

## CARBON MONOXIDE(CO)

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## I.INTRODUCTION

During the late 1960s and early 1980s, carbon monoxide (CO) was the principal source of air pollution emitted by motor vehicles in urban areas. CO was also responsible for more poisoning deaths in the United States than any other agent, with the highest incidence occurring during the cold-weather months. During 1979-1988, from 878 to 1,513 deaths per year were attributed to unintentional CO poisoning (exposure to >500 ppm) in the United States (39). Exposures to CO concentrations of 10 to 200 ppm in ambient air, inside motor vehicles, workplace, and home can exert adverse health effects on the general population (5,10,11,13,20,33,39). The most important health effects associated with exposure to CO are due to its strong bond with the hemoglobin molecule, forming carboxyhemoglobin (COHb).COHb impairs the oxygen-carrying capacity of the blood, putting a strain on tissues with high oxygen demand, such as heart and brain.CO also binds to cytochrome oxidase, which could reduce the cells' ability to

utilize oxygen (20).

Clinical symptoms range from subtle cardiovascular, respiratory, and neurobehavioral effects at low concentrations (10ppm) (11,13,14,39) to unconsciousness and death after prolonged exposures or after acute exposure to high concentration of CO (>500ppm) (38). Even though ambient carbon monoxide concentrations have declined rapidly since 1988, and the annual mean CO concentration in 1997 was below 9 ppm, high short- term peak CO concentration can still occur in metropolitan areas where motor vehicles and other combustion engines sources can emit CO concentration sufficient to exert health effects not only in the general population but also in high risk groups such as people with cardiovascular disease.

## II. DEFINITION AND SOURCES

Carbon monoxide is a colorless, tasteless, odorless, nonirritating, flammable and poisonous gas that is emitted from incomplete combustion of carbonaceous material used as fuels for transportation. Transportation sources include emissions from all mobile sources such as cars, truck, buses, motorcycles, aircraft, locomotives, vessels, farm equipment, industrial and construction machinery, lawnmowers and snowmobiles. CO air concentrations are generally high in areas with heavy traffic congestion. Emissions from vehicles contribute about 60% of all CO emissions. Stationary combustion equipment, such as coal-, gas-, or oil-fired heating or power generating plants, generates CO as a result of inefficient combustion techniques. Industrial processes, solid waste, and other miscellaneous sources also emit it. Solid waste CO emissions result from combustion of waste in municipal and other incinerators, and from the open burning of domestic refuse. Sources of CO emissions, such as burning of forest and agricultural materials, smoldering coal refuse material and structural fires are relatively small. (39). CO emissions are substantially higher in cold weather because cars need more fuel to start at cold temperatures and some emission control devices such as oxygen sensors and catalyst converters operate less efficiently when they are cold. CO emission can also be emitted into the indoor environments. Gas cooking ranges and ovens, gas appliances, unvented gas space heaters, unvented kerosene space heaters, coal-or wood-burning stoves and cigarette combustion are the major indoor sources of CO emissions. In these situations, high levels of CO (100 ppm) can be produced. This concentration of CO can also be produced in locations where many people are smoking. (38,39)

## III. CARBON MONOXIDE EXPOSURE

The majority of the population is exposed to low ambient concentration of CO resulting in average blood level concentration of carboxyhemoglobin of less than 2%. However, high concentration of CO can occur in areas with heavy traffic, as well as the indoor environment and occupational environment (Table 1). High short-term peak CO concentrations (mean 50 ppm) occur in heavy traffic areas in many American cities, exerting adverse health effects in healthy people who spend their days in the normal city streets (bus, truck, and police drivers, vehicle inspectors and parking attendants, pedestrians and cyclists) and people with cardiovascular and respiratory diseases who are at much greater risk. Vehicle drivers are also exposed to CO from traffic, leakage of their own vehicle's exhaust, and any accumulation of cigarette smoke.

