ADVERSE HEALTH EFFECTS OF EXPOSURE TO AMBIENT CARBON MONOXIDE

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I. INTRODUCTION

From the late 1960s through the early 1980s, carbon monoxide (CO) was a major air pollutant of concern. The primary emission source, then and now, was from motor vehicles in urban areas. Inside homes, CO is emitted from natural gas fueled hot water heaters and home heating systems. CO from these sources was responsible for more poisoning deaths in the Unites 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 (1). The death rate from unintentional CO poisoning declined in the 1980s, but nonfatal CO poisoning is even more common causing approximately 10,000 affected individuals to seek medical attention or miss at least 1 day of normal activity annually (2). The adverse health effects associated with CO vary with its concentration and duration of exposure (1,3). CO concentrations of 10 to 100 ppm in ambient air and inside motor vehicles can exert adverse health effects on

the general population (1,2,4,5,6). 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 the heart and the brain. CO also binds to cytochrome oxidase, which could reduce the cells' ability to utilize oxygen (1,2,3,7,8).

Clinical symptoms range from subtle cardiovascular, respiratory, and neurobehavioral effects at low concentrations (10 ppm) to unconsciousness and death after prolonged exposures or after acute exposure to high concentration of CO (>500ppm). Acute clinical poisoning does not occur as a result of exposure to ambient concentrations of CO. However, 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 concentrations (mean 50 ppm) occur in metropolitan areas. In these areas motor vehicles and other combustion engines sources can emit CO concentrations sufficient to cause health effects in the general population and in high risk group (i.e., young children, the elderly, those with heart or lung problems) (1-7).

Despite a successful national program for regulating outdoor CO levels, CO exposure is still detrimental to human health not only in individuals with cardiovascular and respiratory diseases, but also in healthy individuals especially those who work outside in or near traffic.

II. DEFINITION AND SOURCES

Carbon monoxide is a colorless, tasteless, odorless, nonirritating, flammable and poisonous gas emitted from incomplete combustion of carbonaceous material used as fuels for transportation. Transportation sources include emissions from all mobile sources such as cars, trucks, 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, can generate 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. (1,2,7,8).

CO emissions are substantially greater in cold weather because cars need more fuel to start at cold temperatures and some emission control devices such as oxygen sensors and catalytic converters operate less efficiently when they are cold (1,2,8).

III. MECHANISMS OF CARBON MONOXIDE TOXICITY

Absorption and metabolism in tissue: 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 to hemoglobin forming carboxyhemoglobin (COHb). Such binding 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, and compromises the 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. Lower myoglobin levels cause dysfunction by impairing its oxygen carrying capacity and the transportation of oxygen from the blood to the mitochondria. CO also binds with cytochrome oxidase, the terminal enzyme in the mitochondrial electron transport chain that catalyzes the reduction of molecular oxygen to water, thus inhibiting cellular respiration and resulting in anaerobic metabolism and lactic acidosis (1,2,3,8,9).

Distribution through the body: 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 determining 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. CO production results in a basal COHb level of 0.4-0.96% in a healthy unexposed person 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% (1,2,3,8,9).

Elimination from the body: 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 of sedentary adults is 2-5 hours (h) and the elimination becomes slower as the concentration decreases. Only a small amount of CO is metabolized to carbon dioxide (1,2,3,8,9).

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% (1,2,3,8,9).

IV. 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% (Table 1). However, in many American cities, high short-term peak CO concentrations (mean 50 ppm) occur in heavy traffic areas. Exposure to these ambient CO levels may affect groups of people who work on the streets such as bus and truck drivers, police officers, vehicle inspectors, street repair workers, street cleaners, street vendors, parking attendants, pedestrians, and cyclists. Vehicle drivers are also exposed to CO from traffic and leakage of their own vehicle's exhaust (1,2,6,7,8)

CO concentration inside vehicles is generally 25 ppm (8) and CO 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 (1,2,4,5).

TABLE 1. PREDICTED CARBOXYHEMOGLOBIN CONCENTRATIONS

	Predicted COHb Response	
Exposure Conditions	1 hour Light Exercise	8 hours, 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 (from reference 1)

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 (1,2,8,10).

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 (8). Also, maternal smoking during pregnancy exposes the fetus to greater than normal concentrations of CO leading to a decrease in birth weight (1,2,7,8,10).

3) Children are at risk because they spend a great deal of time outdoors and their pulmonary ventilation is greater than in an adult. (1,2,7,8)

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 (1,2,7,8).

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 (1,2,7,8).

6) Individuals with low hemoglobin levels are more sensitive to low-level CO exposure due to their reduced ability to transfer oxygen (1,2,7,8).

7) Smokers can generate COHb levels as high as 15% because cigarette smoke contains high CO levels (1,2,7,8).

