This point of departure is supported by studies in animals reporting minimum lethal COHb levels in rats and mice of about 50-70 % (E.I. du Pont de Nemours and Co., 1981; Rose et al., 1970).
Uncertainty Factors/Rationale: Total uncertainty factor: 1 Interspecies: Not applicable Intraspecies: 3 - an intraspecies uncertainty factor of 3 was supported by information on effects, such as myocardial infarction and stillbirths, reported in more susceptible subpopulations.
Modifying Factor: Not applicable
Animal to Human Dosimetric Adjustment: Not applicable
Time Scaling: A mathematical model (Coburn et al., 1965; Peterson and Stewart, 1975) was used to calculate exposure concentrations in air resulting in a COHb of 40 % at the end of exposure periods of 10 and 30 minutes and 1, 4 and 8 hours.

Data Adequacy:
AEGL-3 values were based analysis of clinical cases of lethal and non-lethal poisoning as well as on old experimental studies in which healthy subjects were exposed to COHb of up to 40-56 %. The AEGL-3 values derived using an intraspecies uncertainty factor of 3 (corresponding to an COHb of about 15 %) are supported by the available case reports of lethal effects (myocardial infarction, stillbirths) in more susceptible subpopulations. Lethal effects from myocardial infarction in hypersusceptible patients with coronary artery disease at even lower CO concentrations, which could be at the upper end of the range of CO concentrations found inside buildings and in ambient air outside, cannot be excluded.