CO concentration inside vehicles is generally 25 ppm (39) and levels depend on traffic speed. When traffic is stopped, concentrations of CO inside a vehicle can reach 45 ppm. Inhalation of a level of CO of 160 ppm for several minutes (equal to ambient levels of CO in heavy automobile traffic) has been shown

to impair left ventricular function in patients with established coronary heart disease (5,11,32,33). Indoor environments including indoor parking garages or buildings with attached indoor parking areas and residences with improperly ventilated space heating equipment, frequently exceed 9 ppm and 35 ppm respectively. Groups of people who work on the streets such as street repair workers, street cleaners, drivers of city delivery trucks, cyclists, and street vendors are exposed to high concentrations of CO. Industrial processes such as steel production, coke ovens, and petroleum, can also expose workers to high levels of CO. A special group of people exposed to CO is smokers, who absorb more CO from tobacco products than from the urban atmosphere. Because cigarette smoke contains 2 to 6 percent carbon monoxide, smokers inhale concentrations as high as 400 ppm and demonstrate elevated carboxyhemoglobin levels. The average COHb level of moderate cigarette smokers is 5 percent. The range of COHb levels found in heavy smokers can be greater than 10 percent and can sometimes be as high as 15% (30).

TABLE 1. PREDICTED CARBOXYHEMOGLOBIN CONCENTRATIONS

Exposure Conditions	Predicted COHb Response	
	1 h, Light Exercise	8 h, Light Exercise
Nonsmoking adults exposed to 25 to 50 ppm CO	2 to 3 %	4 to 7%
Workplace or home with faulty combustion appliances producing CO levels of 100 ppm	4 to 5 %	12 to 13%

Source: Coburn et al., 1965

#### IV. MECHANISMS OF CARBON MONOXIDE TOXICITY

**Absorption and metabolism:** Carbon monoxide is absorbed through the lungs and diffuses across the alveolar capillary membrane. The exchange of carbon monoxide between inhaled air and the blood is controlled by both physical (mass, transport and diffusion) and physiological (alveolar ventilation and cardiac output) mechanisms. Once absorbed, CO diffuses through the plasma, passes across the red blood cell membrane and finally enters the red blood cell stroma where CO binds avidly to hemoglobin forming carboxyhemoglobin (COHb), which reduces the oxygen carrying capacity of blood and interferes with oxygen release at the tissues. The resulting impaired delivery of oxygen can interfere with cellular respiration and cause tissue hypoxia. The affinity of Hb for CO is 210-300 times greater than its affinity for oxygen, and Hb is incapable of combining with oxygen. The presence of CO also alters the dissociation of oxygen from other hemoglobin sites, producing more compromise in delivery of oxygen to the tissues. At the cellular level, carbon monoxide binds with hemoproteins such as myoglobin, cytochrome oxidase, mixed-function oxidases (cytochrome P-450), tryptophan oxygenase, and dopamine hydroxylase. The protein most likely to be inhibited at relevant levels of COHb is myoglobin, which abounds in skeletal muscle and the myocardium, causing dysfunction by impairing its oxygen carrying capacity and the transportation of oxygen from the blood to the mitochondria. CO binds also with cytochrome oxidase, the terminal enzyme in the mitochondrial electron transport chain that catalyses the

reduction of molecular oxygen to water, inhibiting cellular respiration and resulting in anaerobic metabolism and lactic acidosis.

**Distribution:** Although some CO is bound by muscle myoglobin, for the most part CO is bound to hemoglobin in the blood. CO also crosses the placenta, putting the developing fetus at risk. The factors that determine the final levels of COHb in blood are: The amount of inspired CO; the minute alveolar ventilation at rest and during exercise; blood volume, barometric pressure, diffusion capability of the lungs, and endogenous CO supply. Endogenous CO is produced from metabolism of the alpha-methane carbon atom in the protoporphyrin ring by hemoxygenase during Hb catabolism (9,30,37,38). CO production results in a basal COHb level of 0.4-0.96% in a healthy unexposed subject at rest. A pregnant woman produces nearly twice as much endogenous CO. COHb levels for an average adult under conditions of light work and an atmosphere of 35 ppm CO will be 5% (37,38,39).

