scientific basis for an air quality standard for carbon monoxide

Prepared for CONCAWE's Health Management Group by:

Exxon Biomedical Sciences, Inc.

D. King

B.J. Simpson (Technical Co-ordinator)

Brussels
January 1997

CONTENTS

ABSTRACT/SUMMARY

Carbon Monoxide (CO) is emitted into the atmosphere mainly as a product of the incomplete combustion of carbonaceous material. The major sources of CO exposure for the general, non-smoking population are exhaust emissions from combustion engines and the burning of fossil fuels. Smoking provides an additional source of CO for the non-smoking as well as the smoking public. In addition to these exogenous sources, CO is generated endogenously mainly from the breakdown of haem proteins. Healthy individuals can tolerate low level exposures to CO but it can be hazardous at higher concentrations and even at low concentrations for those with unusual susceptibility.

The primary toxic action of carbon monoxide is the inhibition of cell oxidation following exposure by inhalation. The brain, heart, and embryo/foetus have critical needs for oxygen. It follows that the major health effects associated with CO exposure include cardiovascular, central nervous system, and developmental toxicities. Of these, the most critical target of carbon monoxide is the cardiovascular system. Furthermore, the most susceptible populations are those individuals with pre-existing cardiovascular disease.

The absorption and elimination of CO from the body is influenced by concentration, duration of exposure and pulmonary ventilation. Most absorbed CO binds reversibly with haemoglobin (Hb) forming carboxyhaemoglobin (COHb), reducing the oxygen carrying capacity of the blood. The relationship between CO exposure and the formation of COHb has been mathematically described. The extent of COHb saturation may be used as a biological marker of exposure. In addition, specific adverse health effects have been linked to characteristic COHb levels, which have in turn been associated with CO exposure levels, and these relationships can serve as a basis for an Air Quality Standard (AQS).

Chronic angina patients are presently viewed as the most sensitive group at risk after exposure to CO, and the most sensitive health endpoint is earlier onset of angina with exercise. A COHb saturation of 2.5% posed no significant health effect to the non-smoking population including those with angina. This COHb level corresponds to continuous CO exposures at 15 ppm. A safety factor was applied to the CO exposure conditions to adjust for the uncertainty associated with persons having other pre-existing disease conditions, e.g., anaemia or pulmonary disease. This adjustment resulted in a predicted COHb concentration of 1.6%, corresponding to continuous CO exposure at 10 ppm. [Thus, an 8 hour running average of 10 ppm is a scientifically supportable AQS for carbon monoxide.]

1. INTRODUCTION

Carbon monoxide (CO) is a non-reactive, tasteless, odourless gas with low water solubility. Low level exposures to CO in healthy adults seem to present little hazard, although at higher concentrations and for individuals with unusual susceptibility, CO may be hazardous. The purpose of this assessment is to identify the levels of exposure that produce adverse health effects, select the critical health endpoint, and identify sensitive sub-populations. This will allow the development of a scientifically-based air quality standard (AQS) for CO.

To identify the levels of exposure to CO that produce adverse health effects, the key literature for health effects in animals and humans was examined. The goal was to identify the highest CO concentration at which no adverse health effects occur, i.e., the no-observed-effect-level (NOEL). When developing an AQS, a variety of adjustment factors may be applied to the NOEL to extrapolate between and among species, across routes and to account for duration of exposures. These factors are also applied to adjust for a variety of parameters including sensitive sub-populations, pharmacokinetics, and pharmacodynamics.

There are considerable human exposure and effects data for CO; the animal data are used, therefore, as supporting information only. The multiple permutations of concentration and duration of exposure are simplified by the availability of data on an internal marker of exposure, carboxyhaemoglobin (COHb) and mathematical models for predicting COHb concentrations from concentrations of CO in the ambient air. Furthermore, the relationship between COHb and adverse health effects is well described.

2. SOURCES OF CARBON MONOXIDE

Carbon monoxide is one of the most common and widely distributed air pollutants. It is a product of the incomplete combustion of materials containing carbon, but is also produced by some industrial and biological processes. Although there have been many studies in the last decade directed towards the identification and quantification of the various sources and sinks of CO in the atmosphere, it is clear that uncertainty exists about the magnitude of many of the sources of global CO. The relative importance of natural and man-made CO production is still debated.

The global burden of CO appears to be increasing, with long-term implications for stratospheric photochemistry, including the stability of the ozone layer. Furthermore, human activity is responsible for the higher concentrations of CO in urban air that may be of significance to public health. The CO in urban air originates almost entirely from local combustion processes. Rural CO levels are typically low(er), depending on the extent of exposure to local and continental air masses.

Despite rising output, background levels of CO in the lower atmosphere remain relatively stable. There must, therefore, be some atmospheric removal process. One possible mechanism is the reaction with hydrogen radicals (Hampson and Garvin, 1975; Weinstock, 1969):

More significant removal occurs at the earth's surface, where anaerobic soil bacteria oxidize CO to carbon dioxide in the absence of hydrogen, or reduce it to methane in the presence of hydrogen (Inman, Ingersoll, and Levy, 1971). The residence time of tropospheric CO is no more than 0.2 years (Weinstock et al., 1972).

2.1. NATURAL EMISSIONS

As a result of natural processes such as forest fires, oxidation of methane, and biological activity, the background level of CO is estimated to be about 0.05 mg/m^3 (0.04 ppm). According to some authors, natural formation from methane contributes 10 times the anthropogenic output (Jaffe, 1973; Levy, 1973; Maugh, 1972; McConnell et al., 1971). This issue is debatable, but would cast doubt on the importance of global measures for the control of CO.

2.2. ANTHROPOGENIC EMISSIONS

Vehicle exhaust is the principal man-made source of CO. Diesel engine exhaust generally contains less than 0.1% CO whereas gasoline engines may emit up to 4% by volume of CO (Chipman and Massey, 1960; Elliott et al., 1955; Hurn, 1962; Larson, Chipman and Kauper, 1955; Twiss et al., 1955). CO emissions from vehicles have been reduced in recent years due to the influence of increasingly strict regulations (European Community Directives on improved engine design), and pollution management systems, in particular the fitting of catalytic converters to gasoline powered vehicles. For a typical vehicle, a reduction of 70% has been accomplished, compared to the "uncontrolled" car of 1960.

Emission sources other than vehicles also contribute to CO emissions. These include power stations, aircraft, households, and waste treatment and disposal (UK DOE, 1994). Tobacco smoke is the one of greatest contributors to CO exposure for the smoking public.

2.3. TRENDS IN EMISSIONS

Seasonal variations of CO are well established (Dianov-Klokov and Yurganov, 1981; Fraser et al., 1986; Khalil and Rasmussen, 1988; Seiler et al., 1969). High concentrations are observed during the winter in each hemisphere and lower concentrations are seen in late summer. The amplitude of this cycle is largest at high northern latitudes and diminishes as one moves towards the equator. These patterns are expected from the seasonal variation of $OH^{\bullet}$ concentrations. At mid and high latitudes, diminished solar radiation, water vapour, and ozone (O_3) during winter causes the concentrations of hydroxyl radical to be much lower than during summer. Consequently, the removal of CO is slowed down and its concentrations build up. In summer the opposite effects occur thus causing the large seasonal variations of CO.

Other variations in CO concentrations in local ambient air are influenced by operating patterns of vehicles and industrial operations. Sunday CO levels are almost invariably less than those on weekdays. Diurnal concentration patterns follow diurnal traffic patterns with a tendency to peak during morning and evening rush hours.

2.4. INDOOR AIR

The CO levels within offices and homes lag behind outdoor concentrations, and some of the sharper peaks of pollution are not seen (General Electric, 1972; Schaplowsky et al., 1974; Yocom et al., 1971). Nevertheless, CO differs from many pollutants in that it has little tendency to become absorbed on walls and fabrics, so that equilibrium between indoor and outdoor air can be reached relatively quickly. Indoor concentrations may exceed ambient levels if one of the occupants is a smoker, or if there are other local sources of CO such as stoves, heaters or leakage from an attached garage (Benson et al., 1972; General Electric Company, 1972).

3. ECOLOGICAL EFFECTS

Carbon monoxide has not been observed to cause adverse impacts on vegetation at exposure concentrations typical of the ambient environment (Treshow and Anderson, 1989). The US EPA ruled that no CO standard was needed to protect environmental welfare, given the almost non-existent potential for environmental impact of ambient CO concentrations (US EPA, 1985).

Several studies have demonstrated CO impacts on vegetation following exposure to levels much greater than ambient (US EPA, 1979). Key studies are briefly summarized for completeness.