8) Certain occupation groups are at great risk from ambient CO exposure including those who work on city streets (street repairmen, street cleaners, street vendors, deliverymen, and garage attendants, taxi and bus drivers). Individuals who work in industrial processes are also at great risk (1,2,7,8,11).

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. (1,2,7,8,10,12).

V. HEALTH EFFECTS

The adverse health effects associated with exposure to ambient and indoor concentrations of CO are related to concentration of COHb in the blood (Table 2). Health effects observed may include early onset of cardiovascular disease, behavioral impairment; decreased exercise performance of young healthy men, 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	Asymptomatic
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. 8)

Cardiovascular diseases: Individuals with cardiovascular disease are more susceptible to exposure to outdoor and indoor levels of CO. Exposure to concentrations of CO from heavy freeway traffic, or breathing CO levels from 50 ppm to 100 ppm can have direct adverse effect on the heart (4,5,13). 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. Such exposures also 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 (4,14,15,16,17,18,19,20,21).

Allred et al. (14) 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 (manifested by ST- segment changes in the EKG) 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 (4) 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. (15) 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. (16) 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. (17) demonstrated that at an average COHb level of 2.9%, the time to onset of exercise-induced anginal pain was reduced by 6% (p=0.046) in subjects with stable angina pectoris who were exposed to concentration of CO typically found in heavy traffic (100 ppm) (9). In a study of seven US cities, Morris et al. (18) 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 to10-ppm of CO ranged from 1.10 in New York to 1.37 in Los Angeles. Linn et. al (19) investigated the association between air pollution and daily hospital admissions in Los Angeles. CO and NO_2 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. (20) showed the effect of CO on hospital admissions for heart failure may be temperature dependent. This synergy can be attributed cold air exposure which may increase heart rate, systolic and diastolic blood pressure, and cardiac output. (21,22,23). Smoking can further increase these adverse effects. 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 (12,13).

Behavioral impairment: Most of the studies evaluating adverse health effects of carbon monoxide on the central nervous system examine high-level poisoning (COHb levels of >10%). Such poisoning results in symptoms ranging from common flu and cold symptoms (shortness of breath on mild exertion, mild headaches, and nausea) to unconsciousness and death (1,2,8).

There is minimal information available on the relationship between exposures to low ambient levels of carbon monoxide and effects on the central nervous system. A few studies, dating from the 1970s 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%. Beard and Wertheim (24) demonstrate 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. (25) report people with COHb levels between 2-3% are liable to perform routine task in an inefficient manner. At 6.6% (exposure to 111 ppm CO) people loose 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. (26) correlated flu-like symptoms with COHb levels between 2% and 5% in children. Increased metabolic demands on oxygen delivery may make infants more susceptible than adults to CO poisoning (1,8,26).

Decreased exercise performance of young healthy individuals: Exposures to CO sufficient to reach blood COHb concentration of 2-6% decrease exercise performance in young nonsmoking healthy individuals. Horvath et al. (27) 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. (12) found a significant decrease in exercise duration and maximal effort capability at blood COHb concentrations of 4% - 6% in young healthy men.

Effects on fetuses and neonates: CO crosses the placenta by simple diffusion and fetus' COHb depends on maternal COHb concentrations. However, fetal HB has a higher affinity for CO than adult HB, and fetal intoxication can not be assessed by maternal COHb (1,7,8). Maternal COHB levels in non-smokers range between 0.7% and 1.0% whereas fetal blood COHb levels range between 0.7% and 2.5%. Maternal smoking during pregnancy exposes the fetus to grater than normal concentration of CO and COHb of 2.0-8.3% and COHb of 2.4-7.6% can be found in maternal and fetal blood respectively. 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 (1,7,10). Recently, Ritz and Yu (28) 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 exposure to more than 5.5 ppm CO during the last trimester of pregnancy, and it was associated with a 22% increase in LBW.

Sudden Infant Death Syndrome (SIDS) has been also linked to exposure to ambient CO. Hoppenbrouwers et al. (10) 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 demonstrate an association between daily mortality and outdoor and indoor concentrations of CO. Hexter and Goldsmith (29) report an association between daily death rate and exposure to ambient CO in Los Angeles County. They postulate a CO concentration of 20.2 ppm (the highest daily concentration recorded during 4 years) contributed 11 out of 159 total deaths. Studies conducted in Los Angeles (30) and San Paulo (31) also suggest a relationship between daily death rates and CO concentrations. Cohen et al., (32) 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. 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 (33) evaluated the association between air pollution and Mortality in Phoenix, 1995-1997. Cardiovascular mortality was strongly associated with CO and NO_2 ($p< 0.5$).