**Elimination:** Carbon monoxide is not a cumulative poison because COHb is fully dissociable and, once exposure has ceased, the Hb will revert to oxyhemoglobin and CO is eliminated through the lungs. The biological half-life of CO in the blood in sedentary adults is 2-5 h and the elimination becomes slower as the concentration decreases. Only a small amount of CO is metabolized to carbon dioxide.

The principal mechanism of toxic effects at low level CO exposure is the decreased oxygen-carrying capacity of blood and subsequent interference with oxygen release in the tissues caused by the binding of CO with Hb, producing COHb. This induces tissue hypoxia in diverse organ systems, especially organs with the highest oxygen requirement such as heart and brain. The signs and symptoms of CO poisoning appear when COHb concentrations exceed 10%. Even though clinical poisoning does not occur as a result of exposure to ambient concentrations of CO, such exposures (ambient CO levels from 50 to 100 ppm commonly found in heavy freeway traffic) are enough to produce COHb concentrations of 2-6% and induce adverse health effects in sensitive, nonsmoking healthy individuals and groups of people at great risk of ambient CO exposure

There are a number of specific populations at increased risk of adverse effects from CO exposure. 1) In individuals with cardiovascular diseases, COHb levels of 2-6% may impair the delivery of oxygen to the myocardium causing hypoxia and increasing coronary blood flow demand by nearly 30%. When myocardial oxygen demands are increased, as in exercise, the hypoxic effects of CO may exceed the limited coronary reserve producing adverse health effects including earlier onset of myocardial ischemia, reduced exercise tolerance in persons with stable angina pectoris, increased number and complexity of arrhythmias, and increased hospital admissions for congestive heart failure. 2) Fetuses and young infants are more susceptible to CO exposure for several reasons: CO crosses the placenta; fetal Hb has greater affinity for CO than maternal Hb; the half-life of COHb in fetal blood is three times longer than that of maternal blood, and the fetus has high rate of oxygen consumption and lower oxygen tension in the blood than adults (39). Also, maternal smoking during pregnancy exposes the fetus to greater than normal concentrations of CO leading to a decrease in birth weight. 3) Children are at risk because they spend a great deal of time outdoors and their pulmonary ventilation is greater than in an adult. (30,39) 4) Pregnant women have increased alveolar ventilation, increasing the rate of CO uptake from inspired air. Also, a pregnant woman produces nearly twice as much endogenous CO. 5) Individuals with chronic obstructive pulmonary disease such as bronchitis and emphysema are more susceptible to CO effects, since their lungs are less efficient at oxygenating the blood. 6) Individuals with low hemoglobin levels are more sensitive to low-level CO exposure due to their reduced ability to transfer oxygen. 7) Smokers who can generate COHb levels as high as 15% because cigarette smoke contains high CO levels

(5,30,39). 8) Certain occupations are at great risk from ambient CO exposure including those who work on city streets (street repairmen, street cleaners, street vendors, delivery men, garage attendants, taxi and bus drivers). 9) Young healthy individuals who spend a lot of time on the streets doing exercise or heavy work have increased COHb levels and may experience decreased maximal exercise duration and impaired psychomotor task performance. During exercise, after the anaerobic threshold is reached, both lactate levels and the lactate/pyruvate ratio increase as an index of anaerobic metabolism. Concentrations of COHb between 2% and 6% decrease the anaerobic threshold and anaerobic metabolism appears earlier, causing early fatigue of skeletal muscle and decreased maximal effort capability. (26,27,28).

## V.HEALTH EFFECTS

The adverse health effects associated with exposure to ambient CO are related to concentration of COHb in the blood (Table 2). Health effects observed may include precipitation of cardiovascular disease, behavioral impairment; decreased exercise performance of young healthy man, reduced birth weigh, Sudden Infant Death Syndrome (SIDS), and increase daily mortality rate.