A variety of plant species were exposed to CO at concentrations of 115 mg/m^3 to 11,500 mg/m^3 (100 to 10,000 ppm) for 4 to 23 days (Zimmerman et al, 1933 as cited in US EPA, 1979). While practically no growth retardation was noted in plants exposed at the lower level, stem growth was inhibited at the higher concentration by as much as 100% when compared with controls. The effects varied considerably among the different species of plants, tobacco being only slightly retarded while others were affected greatly.

Several studies have demonstrated the influence of CO on sex differentiation in plants (US EPA, 1979). Different varieties of cucumber were exposed to CO at concentrations of 1,150 mg/m^3 to 11,500 mg/m^3 (1,000 to 10,000 ppm) for 50 to 200 hours (Minima and Tylkina, 1947 as cited in US EPA, 1979). The results showed that sexual differentiation was shifted markedly to the expression of female characteristics under the influence of the gas. Thus, at the highest level and with prolonged exposure, plants formed exclusively female flowers. With exposure to CO concentrations of 3,400 to 5,700 mg/m^3 (3,000 - 5,000 ppm) female flowers developed first with the appearance of very few male flowers a week later. Plants treated at the lowest CO level proceeded with the development of male flowers, as is normal for the species studied, and then shifted to female expression at the sixth day.

Elevated CO concentrations ($\geq$115 mg/m^3, or 100 ppm) have been observed to inhibit nitrogen fixation (US EPA, 1979).

The lowest-observed-effect-level (LOEL) of CO producing adverse ecological effects (100 ppm CO) (US EPA, 1985), is above that known to produce adverse human health effects. Therefore, human health effects were considered for determination of the Air Standard for CO.

4. HEALTH EFFECTS

It is the high affinity of CO for haemoglobin and other important haem containing proteins (e.g., cytochromes) that is the key health issue. Impairment of aerobic functions within the body has wide ranging consequences. The anoxic effects of CO exposure at high concentrations (> 10% COHb) are well documented. In this report, attention is paid to the potential effects of CO exposure at concentrations resulting in COHb of 10% or less.

4.1. LITERATURE REVIEW

Adverse health effects associated with exposure to CO include those on the cardiovascular system, central nervous system, and developing embryo/foetus. Cardiovascular effects of CO are directly related to reduced oxygen content of the blood caused by combination of CO with haemoglobin to form COHb resulting in tissue hypoxia. Most healthy individuals have mechanisms (e.g., increased blood flow, blood vessel dilation) which compensate for this reduction in tissue oxygen levels, although the effect of reduced maximal exercise capacity has been reported in healthy persons at COHb levels below 10%. Compensatory mechanisms are less effective in elderly people, pregnant women, small children, and in certain people with anaemia or pulmonary and cardiovascular diseases, thereby increasing their susceptibility to potential adverse effects of CO during exercise (WHO, 1979).

Three types of health effects (**Table 1**) are reported or suggested to be associated with CO exposure (producing COHb levels below 10%) they are :

- cardiovascular effects
- neurobehavioral effects
- developmental effects

Table 1. Human Health Effects Associated with Exposure to Carbon Monoxide: Lowest-Observed-Effect Levels

COHb CONCENTRATION (%)	EFFECTS	REFERENCES
2.3 - 4.3	Statically significant decrease (3 - 7%) in the relation between work time and exhaustion in exercising young healthy men	Horvath et al. (1975) Drinkwater et al. (1974)
2.9 - 4.5	Statistically significant decrease in exercise capacity (i.e., shortened duration of exercise before onset of pain) in patients with angina pectoris and increase in duration of angina attacks	Anderson et al. (1973)
5 - 20	Statistically significant decrease in maximal consumption and exercise time with short duration strenuous exercise in young healthy men	Haider et al. (1974) Winneke (1974) Christensen et al. (1977) Benignus et al. (1977) Putz et al. (1976) Ekblom and Huot (1972) Pirnay et al. (1971) Vogel and Gleser (1972)
< 5	No statistically significant vigilance decrement after exposure to carbon monoxide	Klein et al. (1980) Stewart et al. (1978) Weiser et al. (1979)
5 - 17	Statistically significant diminution of visual perception, manual dexterity, ability to learn, or performance in complex sensorimotor tasks (e.g., driving)	Bender et al. (1971) Schulte (1973) O'Donnell et al. (1971) McFarland et al. (1944) McFarland (1973) Putz et al. (1976) Salvatore (1973) Wright et al. (1973) Rockwell and Weir (1975) Rummo and Sarlanis (1974) Putz (1979)
20 -30	Throbbing headache	UKDOE,1994
30 - 50	Dizziness, nausea, weakness, collapse	UKDOE, 1994
over 50	Unconsciousness and death	UKDOE. 1994

[a] The physiologic norm (i.e., COHb levels resulting from the normal catabolism of haemoglobin and other haem-containing materials) has been estimated to be in the range of 0.3 to 0.7%.

4.2. TOXICOKINETICS/TOXICODYNAMICS

Both the concentration of CO and the duration of exposure are particularly important factors in determining the potential for adverse health effects. The magnitude of the effect and therefore the severity of physical symptoms is related to the toxicokinetics of CO. The following section describes how the body handles the substance including the uptake, distribution and elimination as well as the mechanism(s) of adverse reactions.

4.2.1. Sources

Endogenous production of CO in healthy adults, the body produces a small amount of CO, mainly from the breakdown of haemoglobin. During natural degradation of haemoglobin to bile pigments, a carbon atom is separated from the porphyrin nucleus and subsequently is catabolized by microsomal haemase into CO. The major site of haem breakdown and therefore of endogenous CO is the liver (Berk et

al., 1976). The spleen and erythropoietic system are other important catabolic generators of CO. Because the amount of porphyrin breakdown is stoichiometrically related to the amount of endogenously formed CO, the blood level of COHb or the concentration of CO in the alveolar air have been used as semi-quantitative indices of the rate of haem catabolism (Landaw and Callahan, 1970; Solanki et al., 1988).

Not all of endogenous CO comes from red blood cell (RBC) degradation. Other haemoproteins, such as myoglobin, cytochromes, peroxidases, and catalase contribute approximately 20 to 25% to the total amount of generated CO (Berk et al., 1976). Approximately 0.4 ml/hour of CO is formed by haemoglobin catabolism and about 0.1 ml/hour originates from non-haemoglobin sources (Coburn et al., 1964). Metabolic processes other than haem catabolism contribute only a very small amount.

Variation in CO production occurs due to normal physiological processes. In both males and females, week-to-week variations of CO production are greater than day-to-day or within-day variations. Moreover, in females COHb levels fluctuate with menstrual cycle; the mean rate of CO production in the pre-menstrual, progesterone phase almost doubles (Lynch and Moede, 1972; Delivoria-Papadopoulos et al., 1970). Neonates and pregnant women also show a significant increase in endogenous CO production related to increased breakdown of RBC.

Factors such as hypermetabolism, certain drugs and haemolytic anaemia can also increase the endogenous production of COHb. Any disturbance leading to increased destruction of RBC and accelerated breakdown of other haemoproteins would lead to increased production of CO. Haematomas, intravascular haemolysis of RBC, blood transfusion, and ineffective erythropoiesis all will elevate the CO concentration in blood. Degradation of RBC under pathological conditions such as anaemias (haemolytic, sideroblastic, sickle cell), thalassemia, Gilbert's syndrome with haemolysis, and other haematological diseases also will accelerate CO production (Berk et al., 1976; Solanki et al., 1988). In patients with haemolytic anaemia, CO production rate may be 2 to 8 times higher, and blood COHb concentration 2 to 3 times higher than normal (Coburn et al., 1966). Increased CO-production rates have been reported after administration of phenobarbital, diphenylhydantoin (Coburn 1970), and progesterone (Delivoria-Papadopoulos et al., 1970).

Exogenous sources of CO

Exogenous CO sources contribute an estimated 0.5 to 1.5% COHb to the general population. Tobacco smoke is the one of greatest contributors to CO exposure for the smoking public. For a one-pack-per-day smoker, the mean COHb level is approximately 5% (Stewart et al., 1973).

4.2.2. Absorption, Distribution, and Excretion

The mass transport of CO between the airway opening (mouth and nose) and red blood cell (haemoglobin) is predominantly controlled by physical processes. The CO transfer to the Hb-binding sites is accomplished in two sequential steps: transfer of CO in the gas phase, between the airway opening and the alveoli, and transfer in the dissolved phase, across air-blood interface including the RBC (red blood cell). While the mechanical action of the respiratory system and the molecular diffusion within the alveoli are the key mechanisms of transport in the gas phase, the

diffusion of CO across the alveolar-capillary barrier, plasma, and RBC is the mechanism of the liquid phase.