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 hours and 35 ppm for 1 hour 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 (24) 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-hour exposure to CO 35 ppm and concentrations in the range of 1.4% to 1.9% after 8-hour exposure to CO 9 ppm (2).

VII. CONCLUSIONS

CO exposure continues to be a matter of great concern in the United States due to its association with high incidence of morbidity and mortality. 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 individuals results in decreased exercise performance. Other health effects of ambient CO exposure include increased hospital admission for congestive heart failure, behavioral impairment, reduced birth weigh, an increase in SIDS, and an increased daily mortality rate. Eight-hour exposure to CO concentrations of 10 ppm in outdoor environments results in a COHb of 2%. On this basis, the 8 hour 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, in both healthy and at risk individuals.

VIII. REFERENCES

1. World Health Organization (1999) Carbon Monoxide. Environmental Health Criteria 213. Geneva: World Health Organization.
2. www.epa.gov/ttn/oarpg/t1/memoranda/rprtguid.pdf.
3. Varon J, Marik PE, Fromm RE, Gueler A. (1999) Carbon Monoxide Poisoning: A Review for Clinicians. The Journal of Emergency Med, 17: 87-93.
4. Aronow WS, Harris CN, Isbel MW, Rojaw SN, & Imparato B (1972) Effect of freeway travel on angina pectoris. Ann Intern Med, 79: 392-395.
5. 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.
6. Godin G, Wright G & Shephard RJ (1972) Urban Exposure to Carbon Monoxide. Arch Environ Health, 25: 305-313.
7. Von Burg R (1999) Toxicology Update. J Applied Toxicol, 19: 379-386.

8. Maynard RL & Waller R (1999) Carbon Monoxide. In: Holgate ST, Samet JM, Koren HS & Maynard RL (eds) Air Pollution and Health Academis Press: Harcourt Brace & Company, Publishers, pp. 749-796.
9. Smith RP (1986) Toxic Responses of the Blood. In: Klaassen DD, Amadur MO and Doull J (eds) Casarett and Doulss's Toxicology, 3rd edn. New York: Mc Millan Publishing Company, pp. 223-240.
10. 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.
11. 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.
12. 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.
13. Kuller LH, Radfor EP, Swift D, Perper JA & Fisher R (1975) Carbon Monoxide and Heart Attacks. Arch Environm Health, 30: 477-482.
14. 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.
15. 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.
16. 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 Coo Cardiol, 12: 900-909.

17. 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.
18. 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.
19. 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.
20. 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.
21. Burnett RT, Dales RE, Brook JR, Raizenne ME & Krewki D (1997) Association between Carbon Monoxide Levels and Hospitalizations for Congestive Heart Failure in the Elderly in 10 Canadian cities. Epidemiology, 8: 162-167.
22. Schwartz J. (1997) Air Pollution and Hospital Admission for Cardiovascular Disease in Tucson. Epidemiology, 8: 371-377.
23. Peters A, Perz S, Doring A, Stieber J, Koening W, & Wichmann HE (1999) Increases in Heart Rate during an Air Pollution Episode, Am J Epidem 150: 1094-1098.
24. Beard RR & Wertheim GA (1967) Behavioral Impairment Associated with Small Doses of Carbon Monoxide. A.J Pub Health, 57: 2012-2022.
25. Horvath SM, Raven PB, Dahms TE & Gray DJ (1975) Maximal Aerobic Capacity at different Levels of Carboxihemoglobin. J Appl Physiology, 38: 300-303.
26. Baker MD, Henreting FM & Ludwig S (1988) Carboxyhemoglobin Levels in Children with Nonspecific Flu-like Symptoms. Clinic and Laborat Observat, 501-504.

27. Horvath SM, Dahams TE & O'hanlon JF Carbon Monoxide and Human Vigilance (1971) Arch Environ Health, 23: 343-347.
28. 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.
29. Hexter A & Goldsmith JR (1971) Carbon Monoxide: Association of Community Air Pollution with Moetality. Science, 172: 265-266.
30. Kinney P & Ozkaynak (1991) Association of Daily Mortality and Air Pollution in Los Angeles County. Environm Resear, 54: 99-120.
31. Saldivia PH, Pope CA, Schwartz J, Dockery DW, Lichtenfels AJ, Salge JM, Barone I, Bohm GM. (1995) Air Pollution and Mortality in Elderly People: A Times-Series Study in Sao Paulo, Brazil.
32. Cohen SI, Deane M & Goldsmith JR (1969) Carbon Monoxide and Survival from Myocardial Infarction. Arch Environm health, 19: 510-517.
33. Mar TF, Norris GA, Koening JQ, and Larson TV (2000) Association between Air Pollution and Mortality in Phoenix, 1995-1997. Environm Health Perspect. 108: 347-353.