Table 2. Carboxihemoglobin levels resulting from steady-state exposure to increasing concentrations of CO in ambient air

CO in atmosphere (ppm)	COHb in blood (%)	Signs and symptoms
10	2	
70	10	No appreciable effect, except shortness of breath on vigorous exertion; possible tightness across the forehead; dilation of cutaneous blood vessels.
120	20	Shortness of breath on moderate exertion; occasional headache with throbbing in temples
220	30	Decide headache; irritable; easily fatigued; judgment disturbed; possible dizziness; dimness of vision.
350 - 520	40 – 50	Headache, confusion; collapse; fainting on exertion
800 - 1220	60 – 70	Unconsciousness; intermittent convulsion; respiratory failure, death if exposure is long continued
1950	80	Rapidly fatal

Source: Winter and Miller (1976), Ellenhorn and Barceloux, 1998 (Ref. 39)

## EFFECTS IN PEOPLE WITH CARDIOVASCULAR DISEASES

In individuals with cardiovascular disease, exposure to low concentration of CO from heavy freeway traffic, or breathing CO levels from 50ppm to 100 ppm can have a direct adverse effect on the heart (10). In these individuals, exposure to 50 ppm CO for 2-4 hrs (producing COHb blood concentration of 2% - 5%) can decrease exercise tolerance, cause the appearance of typical anginal pain after exercise, increase the frequency of arrhythmias (23), decrease the time to exercise-induced angina and ST segment depression among subjects with diagnosed coronary artery disease, and increase hospital admissions for congestive heart failure (1,2,4,5,79,13,14).

Allred et al. (2) observed a relationship between doses of CO producing 2-4% of COHb and effects on cardiac function during exercise in subjects with coronary artery disease. There was a decrease of 5.1% ( $P=0.01$ ) in the time to development of ischemic ST- segment changes and a decrease of 4.2% ( $p=0.027$ ) in the time to onset of angina at mean COHb levels of 2.0% as a result of exposure to 117 ppm CO, a concentration commonly found in heavy traffic. In a study conducted by Aronow and Ibell (5) exposure to 50 ppm CO for 2 h produced COHb levels of 2.7% and reduced significantly the time to onset of exercise-induced angina pectoris from 3.74 min (observed after subjects breathed clean air) to 3.13 min (observed after CO exposure). In another study, Anderson et al. (4) reported decreased exercise tolerance and worsening of myocardial ischemia in persons with stable angina pectoris following exposure to 50 ppm CO for 4 h sufficient to cause a mean increase in COHb of 2.9%. In 1988 Adams et al. (1) conducted a study focused on the cardiovascular effects of subjects exposed to 100 or 200 ppm CO reaching COHb levels of 6%. Kleinman et al. (1989) demonstrated that subjects with stable angina pectoris exposed to concentrations of CO typically found in heavy traffic (100 ppm), reduced by 6% ( $p=0.046$ ) the time to onset of exercise-induced anginal pain, at an average COHb level of 2.9% (9). In a study of seven US cities, Morris et al. (13) found an association between ambient CO levels and hospital admission for congestive heart failure among elderly people. The relative risk of hospital admission associated with exposure to 10-ppm of CO ranged from 1.10 in New York to 1.37 in Los Angeles. In San Paolo, after control of particulate matter, a similar association was found with a relative risk of 1.04 for 10 ppm CO. Schwartz (1997) investigated the association between air pollution and hospital admission for cardiovascular disease in Tucson, AZ. Both PM<sub>10</sub> and CO were associated with increased risk of cardiovascular hospital admission. Admission increased 2.75% (95% CL = 0.52%, 5.04%) and 2.79% (95% CL = 0.51%, 5.41%) for PM<sub>10</sub> and CO respectively. This association was independent and additive. Linn et. al (41) also investigated the association between air pollution and daily hospital admissions in Los Angeles. CO and NO<sub>2</sub> showed the strongest relationship ( $p < 0.5$ ) with cardiovascular hospital admissions in the winter when the range of CO concentrations was 1.1 to 2.2 ppm and the increase in cardiovascular admissions was 4.0%. A study conducted by Morris et al. (1998) showed that the effect of CO on hospital admissions for heart failure may be temperature dependent (7,12). This synergy can be attributed to the effect of exposure to cold air, which can increase heart rate, systolic and diastolic blood pressure, and cardiac output. (14,27). Those adverse effects can be increased among cigarette smokers. The risk increases with the number of cigarettes smoked. Levels of COHb at 2%-5% due to smoking or environmental exposure may aggravate the course of an acute myocardial infarction in patients with coronary artery disease (10,26).