In order to reach Hb-binding sites, CO has to pass across the alveoli-capillary membrane, diffuse through the plasma, pass across the RBC membrane, and finally the RBC stroma before reaction between CO and Hb can take place. The molecular transfer across the membrane and the blood phase is governed by general physicochemical laws, particularly by Fick's first law of diffusion. The exchange and equilibration of gases between the two compartments (air and blood) is very rapid. The dominant driving force is a partial pressure differential of CO across this membrane. For example, inhalation of a bolus of air containing a high level of CO will rapidly increase blood COHb. By immediate and tight binding of CO to Hb the partial pressure of CO within the RBC is kept low, thus maintaining a high concentration differential between air and blood, and consequent diffusion of CO into blood. Subsequent inhalation of CO-free air progressively decreases the gradient to the point of its reversal (higher CO pressure on the blood side than alveolar air) and CO will be released into alveolar air. Because binding of CO to Hb is a much stronger and considerably faster reaction than clearance of CO by ventilation, the air-blood concentration gradient is usually higher than the blood-air gradient, and the CO uptake will be a proportionally faster process than CO elimination.

Diffusion is dependent on body-position and ventilation. In a supine position at rest, CO diffusion may be significantly higher than that at rest in a sitting position. In both positions, CO diffusion during exercise is greater than at rest (McClean et al., 1981). Carbon monoxide diffusion will increase with exercise, and at maximum work rates, the diffusion will be maximal regardless of position. This increase is attained by increases in both the membrane-diffusing component and the pulmonary capillary blood flow (Stokes et al., 1981). Diffusion seems to be relatively independent of lung volume within the mid-range of vital capacity. However, at extreme volumes, the differences in diffusion rates could be significant, at total lung capacity, the diffusion is higher than average, while at residual volume it is lower than the average (McClean et al., 1981). On average, smokers show lower diffusion rates than non-smokers (Knudson et al., 1989).

Physiological processes will minimally affect COHb formation in healthy individuals exposed to low and relatively uniform levels of CO. If sufficient time is allowed for equilibration, the sole determinant of COHb concentration in blood will be the ratio of CO to oxygen. However, the shorter the half-time for equilibration (e.g., due to hyperventilation, high concentration of CO, increased cardiac output, etc.) the more involved these mechanisms will become in modulation of the rate of CO uptake (Pace et al., 1950; Coburn et al., 1965). During high transient CO exposure in resting individuals both cardiac and lung function will control the rate of CO uptake.

The extensive amount of data available on the rate of CO uptake and the formation of COHb contrast sharply with the limited information available on the dynamics of CO washout from body stores and blood. Although the same factors that govern CO uptake will affect CO elimination, the relative importance of these factors might not be the same (Landaw, 1973; Peterson and Stewart, 1970).

The half-life of CO disappearance from blood under normal recovery conditions shows considerable inter-individual variance. For COHb concentrations of 2 to 10%, the half-life may rang from 3 to 5 hours (Landaw, 1973); others have reported a range between 2 to 6.5 hours for slightly higher initial concentrations of COHb (Peterson and Stewart, 1970). Increased inhaled concentration of oxygen

accelerated elimination of CO; by breathing 100% the half-life was shortened by almost 75% (Peterson and Stewart, 1970). The elevation of oxygen partial pressure to three atmospheres reduced the half-life to about 20 minutes, which approximated to a 14-fold decrease over that seen when breathing room air (Britten and Myers, 1985; Landaw, 1973).

The elimination rate of CO from an equilibrium state will follow a monotonically decreasing, second-order (logarithmic or exponential) function (Pace et al., 1950). The rate, however, might not be constant following transient exposures to CO, where at the end of exposure, steady-state conditions may not be reached. In this situation, particularly after very short and high CO exposures, it is possible that COHb decline could be biphasic, and can be approximated best by a double-exponential function. The initial rate of decline or "distribution" may be considerably faster than the later "elimination" phase (Wagner et al., 1975). Reported divergence of COHb decline rate in blood and in exhaled air suggests that CO elimination rate(s) from extravascular pools are slower than that reported for blood (Landaw, 1973). Although the absolute elimination rates appear to be independent of the initial concentration of COHb (Wagner et al., 1975).

The relationship between external CO exposure concentrations and increases in blood COHb above pre-existing endogenous levels has been well studied. The classical CO absorption curve of resting individuals was developed by Forbes et al. (1945). Since that time, investigators have expanded the relationship to include differing CO exposure concentrations and durations of exposure as well as different levels of physical activity (**Figure 1**). From these studies, the relationship of CO exposure and COHb can be determined. For example, Peterson and Stewart (1970) exposed human volunteers to a variety of different CO concentrations for periods ranging from 0.5 to 24 hours. Using regression analysis, they derived the following relationship for blood COHb as a function of ambient CO concentration and exposure time:

Equation 1: $\text{Log10 } y = [0.85733 (\log 10)\, x + 0.62995 (\log 10\, t)] - 2.29519$

where: y = % COHb,
x = CO concentration in ppm, and
t = time in minutes

This equation is only valid for constant CO and for shorter periods of exposure (Ott and Mage, 1978).

The relationship of COHb concentrations below 2.5% and CO in air at maximum levels of activity, determined by a mathematical formula are:

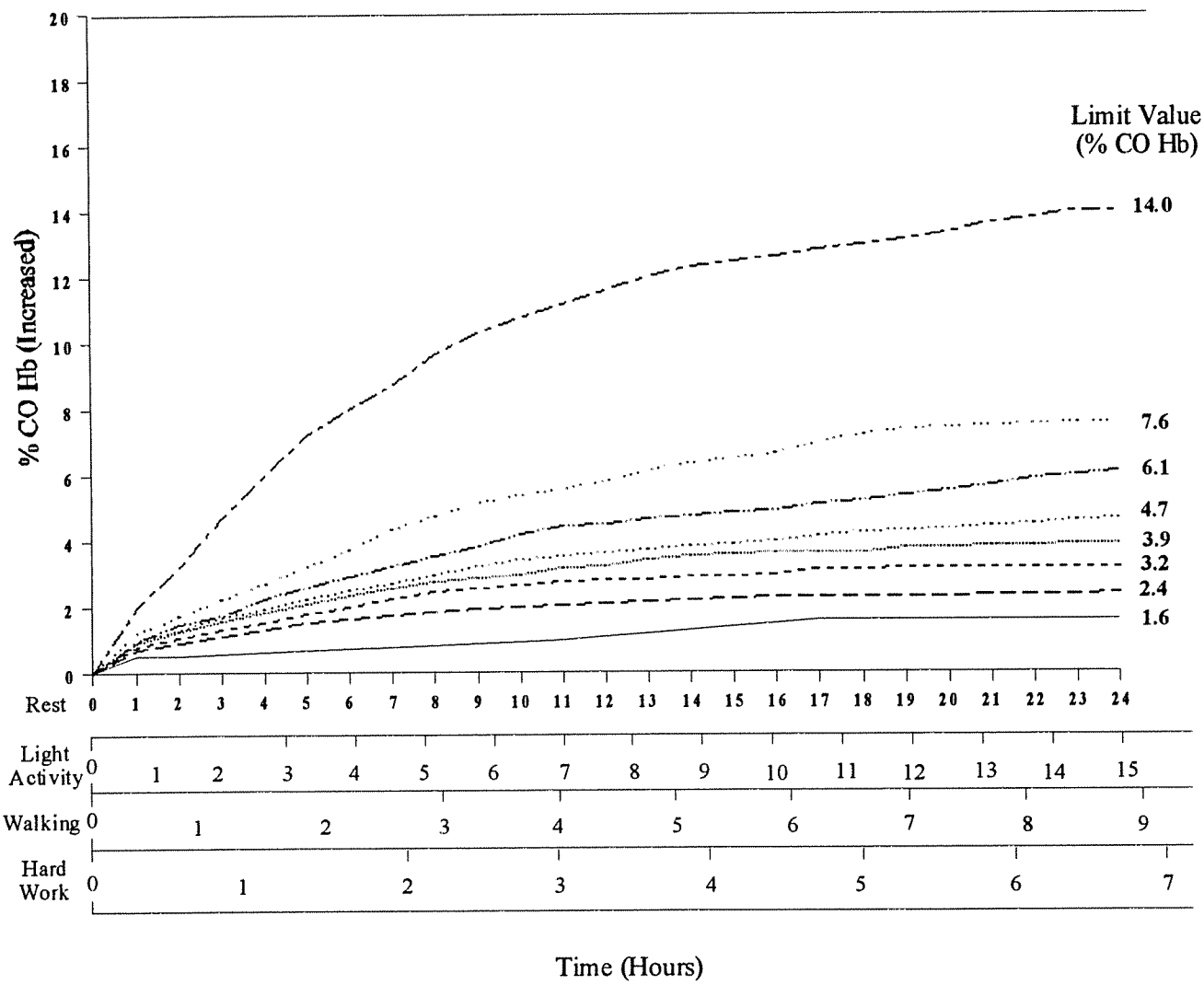
25 ppm for 1 hour
50 ppm for 30 minutes
87 ppm for 15 minutes

The actual COHb level in any individual may differ from the predicted figure depending upon the exposure conditions.