## BEHAVIORAL IMPAIRMENT

Most of the studies evaluating adverse health effect of carbon monoxide on the central nervous system have focused on high levels of poisoning (COHb levels of >10%) resulting in symptoms that range from common flu and cold symptoms (shortness of breath on mild exertion, mild headaches, and nausea.) to

unconsciousness and death.

There is minimal information available on the relationship between exposures to low or ambient levels of carbon monoxide and effects on the central nervous system. A few studies, which date from the 70s and 80s, report an association between exposure to 100 ppm CO and behavioral changes such as decrements in visual, auditory and cognitive function at COHb levels of 5% (19). Beard and Wertheim (1967) demonstrated that exposures to 50 ppm CO for 90 minutes caused a progressive deterioration in subjects' abilities to estimate the passage of time. Horvath et al. (1971) reported that people with COHb levels between 2-3% are liable to perform routine task in an inefficient manner and at 6.6% (exposure to 111 ppm CO) lost vigilance. Chronic occult CO poisoning is commonly misdiagnosed as an influenza-like viral illness. Symptoms such as headache; dizziness, weakness, nausea, vomiting, and drowsiness are frequent with COHb blood levels at 2-5% in both adults and children. Baker et al. (25) correlated flu-like symptoms with COHb levels between 2% and 5% in children. It has been hypothesized that increased metabolic demands on oxygen delivery make infants more susceptible than adults to CO poisoning (25,38,39).

### DECREASED EXERCISE PERFORMANCE OF YOUNG HEALTHY MAN

Exposures to CO sufficient to reach blood COHb concentration of 2-6% decrease exercise performance in young nonsmoking healthy individuals. Horvath et al. (1975) reported a reduction of 5 and 7% in work time to exhaustion at 3.3 and 4.3% COHb levels respectively. A 38% reduction in work time had been previously reported at 7% COHb. Adir et al. (1999) found a significant decrease in exercise duration and maximal effort capability at blood COHb concentrations of 4% - 6% in young healthy men.

### REDUCED BIRTH WEIGH

To date, few studies have investigated the effects on ambient CO levels and low birth weigh (LBW). The majority of the studies have been focused on the relationship between LBW and smoking during pregnancy. Recently, Ritz and Yu (1999) evaluated the effects of CO exposures during the last trimester of pregnancy on the frequency of LBW among neonates born 1989-1999 to women living in the Los Angeles, California, area. They found that exposure to more than 5.5 ppm CO during the last trimester of pregnancy was associated with a 22% increase in LBW.

### SUDDENTH INFANT DEATH SYNDROME

Sudden Infant Death Syndrome (SIDS) has been linked to exposure to ambient CO. Hoppenbrouwers et al. (1981) reported a statistical association between the daily incidence of SIDS and levels of CO in Los Angeles County. Fetal hypoxia caused by exposure to CO could be a factor contributing to SIDS deaths.

### INCREASED DAILY MORTALITY

Some studies have demonstrated an association between daily mortality and ambient concentrations of CO. Hexter and Goldsmith (1971) reported an association between daily death rate and exposure to ambient CO in Los Angeles County. They found that when CO concentration was 20.2 ppm (the highest daily concentration recorded during 4 years), it contributed 11 out of 159 total deaths. Studies conducted in Los Angeles (Kinney et al., 1995) and San Paulo (Saldivia et al., 1995) also suggested a relationship between daily death rates and CO concentrations. Cohen et al., (1969) studied case fatality rates for patients admitted with myocardial infarction (MI) in Los Angeles. They demonstrated that high CO pollution areas (7-12 ppm) had greater admission case fatality rate than low CO pollution areas. The

mean case fatality rate per 100 admissions was 27.3 and 19.1 for high and low pollution areas respectively (8). This study did not control for smoking, diet, occupational status and physical activity. However, this effect was seen during periods of relatively increased CO pollution suggesting that an association between MI case fatality rate and ambient CO levels could exist. Mar et. al (2000) evaluated the association between air pollution and Mortality in Phoenix, 1995-1997. Cardiovascular mortality was strongly associated with CO and NO<sub>2</sub> (p< 0.5).

## VI. NATIONAL AMBIENT AIR QUALITY STANDARD

In 1971, the U.S. Environmental Protection Agency (EPA) promulgated the National Ambient Air Quality Standard (NAAQS) for CO of 9 ppm for 8 h and 35 ppm for 1 h to protect susceptible population groups from adverse effects resulting from CO exposures in the outdoor environment. Originally, the CO standards were based on human neurobehavioral studies by Beard and Wertheim, who reported impairment in the ability to discriminate time intervals at COHb levels as low as 1.8%. Subsequent studies by Aronow and Isbell and by Anderson that showed a decrease in the time to the onset of angina during exercise in subjects with coronary artery disease were used to justify the NAAQS for CO. According to estimates by the EPA, an adult involved in moderate activity would have a COHb level of approximately 2.0% after 1-h exposure to CO 35 ppm and concentrations in the range of 1.4% to 1.9% after 8-hr exposure to CO 9 ppm (40).

## VII. CONCLUSIONS

There are few studies evaluating the effects of exposure to ambient CO concentrations. Chamber studies of patients with coronary artery disease have shown that exposure to CO raising COHb concentrations to about 2% results in reduced exercise tolerance due to increased chest pain and reduced time to ST segment change. This same CO concentration in healthy men results in decreased exercise performance. Other health effects of ambient CO exposure include increased hospital admission for congestive heart failure, behavioral impairment, reduced birth weight, an increase in SIDS, and an increased daily mortality rate. Eight hour exposure to CO concentrations of 10 ppm results in a COHb of 2%. On this basis, the 8-hr average CO NAAQS of 10-ppm was established. However, in heavy traffic areas the concentration of CO may exceed the ambient standard reaching levels up to 50 ppm. At these exposure concentrations, the resulting COHb may exceed 2%. This COHb concentration may exert adverse CO health effects, particularly in sensitive populations.

## VIII. REFERENCES

1. Adams KF, Koch G, Chatterjee B, Goldstein GM, O'Neil JJ, Bromberg PA, Sheps DS, Mc Allister S, Price CJ, & Bissette J (1988) Acute Elevation of Blood Carboxihemoglobin to 6% Impairs Exercise Performance and Aggravates Symptoms in Patients with Ischemic Heart Disease. *J Am Coll Cardiol*, 12: 900-909.
2. Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, Hayes D, Pagano M, Selvester RH, Walden SM & Warren J (1989a) Short-term Effects of Carbon Monoxide Exposure on the Exercise Performance of subjects with Coronary Artery Disease. *N Engl J Med*, 321: 1426-1432.
3. Allred EN, Bleecker ER, Chaitman BR, Dahms TE, Gottlieb SO, Hackney JD, Hayes D, Pagano M, Selvester RH, Walden SM & Warren J (1991a) Effects of Carbon Monoxide on Myocardial Ischemia,

Environ Health Perspect, 91: 89-132.