The CO - COHb relationship holds for CO uptake in individuals exposed to present-day ambient concentrations of CO. The absorption and elimination of CO is most influenced by CO concentrations, duration of exposure and alveolar ventilation. Under pathologic conditions, where one or several components of the air-blood

interface might be severely affected, as in emphysema, fibrosis, or oedema, both the uptake and elimination of CO may be affected.

Figure 1: Uptake of CO by blood



Each curve represents the time course of the increase in blood levels of carboxyhaemoglobin with continuing exposure to a specified concentration of carbon monoxide. The rate of increase is affected by the level of exercise and this is indicated by the various scales on the X-axis. (From UKDOE, 1994)

4.2.3. Mechanism of Action

The primary toxic action of CO is the inhibition of cell oxidation. Approximately 80-90% of the absorbed CO binds reversibly with haemoglobin forming COHb, resulting in a reduction in the oxygen carrying capacity of the blood. The affinity of haemoglobin for CO is approximately 200 times that for O_2. Two organs with critical needs for oxygen are the brain and heart, and are, therefore, major target organs for CO. In addition, developing offspring depend on the maternal system for their high oxygen demands.

The principal cause of CO toxicity is tissue hypoxia due to CO binding to hemoglobin. However, another site of toxicity may involve CO binding to the heme group in cytochrome oxidase, causing direct inhibition of mitochondrial oxygen utilization and respiration. CO may also bind to other heme proteins, such as myoglobin in muscle tissue, leading to depressed cardiac function and muscle oxygenation. Other proteins to which CO may bind include cytochrome P-450 and the hydroperoxidases (ACGIH, 1991, US EPA, 1991).

4.2.4. Adaptation

Adaptation to or compensation for chronic exposure to relatively high CO levels appears to occur. For example, smoking, chronic anaemia and living at high altitudes produce elevated COHb levels which are most likely compensated by changes in haematological parameters, e.g., increased red cell mass. There is limited evidence of adaptation by alteration of the dissociation curve or changes in the 2,3-diphosphoglycerate compounds (phosphorylated by-products of glycolysis) (WHO, 1979). Red cell levels of 2,3-diphosphoglycerate compounds are higher in individuals with anaemia and also during residences at high altitudes. Increases in 2,3-diphosphoglycerate shift the oxyhaemoglobin dissociation curve to the left. A shift in the dissociation curve does not appear to be a significant method of adaptation to short term exposure to elevated levels of CO.

4.3. CARDIOVASCULAR EFFECTS

Decreased oxygen uptake and resultant decreased work capacity under maximal exercise conditions have been shown to occur in healthy young adults starting at 5% COHb (**Table 1**). These cardiovascular effects may have health implications for the general population in terms of potential curtailment of certain physically demanding occupational or recreational activities. However, of greater concern at more typical ambient CO exposure levels are certain cardiovascular effects which may occur in a smaller, but sizeable segment of the general population.

In addition to the human studies cited in **Table 1**, there is also strong evidence from both theoretical considerations and experimental studies in animals that CO can adversely affect the cardiovascular system. Disturbances in cardiac function have been reported in cases of acute carbon monoxide poisoning (Lazarev, 1965). Corya et al., (1976) were the first to report evidence of left ventricular abnormality in 5 cases of nonfatal poisoning with COHb levels of 20%.

Table 2 summarises the data pertinent to the effects of CO on the cardiovascular systems of experimental animals. Accordingly, disturbances in cardiac rhythm and conduction have been noted in healthy and cardiac-impaired animals at CO concentrations of 50 to 100 ppm (COHb = 2.6 to 12%); alterations in various

haemodynamic parameters have been observed at CO concentrations of 150 ppm (COHb = 7.5%); cardiomegaly has been reported at CO concentration of 200 ppm (COHb = 12%) and 60 ppm in adult and foetal animals, respectively; changes in haemoglobin concentrations have been reported at CO concentrations of 100 ppm (COHb = 9.26%) and 60 ppm in adult and foetal animals, respectively.

Additional data from animal studies show that CO can disturb cardiac conduction and cause cardiac arrhythmias. DeBias et al. (1973) studied the effects of breathing CO (96 to 102 ppm; COHb = 12.4%) continuously (23 hours/day; for 24 weeks) on the electrocardiograms of healthy monkey and monkeys with myocardial infarcts induced by injecting microspheres into the coronary circulation. Although there was a greater incidence of T-wave inversion in the infarcted monkey the effects were transient and of such low magnitude that accurate measurements of amplitude were not possible (EPA, 1979). On the other hand, several groups have reported no effects of CO on the ECG or on cardiac arrhythmias. Musselman et al. (1959) observed no changes in the ECG of dogs exposed continuously to CO (500 ppm) for three months. Their observations were confirmed by Malinow et al. (1976) who reported no effects on the ECG in monkeys exposed to CO for 14 months (500 ppm-pulsed; COHb = 21.6%). The effects of COHb levels ranging from 5 to 15% in resistant and susceptible dogs were studied, and it was found that acute exposure to CO in dogs that have survived myocardial infarction is seldom arrhythmogenic (Farber et al., 1990).

Table 2 Effects of Exposure to Carbon Monoxide in Animals

CO EXPOSURE[a]	COHb[b]	ANIMAL	EFFECTS	REFERENCE
100 ppm, 2 hours	6.3%	Dog	Reduced VFT in normal and ligated dogs.	Aronow et al., 1979
100 ppm, 6 hours	9.3%	Monkey	Abnormal ECG and increased sensitivity to fibrillation voltage.	DeBias et al., 1973
100 ppm for 46 days 200 ppm for 30 days 500 ppm for 20-42 days	9.2% 15.8% 41.1%	Rat	Hypertrophy of both right ventricles; LDH increase.	Penney et al., 1974
20 ppm for 22 hours/day, 7 day/week, 2 year	3.4%	Monkey	No changes in haemoglobin or haematocrit, No histopathology in heart, brain or lung.	Eckhardt, 1972
20 ppm for 2 hour/day, 7 day/wk, 2 year	7.4%	Monkey	No histopathology in heart, brain and lung.	Eckhardt, 1972
CO air concentrations sufficient to reach 5, 10 or 15% COHb	5-15%	Dog; with healed anterior myocardial infarction; susceptible (develop ventricular fibrillation with exercise and myocardial ischaemia) and resistant (survive the test without arrhythmia)	Seldom arrhythmogenic; CO exposure increases heart rate at rest and during moderate exercise	Farber et al. 1990

[a] Exposure concentration and duration activity levels.
[b] Measured blood COHb (carboxyhaemoglobin) level after CO exposure.

4.4. NEUROBEHAVIORAL EFFECTS

A variety of Central Nervous System (CNS) effects have been found to be associated with CO exposures which result in COHb levels of 5 to 20%. These effects include changes in visual perception, hearing, motor performance,

sensorimotor performance, vigilance and other measures of neurobehavioral performance.

Of the behavioural effects studied, the most sensitive to disruption by COHb are those that require sustained attention or performance. For example, the group of studies on motor and sensimotor performance, which have used a variety of measures (e.g., fine motor skills, reaction time and tracking), offer the most consistent evidence for effects occurring at COHb levels as low as 5%. Although Winneke (1973) found some effects on steadiness and precision at 10% COHb, several other investigators reported no effect at COHb levels ranging from 5.5 to 12.7%. Reaction time was unaffected by COHb levels of 7 and 10%, and the general conclusion is that COHb elevation does not affect reaction time for COHb levels as high as 20%.

No reliable evidence demonstrating decrements in neurobehavioral function in healthy young adults has been reported at COHb saturation levels below 5%. Results of studies conducted at or above 5% COHb are ambiguous. Much of the research at 5% COHb does not show any effects. From the empirical evidence it can be said that COHb levels $\geq$ 5% do produce decrements in neurobehavioral function. It cannot be said confidently, however, that COHb levels lower than 5% would be without effect. The question of groups at special risk for neurobehavioral effects are those taking drugs that have primary or secondary depressant effects, which would be expected to exacerbate CO-related neurobehavioral decrements. Other groups, at possibly increased risk for CO-induced neurobehavioral effects, are the aged and ill, but these groups have not been evaluated for such risk.

Overall, it may be concluded that the central nervous system is not as sensitive to the effects of CO as the cardiovascular system.

4.5. DEVELOPMENTAL EFFECTS

The foetus may be particularly vulnerable to the toxic effects of CO exposures because foetal development often occurs at or near critical tissue oxygen levels (Longo and Hill, 1977). COHb levels tend to be elevated in the foetus due to differences in uptake and elimination of CO from foetal haemoglobin.