4. Anderson EW, Andelman RJ, Strauch JM, Fortuin NJ, & Knelson JH (1973) Effect of Low-level Carbon Monoxide Exposure on onset and duration of Angina Pectoris: A Study in a ten patients with Ischemic Heart Disease. *Ann Intern Med*, 79: 46-50.
5. Aronow WS, Harris CN, Isbel MW, Rojaw SN, & Imperato B (1972) Effect of freeway travel on angina pectoris. *Ann Intern Med*, 79: 392-395 Akland GC, Hartwell TD, Johnson TR, & Whitmore RW (1985) Measuring Human Exposure to Carbon Monoxide in Washington, D.C., and Denver, Colorado, during the winter of 1982-1983.
6. Ayres SM, Evans R, Lich D, Griesbach J, Reimold F, Ferrand E, & Criscitiello A (1973) Health Effects of Exposure to High Concentrations of Automotive Emissions. *Arch Environ Health* 27: 168-178.
7. Burnett RT, Dales RE, Brook JR, Raizenne ME & Krewski D (1997) Association between Carbon Monoxide Levels and Hospitalizations for Congestive Heart Failure in the Elderly in 10 Canadian cities. *Epidemiology*, 8: 162-167.
8. Cohen SI, Deane M & Goldsmith JR (1969) Carbon Monoxide and Survival from Myocardial Infarction. *Arch Environm health*, 19: 510-517.
9. Kleinman MT, Davidson DM, Vandagriff RB, Caiozzo VJ & Whittenberger JL (1989) Effects of Short-term Exposure to Carbon Monoxide in Subjects with Coronary Artery Disease. *Arch Environm Health*, 44: 361-369.
10. Kuller LH, Radfor EP, Swift D, Perper JA & Fisher R (1975) Carbon Monoxide and Heart Attacks. *Arch Environm Health*, 30: 477-482.
11. Kurt TL, Mogielnicki RP & Chandler JE (1978) Association of the frequency of Acute Cardiorespiratory Complaints with Ambient Levels of Carbon Monoxide. *Chest*, 74: 10-14.
12. Morris RD & Naumova EN (1998) Carbon Monoxide and Hospital Admissions for Congestive Heart Failure: Evidence an Increased Effect at Low Temperature. *Environm Health Perspect* 106: 649-653.
13. Morris RD, Naumova EN & Munasinghe RL (1995) Ambient Air Pollution and Hospitalization for Congestive Heart Failure among Elderly People in Seven Large US Cities. *Am J Public Health*, 85: 1361-1365.
14. Schwartz J. (1997) Air Pollution and Hospital Admission for Cardiovascular Disease in Tucson. *Epidemiology*, 8: 371-377.
15. Walden M & Gottlieb SO (1990) Urban Angina, Urban Arrhythmias: Carbon Monoxide and the Heart. *Ann Intern Med*, 113: 337-339
16. Kinney P & Ozkaynak (1991) Association of Daily Mortality and Air Pollution in Los Angeles County. *Environm Resear*, 54: 99-120.
17. Hoppenbrouwers T, Calub M, Arakawa K & Hodgman J (1981) Seasonal Relationship of Sudden Infant Death Syndrome and Environmental Pollutants. *A. J Epidemiol*, 113: 623-635.
18. Ritz B. and Yu F (1999) The Effect of Ambient Carbon Monoxide on Low Birth Weigh among