Human data on the developmental toxicity of CO are very limited for obvious ethical reasons. Maternal smoking, however, has been associated with a number of adverse health effects, many of which may be attributed to very high CO exposures (500-1000 ppm) from cigarette smoke. These effects include spontaneous abortion and foetal death due to depressed birth weight. In addition, children subjected to CO exposures from maternal smoking, experience increased hospital admissions during the first 5 years of life and poorer than predicted school performance during the first 11 years of life. While the available human data are insufficient to determine a cause and effect relationship for CO exposure and developmental toxicity, animal studies have provided evidence of foetal mortality, developmental toxicity, reduced body weight, morphological changes, altered cardiovascular development, and neurochemical changes. However, as these studies were often conducted at CO levels much greater than those found in the ambient air, extrapolation to human health effects at ambient CO exposures remains very difficult.

4.6. OTHER HEALTH EFFECTS

Other effects related to CO exposures have been reported. Many of the studies are in animals or case reports and their relevance to the general human population has not been established. For example, extensive experimental work has been conducted on animals showing that prolonged exposure to moderate levels of CO can produce atherosclerotic changes, particularly with elevated cholesterol diets (WHO, 1979). Only relatively weak evidence points toward possible CO effects on fibrinolytic activity, generally only at high CO exposure levels.

There is a lack of information of the combined effect of CO exposure and other chemicals and drugs. Because of the generalised effects of CO and the severity of the consequences of high exposures, the significance of co-exposure to other air pollutants, drugs and social habits (e.g., smoking and ethanol consumption) needs clarification.

5. STANDARDS

5.1. OCCUPATIONAL EXPOSURE LIMITS

Occupational exposure limits for CO in various countries are summarised in **Table 3**.

Table 3: Occupational Exposure Limits for CO

COUNTRY	8h TIME WEIGHTED AVERAGE mg/m^3 (ppm)	SHORT TERM EXPOSURE mg/m^3 (ppm)
Australia (1990)	55 (50)	440 (400)
Germany (1995)	33 (30)	66 (60)[a]
Sweden (1984)	40 (35)	120 (100)[b]
United Kingdom (1995)	55 (50)	340 (300)[c]
US - ACGIH (1992)	29 (25)	-[d]
US - NIOSH (1972)	40 (35)	229 (200)[e]
US - OSHA (1993)	55 (50)	-

Adopted from ACGIH TLV documentation (1991)

[a] Short-term level for 30 minutes, 4 times per shift. Classified as Pregnancy Group B; risk of damage to the developing embryo or foetus cannot be excluded even when MAK values are observed.
[b] 15-minute short-term value
[c] 10-minute STEL
[d] No STEL proposed
[e] Ceiling value; IDLH value of 1200 ppm recommended in 1994

5.2. AIR QUALITY STANDARDS

Several countries and the World Health Organisation (WHO) have established air quality standards or guidelines for CO (**Table 4**). The critical effect on which all of these standards/guidelines are based is COHb concentrations associated with cardiovascular effects (Beard and Wertheim, 1967).

Current Canadian recommendations specify three control levels: the maximum desirable level, the maximum acceptable level and the maximum tolerable level (Health and Welfare Canada, 1985). The maximum desirable level is equivalent to the WHO Level I (WHO, 1964), where pollution can be detected, but there are no physiological changes or other adverse effects upon human health. The maximum acceptable level of pollution is the level in which the body can compensate for the impact on physiology (Hatch, 1962).

Table 4: CO Air Quality Standards[a]

	WHO[b]	UK[c]	US[d]	CANADA[e]			GERMANY[b]	JAPAN[b]
AVERAGE PERIOD	ppm	ppm	ppm	MAXIMUM DESIRABLE ppm	MAXIMUM ACCEPTABLE ppm	MAXIMUM TOLERABLE ppm	ppm	ppm
1-hour	25		35	13	30	--	9	10
8-hour	10	10[f]	9	5	13	17	26	20

[a] 1 part per million (ppm) is one part, by volume, in one million; 1 ppm of CO is 1.165 mg/m^3 at 20°C and 1013 millibars.
[b] Source: WHO 1979
[c] Source: UKDOE, 1994
[d] Source: Federal Register, 1994
[e] Source: Health and Welfare Canada (1985)
[f] To ensure that maximum concentrations are not miscued by arbitrary averaging periods, it is recommended that a running 8 hour average be used. Running 8-hour average CO concentrations are calculated by first calculating the hourly average CO concentrations over fixed periods, from 00.00 to 00.59 onwards. These averages are then taken consecutively in groups of eight and the 8-hour averages are calculated for 00.00-07.59, 01.00-08.59 etc. onwards.

The UK Expert Panel on Air Quality Standards for CO concluded that CO concentrations should be such that the concentration of COHb in the blood of people breathing the air should not exceed 2.5% [Ref EPAQS]. Based on air monitoring in the UK, an 8-hour running average standard was recommended, to ensure that short duration high concentrations of CO were not missed.

5.3. BASIS FOR AN AQS

Acute high level exposure to CO can produce death and lower levels of exposure have been associated with toxic effects. In determining an AQS for CO, continuous exposure must be considered, as well as maximum excursions of CO air concentrations.

5.3.1. Critical Endpoint and Sensitive Subpopulation

Cardiovascular Effects

Several important studies have appeared since the first studies on the effects of CO exposure in persons with cardiovascular disease, expanding the data base (**Table 5**). The NOEL for arrhythmia induction associated with CO exposure is at 4% COHb (Sheps et al., 1990), but those patients with angina appear to be more sensitive to CO. Patients with reproducible exercise-induced angina have experienced earlier onset of angina with post-exposure COHb levels as low as 3.2% (Allred et al., 1989). Sheps et al. (1987) also found similar effects in a group of patients with angina at COHb levels of 3.8%. Kleinman et al. (1989) studied subjects with angina and found that the time to onset of angina was decreased at 3% COHb. Thus, the LOEL for patients with stable angina is between 3 and 4% COHb, representing an increase above baseline of 1.5 to 2.2%.

5.3.2. Application of Safety Factors

In this section we integrate the scientific determination of the LOEL and/or NOEL with judgmental factors which must be considered as part of any exercise designed to protect public health.

Table 5: Summary of Effects of Carbon Monoxide Exposure in Patients with Angina

EXPOSURE[a]	COHb[b]	COHb[c]	SUBJECT(S)	OBSERVED EFFECTS	REFERENCE
50 ppm CO 100 ppm CO for 50 minute of each hour x 4 hour; postexposure exercise on a treadmill	2.9% 4.5%	1.6% 3.2%	10 males, 5 smokers and 5 nonsmokers, with reproducible exercise-induced angina; average 49.9 years	Duration of exercise before onset of angina was significantly shortened at 2.9 and 4.5% COHb; duration of angina was significantly prolonged at 4.5% but not at 2.9% COHb. The response of smokers was not significantly different from that of nonsmokers.	Anderson et al., (1973)
100-200 ppm CO for 60 minute; postexposure incremental exercise at 317 KPM on a cycle ergometer	3.8%	2.2%	25 male 5 female nonsmokers with evidence of exercise-induced angina on at least one day; 58 ± 11 years (36-75 years)	No significant difference in time to onset or duration of angina. No significant difference in maximal exercise time, maximal ST segment depression, or time to significant ST segment depression during exercise.	Sheps et al., (1987)
100 ppm CO for 60 minute; postexposure incremental exercise at 48.6 L/minute on a cycle ergometer	3.0%	1.5%	24 male nonsmokers with reproducible exercise-induced angina; 59 ± 1 years (49-66 years)	Time to onset of angina decreased; no significant effect on the duration of angina. O_2 uptake at angina was reduced; there were no significant changes in heart rate or systolic blood pressure at angina.	Kleinman et al., (1989)
117 ppm CO 253 ppm CO for 50-70 minute; pre- and post-exposure incremental exercise at ~6 METS[d] on a treadmill	3.2% 5.6%	2.0% 4.4%	63 males nonsmokers with reproducible exercise-induced angina; 62 ± 8 years (41-75 years)	Earlier onset of myocardial ischemia was found with CO exposure: time to ST endpoint decreased and time to angina onset decreased at 2.0 and 3.9% COHb; mean duration of exercise was significantly shorter at 3.9% COHb. Changes in performance are clinically significant.	Allred et al. (1989)
100 ppm CO 200 ppm CO supine bicycle exercise test	4.0% 5.9%	3.2% 5.1%	41 subjects (nonsmokers) with documented coronary artery disease; 16 never smoked, 25 previous smokers; average 63 years old, 5 females and 36 men	Frequency of single premature ventricular contractions per hour during exercise was significantly greater at 6% COHb; frequency of multiple premature ventricular contractions per hour was significantly greater during exercise with 6% COHb; patients developing increased arrhythmias during exercise at 6% COHb were significantly older, exercised longer and had a higher peak workload during exercise; No effect of carbon monoxide seen at 4% COHb.	Sheps et al., 1990
Two CO levels 150 minute exposure, 2 minute interval walks, increasing workload by 1 MET each stage, maximum workload 11 METs	3.2% 5.1%	2.5% 4.5%	30 subjects with documented ischemic heart disease; 25 men and 5 women; average age 65 years	No increase in ventricular arrhythmia frequency after exposure; frequency of complex ventricular ectopy was not altered	Chaitman et al., 1992

[a] Exposure concentration, duration, and peaks activity levels.
[b] Measured blood COHb (carboxyhemoglobin) level after CO exposure.
[c] Postexposure increase in COHb over baseline.
[d] MET - basal metabolic equivalent

Cardiovascular Disease

From **Table 5**, the database would indicate that a COHb concentration between 3 and 4% clearly produces effects in angina patients. COHb levels of 2.5% appear to be a reasonable NOEL for the production of exercise induced angina in patients with cardiovascular disease. The relationship of carboxyhaemoglobin concentrations below 2.5% to breathing CO air concentrations at maximum levels of activity determined by mathematical formula are:

15 ppm for 8 hours
25 ppm for 1 hour
50 ppm for 30 minutes
87 ppm for 15 minutes

The actual COHb level in any individual may differ from the predicted figure depending upon the exposure conditions.

For physical activities ranging from rest to hard work, the corresponding ambient CO level resulting in COHb concentration that would never exceed 2.5% would be 15 ppm. Thus, for the general, non-smoking population, including those with angina, 8 hour continuous exposure to CO at 15 ppm and resulting in a COHb of approximately 2.5% would not be hazardous.

Pre-existing Pathology

It is likely that people having diseases that affect the delivery of oxygen to the heart or brain may be at particular risk with additional impairment of oxygen delivery posed by exogenous CO exposures. This has been established for those with angina, but others with anaemia, and heart and lung disease may also be susceptible. However, individuals with pulmonary disease may absorb less CO and may compensate for this by increased erythropoiesis and a shift of the dissociation curve to the right (WHO, 1979).

There are no data to suggest that these individuals are any more susceptible than those with angina. However, uncertainty does exist as to the NOEL for CO exposure in these individuals. A safety factor of 1.5 is, therefore, applied to protect for the potential sensitivity of this sub-population. Applying this safety factor, results in a predicted 1.6% COHb concentration. Continuous exposure to CO at 10 ppm would not exceed 1.6% COHb, thus an adequate margin of safety would exist for the identified sensitive sub-populations.

Developing Foetus

The effects of CO exposure on the foetus during intrauterine development are not clear. Pregnant women produce greater levels of endogenous CO. The source may be related to progesterone levels (Delivoria-Papadopoulos et al., 1970). There may be compensation for the elevated COHb levels of pregnancy, in part, by hyperventilation. Maternal COHb is 13% above that of non-pregnant women (Longo, 1970). Studies have predicted changes in foetal oxygenation as a result of maternal COHb levels of about 5%. Prolonged CO exposure at 30 ppm could attain such results (UKDOE, 1994). Therefore, no additional safety factor needs to be applied to an AQS of 10 ppm for the developing foetus.

High Altitude

While there are many studies comparing the effects of CO exposure with those of high altitude exposure, there are relatively few reports on the effects of both combined (i.e., CO exposure at high altitude). It has been assumed that CO-induced hypoxia and altitude-induced hypoxia are additive, however, there are only limited data to support this contention. There are even fewer studies of the long-term effects of CO at high altitude and at the low concentrations pertinent to ambient air standards. Given that there is little reliable information on this subject, no additional safety factors were incorporated for the subpopulation of individuals living at high altitudes.

Smoking

It is well known that cigarette smoking causes serious health effects, however, it is difficult to separate the effects of CO exposures from those of other substances present in inhaled smoke. Tobacco smoking, particularly cigarettes, increases COHb levels substantially above those of the non-smoking population. Concentrations of 5-15% COHb are commonly found in smokers (WHO, 1979). It is recognised that the effects of smoking and exposure to CO in ambient air are not simply additive and that the resulting COHb levels depend on other factors. Regular smokers are not likely to be affected by ambient CO concentrations since their blood levels of COHb already exceed that which would be produced by the ambient concentration (UK DOE, 1994).

Smoking is another (and substantial) exogenous source for CO exposure. Smoking is a voluntary act subjecting the smoker to increased risk of adverse health effects. For these reasons, smokers are not considered a sensitive sub-population and no additional safety factor is required.

5.3.3. Air Quality Standard

Because levels of CO causing human health effects are lower than those causing eco effects the health effects need to be taken as the basis for the development of an AQS. The most sensitive health endpoint is the cardiovascular system and the most sensitive sub-population has been identified as those with angina. The NOEL for this endpoint in the general population is estimated to be the level of CO producing a COHb concentration of 2.5%. From **Figure 1**, the CO concentration producing this condition after 8 hours of exposure would be 15 ppm. A safety factor is applied to this concentration for the uncertainty of protecting those individuals with pre-existing pathology, e.g. anaemia and pulmonary disease.

2.5% COHb (15 ppm)/ Safety Factor (1.5) = 1.6% COHb (10 ppm)

Continuous exposure of the non-smoking population to 10 ppm CO would produce COHb concentrations that would not exceed 1.6%. This would be true of sedentary individuals as well as those involved in heavy physical activity (**Figure 1**). To obtain these conditions, running 8 hour averages should not exceed 10 ppm of CO.

An exposure standard based on an eight-hour averaging time is of sufficient duration to protect the population against continuous lifetime exposure.

6. DATA GAPS/RECOMMENDATIONS

A common problem associated with the available human data is that only a small proportion comes from controlled laboratory studies. In laboratory studies, the exposure levels are generally near or below threshold. Other human data comes from case studies or occupational settings where exposures are not controlled. These data are complicated by lack of exposure information, co-exposure to other substances and often high level exposures. Extrapolation of the effects seen at acute high level exposures to chronic, low level exposure scenarios is wrought with problems and uncertainty.

In spite of the extensive research which has been conducted on carbon monoxide over the past decades, there are still deficiencies in the knowledge about this substance which make it impossible to precisely determine its potential to produce adverse effects at low ambient exposure levels. The major data gaps include the following:

- There is a need for more data on various high risk groups (the foetus and new-born, the elderly, patients with anaemia, surgical shock, chronic respiratory disease, and cerebrovascular disease) and possible interactions with other stress factors, such as high altitude.

- There is a need for information of the interaction of CO exposure with exposure to other air pollutants, drugs and social habits.

- To date, the exact mechanisms responsible for the adverse effects of carbon monoxide-induced hypoxia are not known in detail.

- While COHb appears to be a reliable marker of exposure, it does not necessarily reflect the effect at the tissue level. The emergence of biological markers of effect, based on rapid advances in molecular biology, would complement traditional markers and be capable of linking effects to exposure.

7. REFERENCES

Allred, E.N. et al (1989) Short-term Effects of Carbon Monoxide Exposure on Exercise Performance of Subjects with Coronary Artery Disease. *N Engl J Med* 321:1426-1432

American Conference of Governmental Industrial Hygienists (1991) Carbon Monoxide. Documentation of the Threshold Limit Values and Biological Exposure Indices, Sixth Edition. ACGIH, Cincinnati, OH

American Conference of Governmental Industrial Hygienists (1991) Threshold Limit Values for Chemical Substance and Physical Agents and Biological Exposure Indices 1991-1992. ACGIH, Cincinnati, OH

Anderson, E.W. et al (1973) Effect of low-level Carbon Monoxide Exposure on Onset and Duration of Angina Pectoris: A Study in Ten Patients with Ischemic Heart Disease. *Ann Intern Med* 79:46-50

Aronow, W.S. et al (1977) Effect of Carbon Monoxide on exercise performance in Chronic Obstructive Pulmonary Disease. *Amer J Med* 63:904-908

Aronow, W.S. et al (1979) Carbon Monoxide and Ventricular Fibrillation Threshold in Normal Dogs. *Arch Environ Health* 34:184-186

Aronow, W.S. et al (1974) Effect of Carbon Monoxide Exposure on Intermittent Claudication. *Circulation* 49:415-417

Astrup, P. et al (1972) Effect of Moderate Carbon Monoxide Exposure on Fetal Development. *Lancet* (ii) 1220-1222

Ayres, S.M. et al (1969) Systemic and Myocardial Hemodynamic Responses to Small Concentrations of Carboxyhemoglobin. *Arch Environ Health* 18:699-709