- Children Born in Southern California between 1989 and 1993. *Environm Health Perspect*, 107: 17-24.
19. Beard RR & Wertheim GA (1967) Behavioral Impairment Associated with Small Doses of Carbon Monoxide. *A.J Pub Health*, 57: 2012-2022.
20. Heckerling PS, Leikin JB, Terzian CG & Maturen A (1990) Occult Carbon Monoxide Poisoning in Patients with Neurologic Illness. *Cl Toxicology* 28(1): 29-44. Von Burg R (1999) Toxicology update. *J. Appl. Toxicol.* 19: 379-386.
21. Horvath SM, Dahams TE & O'hanlon JF Carbon Monoxide and Human Vigilance (1971) *Arch Environ Health*, 23: 343-347.
22. Stewart RD, Peterson JE, Baretta E, Bachand RT, Hoski MJ, & Herrmann AA (1970). Experimental Human Exposure to Carbon Monoxide. *Arch Environ Health*, 21: 154-164
23. Marshall MD, Kales SN, Christiani DC & Goldman RH (1995) Are Reference Intervals for Carboxyhemoglobin Appropriate? A Survey of Boston Area Laboratories. *Clin. Chem.* 41: 1434-1438
24. Varon J, Marik PE, Fromm RE & Gueler A (1999) Carbon Monoxide Poisoning: A Review for Clinicians. *J. Emerg Med*, 17: 87-93.
25. Baker MD, Henreting FM & Ludwig S (1988) Carboxyhemoglobin Levels in Children with Nonspecific Flu-like Symptoms. *Clinic and Laborat Observat*, 501-504.
26. Adir Y, Merdler A, Ben Haim S, Front A, Harduf R & Bitterman H (1999) Effects of Exposure to Low Concentrations of Carbon Monoxide on Exercise Performance and Myocardial Perfusion in Young Healthy Men. *Occup Environm Med*, 56: 535-538.
27. Peters A, Perz S, Doring A, Stieber J, Koenig W, & Wichmann HE (1999) Increases in Heart Rate during an Air Pollution Episode, *Am J Epidem* 150: 1094-1098.
28. Peterson JE & Stewart RD (1970) Absorption and Elimination of Carbon Monoxide by Inactive Young Men. *Arch Environ Health*, 21: 165-171.
29. Horvath SM, Raven PB, Dahms TE & Gray DJ (1975) Maximal Aerobic Capacity at different Levels of Carboxihemoglobin. *J Appl Physiology*, 38: 300-303.
30. Von Burg R (1999) Toxicology Update. *J Applied Toxicol*, 19: 379-386.
31. Akland GG, Hartwell TD, Johnson TR & Whitmore RW (1985) Measuring Human Exposure to Carbon Monoxide in Washington, D.C., and Denver Colorado, during the Winter of 1982-1983. *Environ. Sci. Technol*, 19: 911-918
32. Atimay AT, Emri S, Bagci T & Demir A (2000). Urban CO Exposure and Its Health Effects on Traffic Policemen in Ankara. *Environ. Research*, 82: 222-230.
33. Godin G, Wright G & Shephard RJ (1972). Urban Exposure to Carbon Monoxide. *Arch Environ Health*, 25: 305-313.
34. McGuffie C, Wyatt JP, Kerr GW & Hislop WS (2000) Mass Carbon Monoxide Poisoning. *J Accid Emerg Med* 17: 38-39.

35. Wright GR, Jewczyk S, Onrot J, Tomlison P & Shephard RJ (1975) Carbon Monoxide in the Urban Atmosphere. *Arch Environ Health* 30: 123-129.
36. Hexter A & Goldsmith JR (1971) Carbon Monoxide: Association of Community Air Pollution with Mortality. *Science*, 172: 265-266.
37. Smith RP (1986) Toxic Responses of the Blood. In: Klaassen DD, Amadur MO and Doull J (eds) *Casarett and Doull's Toxicology*, 3<sup>rd</sup> edn. New York: Mc Millan Publishing Company, pp. 223-240.
38. Maynard RL & Waller R (1999) Carbon Monoxide. In: Holgate ST, Samet JM, Koren HS & Maynard RL (eds) *Air Pollution and Health* Academic Press: Harcourt Brace & Company, Publishers, pp. 749-796.
39. World Health Organization (1999) Carbon Monoxide. *Environmental Health Criteria* 213. Geneva: World Health Organization.
40. [www.epa.gov/ttn/oarpg/t1/memoranda/rprtguid.pdf](http://www.epa.gov/ttn/oarpg/t1/memoranda/rprtguid.pdf).
41. Linn WS, Szlachcic Y, Gong H, Kinney PL, and Berhane T (2000) Air Pollution and Daily Hospital Admissions in Metropolitan Los Angeles. *Environm. Health Perspect* 105: 427-434.
42. Mar TF, Norris GA, Koenig JQ, and Larson TV (2000) Association between Air Pollution and Mortality in Phoenix, 1995-1997. *Environm Health Perspect*. 108: 347-353.