Beard, R.R. and Wertheim, G.A. (1967) Behavioral Impairment Associated with Small Doses of Carbon Monoxide. *American Public Health Journal* 57:2012-2022

Bender, E. et al (1971) The Effects of Low Concentrations of Carbon Monoxide in Man. *Arch Toxicol* 27:142-158

Benignus, V.A. et al (1977) Lack of Effects of Carbon Monoxide on Human Vigilance. *Percept Mot Skills* 45:1007-1014

Benson, F.B. et al (1972) Indoor-outdoor air pollution relationships: a literature review. U.S. Environmental Protection Agency, Publ. AP 112, Research Triangle Park, NC

Berk, P.D. et al (1976) A New Approach to Quantitation of Various Sources of Bilirubin in Man. *Journal Lab Clin Med* 87:767-780

Britten, J.S. and Myers, R.A.M. (1985) Effects of Hyperbaric Treatment on Carbon Monoxide Elimination in Humans. *Undersea Biomed Res* 12:431-438

Chaitman, B.R. et al (1992) Carbon Monoxide Exposure of Subjects with Documented Cardiac Arrhythmias. Health Effects Institute, Research Report Number 52

Chipman, J.C. and Massey, M.T. (1960) Propositional Sampling System for the Collection of an Integrated Auto Exhaust Gas Sample. *J.A.P.C.A*. 10:60-69

Christensen, C.L. et al (1977) Effects of Three Kinds of Hypoxias on Vigilance Performance. *Aviat Space Environ Med* 48:491-496

Clark, B.J. and Colburn, R.T. (1975) Mean Myoglobin Tension During Exercise at Maximal Uptake. *J Appl Physiol* 39:135-144

Coburn, R.F. et al (1964) Effect of Erythrocyte Destruction on Carbon Monoxide Production in Man. *J Clin Invest* 43:1098-1103

Coburn, R.F. et al (1965) Considerations of the Physiological variables that Determine the Blood Carboxyhemoglobin Concentration in Man. *J Clin Invest* 44:1899-1910

Coburn, R.F. et al (1966) Endogenous Carbon Monoxide Production in Patients with Hemolytic Anemia. *J Clin Invest* 45:460-468

Coburn, R.F. (1970) Enhancement by Phenobarbital and Diphenlhydantoin of Carbon Monoxide Production in Normal Man. *N Engl J Med* 283:512-515

Corya, B.C. et al (1976) Echocardiographic Findings After Acute Carbon Monoxide Poisoning. *Br Heart J* 38:712-717

Dahms, T.E. and Horvath, S.M. (1974) Rapid, Accurate Technique for Determination of Carbon Monoxide in Blood. *Clin Chem* 20:533-537

DeBias, D.A. et al (1973) Carbon Monoxide Inhalation Effects Following Myocardial Infarction in Monkeys. *Arch Environ Health* 27:161-167

Delivoria-Papadopoulos, M. et al (1970) Cyclical Variation of Rate of Heme Destruction and Carbon Monoxide Production (V_{co}) in Normal Women. *Physiologist* 13:178

Dianov-Klokov, V.I. and Yurganov, L.N. (1981) A Spectroscopic Study of the Global Space-Time Distribution of Atmospheric Carbon Monoxide. *Tellus* 33:262-273

Drinkwater, B.L. et al (1974) Air Pollutant, Exercise, and Heat Stress. *Arch Environ Health* 28:177-181

Eckardt, R.E. et al (1972) The Biologic Effect from Long-term Exposure of Primates to Carbon Monoxide. *Arch Environ Health* 25:381-387

Ekblom, B. and Huot, R. (1972) Response to Submaximal and Maximal Exercise at Different Levels of Carboxyhemoglobin. *Acta Physiol Scand* 86:474-482

Elliott, M.A. et al (1955) The Composition of Exhaust Gases from Diesel, Gasoline and Propane-Powered Motor Coaches. *J.A.P.C.A.* 5:103-108

Farber, J.P. et al (1990) Carbon Monoxide and Lethal Arrhythmias. Health Effects Institute, Research Report Number 36

Fechter, L.D. and Annau, Z. (1976) Effects of Prenatal Carbon Monoxide Exposure on Neonatal Rats. *Adverse Effects of Environmental Chemicals and Psychotropic Drugs-Neurobehavioral and Behavioral Test* Vol. 2, Horvath, M. and Frantek, E. (Eds.) New York, Elsevier, pp. 219-227

Federal Register (1994) 40 CFR Part 50

Forbes, W.H. et al (1945) The Rate of Carbon Monoxide Uptake by Normal Men. *Amer J Physiol* 143:594-608

Frasier, P.J. et al (1986) Methane, Carbon Monoxide and Methyl chloroform in the Southern Hemisphere. *J Atmos Chem* 4:3-42

General Electric (1972) Indoor-Outdoor Carbon Monoxide Pollution Study. U.S. EPA-RA-73-020

Gothe, C.J. et al (1969) Carbon Monoxide Hazard in City Traffic. *Arch Environ Health* 19:310-314

Grut, A. (1949) Chronic Carbon Monoxide Poisoning. Ejnar Munksgaard, Copenhagen

Guest, A.D. et al (1970) Carbon Monoxide and Phenobarbitone: A Comparison of Effects on Auditory Flutter Fusion Threshold and Critical Flicker Fusion Threshold. *Ergonomics* 13:587-594

Haider, M. et al (1974) Effects of Moderate Carbon Monoxide Dose on the Central Nervous System--Electrophysiological and Behaviour Data and Clinical Relevance. *Clinical Implications of Air Pollution Research: Air Pollution Medical Research Conference*, Publishing Science Group, Inc., San Francisco, CA, Acton, MA, pp. 217-232

Hampson, R.F. and Garvin, D. (1975) Chemical Kinetic and Photochemical Data for Modeling Atmospheric Chemistry. NBS Techn. Note 866, U.S. Dept. of Commerce, pp. 1-112

Hatch, T.F. (1962) Changing Objective in Occupational Health. *Amer Ind Hygiene Assoc J* 23:1-7

Health and Welfare Canada (1985) Carbon monoxide. Ministry of National Health and Welfare, Publication 83-EHD-85

Hernberg, S. et al (1976) Angina Pectoria, ECG Findings and Blood Pressure of Foundry Workers in Relation to Carbon Monoxide Exposure. *Scand J Work Environ Health* 2(Suppl. 1):54-63

Horvath, S.M. et al (1975) Maximal Aerobic Capacity at Different Levels of Carboxyhemoglobin. *J Appl Physiol* 38:300-303

Horvath, S.M. et al (1988) Maximal Aerobic Capacity at Several Ambient Concentrations of Carbon Monoside at Several Altitudes. Health Effects Institute, Research Report Number 21

Hurn, R.W. (1962) Comprehensive Analysis of Automotive Exhausts. *Arch Environ Health* 5:592-596

Inman, R.E. et al (1971) Soil: A Natural Sink for Carbon Monoxide. *Science* 172:1229-1231

Jaffe, L.S. (1973) Carbon Monoxide in the Biosphere: Sources, Distribution, and Concentrations. *J Geophys Res* 78:5293-5305

Johnson, B.L. et al (1974) Field Evaluation of Carbon Monoxide Exposed Toll Collectors. In: Behavioral Toxicology, U.S. Dept. of Health, Education and Welfare NIOSH Report, 74-126:306-328

Khalil, M.A.K. and Rasmussen, R.A. (1988) Carbon Monoxde in the Earth's Atmosphere: Indication of a Global Increase. *Nature* (London), 332:242-245

Klein, J.P. et al (1980) Hemoglobin Affinity for During Short-term Exhaustive Exercise. *J Appl Physiol* 48:236-242

Kleinman, M.T. et al (1989) Effects of short term Exposure to Carbon Monoxide in Subjects with Coronary Artery Diseases. *Arch Environmental Health* 44:361-369

Knudson, R.J. et al (1989) The Effects of Cigarette Smoking and Smoking Cessation on the Carbon Monoxide Diffusing Capacity of the Lung in Asymptomatic Subjects. *Am Rev Respir Dis* 140:6745-651

Landaw, S.A. et al (1970) Catabolism of Heme in vivo Comparison of the Simultaneous production of Bilirubin and Carbon Monoxide. *J Clin Investigation* 49:914-925

Landaw, S.A. (1973) The Effects of Cigarette Smoking on Total Body Burden and Excretion Rates of Carbon Monoxide. *Journal of Occupational Medicine* 15:231-235

Larson, G.P. et al (1955) Study of the Distribution and Effects of Auto Exhaust Gases. *J.A.P.C.A.* 5:84-90

Lazarev, N.V. (1965) Carbon Monoxide. *Toxic Substances in Industry* Vol. 2, pp. 198-218

Levy, H. II. (1973) Tropospheric Budgets for Methane, Carbon Monoxide and Related Species. *J Geophys Res* 78:5325-5332

Longo, L.D. (1970) Carbon Monoxide in the Pregnant Mother and Fetus and its Exchange Across the Placenta. *Ann NY Acad Sci* 174:313-341

Longo, L.D. and Hill E.P. (1977) Carbon Monoxide Uptake and Eliminate in Fetal and Maternal Sheep. *Amer J Physiol* 232:324-333

Lynch, S.R. and Moede, A.L. (1972) Variation in the Rate of Endogenous Carbon Monoxide Production in Normal Human Beings. *J Lab Clin Med* 79:85-95

Malinow, M.R. et al (1976) Failure of Carbon Monoxide to Induce Myocardial Infarction in Cholesterol-Fed Cynomolgus Monkeys. *Cardiovasc Res* 10:101-108

Maugh, T.H. (1972) Carbon Monoxide: Natural Sources Dwarf Man's Output. *Science* 177:338-339

McClean, P.A. et al (1981) Changes in Exhaled Pulmonary Diffusing Capacity at Rest and Exercise in Individuals with Impaired positional diffusion. *Bull Eur Phsiopathol Respir* 17:179-186

McConnell, J.C. et al (1971) Natural sources of atmospheric CO. *Nature* (London), 233:187-88

McFarland, R.A. (1973) Low Level Exposure to Carbon Monoxide and Driving Performance. *Arch Environ Health* 27:355-359

McFarland, R.A. et al (1944) The Effects of Carbon Monoxide and Altitude on Visual Thresholds. *J Aviat Med* 15:381-394

Minima, E.G. and Tylkina, L.G. (1947) Physiological Study of the Effect of Gases upon Sex Differentiation in Plants. *Dokl Akad Nauk* SSSR 55:165-168

Musselman, N.P. et al (1959) Continuous exposure of laboratory animals to low concentration of carbon monoxide. *Aerosp Med* 30:524-529

O'Donnell, R.D. et al (1971) Low Level Carbon Monoxide Exposure and Human Psychomotor Performance. *Toxicol Appl Pharmacol* 18:593-602

Oski, F.A. and Altman, A.A. (1962) Carboxyhemoglobin Levels in Hemolytic Disease of the Newborn. *J Pediatri* 61:709-713

Ott, W.R. and Mage, D.T. (19??) Interpreting urban carbon monoxide concentrations by means of a computerized blood COHb model. *J Air Pollut Control Assoc* 28:911-916

Pace, N. et al (1950) Acceleration of Carbon Monoxide Elimination in Man by High Pressure. *Science* 111:652- 654

Penney, D. et al (1974) Chronic Carbon Monoxide Exposure: Time Course of Hemoglobin, Heart Weight and Lactate Dehydrogenase Isozyme Changes. *Toxicol Appl Pharmacol* 28:493-497

Peterson, J. E. and Stewart, R.D. (1970) Absorption and Elimination of Carbon Monoxide by Inactive Young Men. *Arch Environmental Health* 21:165-171

Pirnay, J. et al (1971) Muscular Exercise During Intoxication by Carbon Monoxide. *J Appl Physiol* 31:573

Putz, V.R. (1979) The Effects of Carbon Monoxide on Dual-Task Performance. *Human Factors* 21:13-24

Putz, V.R. et al (1976) Effects of CO on Vigilance Performance: Effects of Low Level Carbon Monoxide on Divided Attention, Pitch Discrimination, and the Auditory Evoked Potential. Cincinnati, OH, U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, available from NTIS, Springfield, VA, PB-274219

Rockwell, T.J. and Weir, F.W. (1975) The Interactive Effects of Carbon Monoxide and Alcohol on Driving Skills. Columbus, OH, The Ohio State University Research Foundation, CRC-APRAC project CAPM-9-69, available from NTIS, Springfield, VA, PB-242266

Rummo, N. and Sarlanis, K. (1974) The Effect of Carbon Monoxide on Several Measures of Vigilance in a Simulated Driving Task. *J Saf Res* 6:126-130

Salvatore, S. (1973) Performance Decrement Caused by Mild Carbon Monoxide Levels on Two Visual Functions. *J Saf Res* 6:131-134

Schaplowsky, A.F. et al (1974) Carbon Monoxide Contamination of the Living Environment. *J Environ Health* 36:569-573

Schulte, J.H. (1973) Effects of Mild Carbon Monoxide Intoxication. *Arch Environ Health* 7:524-530

Seiler, W. and Junge, C. (1969) Decrease of Carbon Monoxide Mixing Ratio Above the Polar Tropopause. *Tellus* 21:447-449

Solanki, D.L. et al (1988) Hemolysis in Sickle Cell Disease as Measured by Endogenous Carbon Monoxide Production: A Preliminary Report. *American Journal Clin Pathol* 89:221-225

Sheps, D.S. et al (1987) Lack of Effect of Low Levels of Carboxyhemoglobin on Cardiovascular Function in Patients with Ischemic Heart Diseases. *Arch Environ Health* 42:108-116

Sheps, D.A. et al (1990) Effects of 4 Percent and 6 Percent Carboxyhemoglobin on Arrhythmia Production in Patients with Coronary Artery Disease. Health Effects Institute, Research Report Number 41

Stewart, R.D. et al (1973) Normal Carboxyhemoglobin Level of Blood in Donor in the U.S. Report ENVIR-MED-MCW-CRC-COHb-73-1. Medical College of Wisconsin

Stewart, R.D. et al (1978) The Effect of a Rapid 4% Carboxyhemoglobin Saturation Increase on Maximal Treadmill Exercise. New York, NY, Coordinating Research Council, Inc., Report No. CRC-APRAC-CAPM-22-75, available from NTIS, Springfield, VA, PB-296627

Stokes, D.L. et al (1981) Nonlinear increases in Diffusing Capacity During exercise by Seated and Supine Subjects. *J Appl Physiol Respir Environ Exercise Physiol* 51:858-863

Treshow, M. and Anderson, F.K. (1989) Plant stress from air pollution. John Wiley & Sons, Ltd, New York

Twiss, S.B. et al (1955) Application of Infra-Red Spectroscopy to Exhaust Gas Analysis. *J.A.P.C.A.* 5:75-83

United Kingdom, Department of the Environment (UK DOE) (1994) Expert Panel on Air Quality Standards CARBON MONOXIDE

US Environmental Protection Agency (1979) Air Quality Criteria for Carbon Monoxide. EPA-600/8-79-022. Environmental Criteria and Assessment Office. Office of Health and Environmental Assessment. Office of Research and Development. Washington, D.C.

US Environmental Protection Agency (1985) Review of the National Ambient Air Quality Standard for Carbon Monoxide. Federal Register 50(178):37484

US Environmental Protection Agency (1991) Air Quality Criteria for Carbon Monoxide. EPA/600/8-90/045F. Office of Research and Development, Washington, D.C.

Vogel, J.A. and Gleser, M.A. (1972) Effect of Carbon Monoxide on Transport During Exercise. *J Appl Physiol* 32:234-239

Wagner, J.A. et al (1975) Carbon Monoxide Elimination. *Respir Physiol* 23:41-47

Weiser, P.C. et al (1979) Environmental Stress: Individual Human Adaptations. Academic Press, New York, NY. Effects of Low-Level Carbon Monoxide Exposure on the Adaptation of Healthy Young Men to Aerobic Work at an Altitude of 1610 meters, pp. 101-110

Weinstock, B. (1969) Carbon Monoxide: Residence Time in the Atmosphere. *Science* 166:224-225

Weinstock, B. and Niki, H. (1972) Carbon Monoxide Balance in Nature. *Science* 176:290-292

Winneke, G. (1973) Behavioral Effects of Methylene Chloride and Carbon Monoxide as Assessed by Sensory and Psychomotor Performance. *Behavioral Toxicology: Early Detection of Occupational Hazards Proceedings of a Workshop*, Cincinnati, OH. U.S. Department of Health, Education and Welfare, National Institute for Occupational Safety and Health, pp. 130-144. DHEW Publication No. (NIOSH) 74-126

World Health Organization (1964) Atmospheric Pollutants. Tech Report 271

World Health Organization (1979) Carbon Monoxide. Environmental Health Criteria 13

Wright, G. et al (1973) Carbon Monoxide and Driving Skills. *Arch Environ Health* 27:349-354

Yocom, J.E. et al (1971) Indoor/Outdoor Air Quality Relationships. *J.A.P.C.A.*

Zimmerman, P.W. et al (1933) The Effect of Carbon Monoxide on Plants. *Contrib Boyce Thompson Inst* 5:195-211