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OCCUPATIONAL EXPOSURE T O

CARBON MONOXIDE

U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE Health Services and Mental Health Administration National Institute for Occupational Safety and Health

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health of workers exposed to an ever increasing number of potential hazards at their workplace. To provide relevant data from which valid criteria and effective standards can be deduced, the National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices.

It is intended to present successive reports as research and epidemiologic studies are completed and sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on carbon monoxide by members of my staff and the valuable constructive comments by the Review Consultants on Carbon Monoxide to NIOSH, the ad-hoc committee of the American Industrial Hygiene Association, and the ad-hoc committee of the American Medical Association. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on carbon monoxide. A list of the Review Consultants appears on pages iv and v. The contributions of others are also acknowledged:

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I. RECOMMENDATIONS FOR A CARBON MONOXIDE STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to carbon monoxide (CO) at the workplace be controlled by requiring compliance with the standard set forth in the following eight sections.

Control of employee exposure to CO at his place of employment at the limits stated will (1) prevent acute CO poisoning, (2) protect the employee from deleterious myocardial alterations associated with levels of carboxyhemoglobin (COHb) in excess of 5 percent and (3) provide the employee protection from adverse behavioral manifestations resulting from exposure to low levels of CO.

The recommended standard is measurable by techniques that are valid, reproducible and currently available to industry and governmental agencies and is attainable with existing technology. The recommended standard is designed to protect the safety and health of workers who are performing a normal 8-hour per day, 40-hour per week work assignment. It is not designed for the population-at-large and any extrapolation beyond the general worker population is unwarranted. Because of the well-defined relationship between smoking and the concomitant exposure to CO in inhaled smoke the recommended standard may not provide the same degree of protection to those workers who smoke as it will to nonsmokers. Likewise, under conditions of reduced ambient oxygen concentration, such as would be encountered by workers at very high altitudes (e.g., 5,000 - 8,000 feet above sea level), the permissible exposure stated in the recommended standard should be appropriately lowered to compensate for loss in the oxygen-carrying capacity of the blood. In

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addition, workers with physical impairments that interfere with normal oxygen delivery to the tissues (e.g., emphysema, anemia, coronary heart disease) will not be provided the same degree of protection as the healthy worker population. The criteria and the standard recommended in this document will be reviewed and revised as necessary.

Section 1 - Work Environment

(a) Concentration

(1) Occupational exposure to carbon monoxide shall be controlled so that no worker shall be exposed at a concentration greater than 35 ppm determined as a time-weighted average (TWA) exposure for an 8-hour workday, as measured with a portable, direct reading, hopcalite-type carbon monoxide meter calibrated against known concentrations of CO, or with gas detector tube units certified under Title 42 of the Code of Federal Regulations, Part 84.

(2) No level of carbon monoxide to which workers are exposed shall exceed a ceiling concentration of 200 ppm.

(b) Calibration, Sampling and Analysis

Procedures for calibration of equipment, sampling and analysis of CO samples shall be followed as provided in Appendix I.

Section 2 - Medical Recommendations

Because employees with overt cardiovascular disease may not be protected by an occupational exposure to 35 ppm of CO, a medical program should be instituted consisting of preplacement and periodic examinations with special attention to the cardiovascular system and to medical conditions which could be exacerbated by exposure to CO. Such a medical program could also provide the opportunity for conducting antismoking programs for high-risk employees.

Section 3 - Labeling

(a) Cylinders and other containers of CO shall carry a label stating:

CARBON MONOXIDE (CO)

DANGER COLORLESS ODORLESS GAS May be fatal if inhaled Do not breathe gas High concentrations in air may be explosive

First Aid: Remove victim immediately to an uncontaminated atmosphere. Call a physician immediately. If breathing has stopped, give artificial respiration. Administer oxygen.

(b) Areas where significant exposure to carbon monoxide is likely to occur shall be posted with a sign stating:

CARBON MONOXIDE (CO)

DANGER High concentrations may be fatal Provide adequate ventilation High concentrations in air may be explosive

Seek immediate medical attention if you experience any of the below symptoms: 1 - Severe Headache 2 - Dizziness 3 - Nausea and vomiting

Gas masks are located: (Specific location to be filled in by employer)

For purposes of this section the term "significant exposure to carbon monoxide" refers to eight-hour TWA exposures exceeding 25 ppm but excludes such exposure as may be self-administered through smoking.

Section 4 - Respiratory Protection

In the event of an emergency or when a variance has been allowed and the use of respiratory protective equipment authorized by the Secretary of Labor, the employer shall provide and insure that the employee wears, as appropriate, one of the following respiratory protective devices approved by NIOSH or the Bureau of Mines as provided in Part 11 of Title 30, Code of Federal Regulations:

(a) Type N Gas Mask (Emergency Situation):

For entry into or escape from an environment containing not over 20,000 ppm, which is not deficient in oxygen, for a total exposure period of not more than 30 minutes.

- (b) Demand Type Self-Contained Breathing Apparatus (Variance Situation): For work in atmospheres containing not over 5,000 ppm carbon monoxide.
 - (c) Pressure Demand Type Self-Contained Breathing Apparatus (Variance Situation):

For work in atmospheres containing up to 100 percent CO.

(d) Fire Fighting Applications:

A demand or pressure demand type self-contained breathing apparatus. All respiratory protective equipment shall be selected so as to insure satisfactory face piece fit. Each user shall be instructed and tested in the proper use of respiratory protective devices and each such device shall be used and maintained in accordance with the provisions of the American National Standard Practices for Respiratory Protection ANSI Z-88.2, 1969.

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Section 5 - Emergency Procedures

(a) Appropriate measures shall be implemented to assure that the release into the work environment of carbon monoxide in excess of the ceiling value of 200 ppm is prevented.

(b) Massive Release of Carbon Monoxide

Areas in which large amounts of CO are stored, used or emitted, or areas within the workplace through which large amounts of CO are transported, shall be provided with sufficient respiratory protective devices of the types specified in Section 4 and shall be readily accessible to persons who may be located in the area to assure a timely, orderly evacuation of the area by all persons in the event of accidental, massive release of CO. An automatic visual and audible alarm that is set to be activated when the CO concentration reaches 500 ppm should be employed in such areas. Employees working in such areas shall be informed of the hazards and symptoms of acute CO poisoning (see Section 6) and shall be trained to implement an emergency evacuation plan designed for such an occurrence. Periodic drills, held not less frequently than every six months, shall be conducted to assure that such plans are adequate and effective in case of an emergency situation.

(c) Fire Hazards

Adequate fire extinguishing agents shall be readily available in the areas outlined in paragraph (b) of this section since CO will burn when mixed with air and may be explosive when concentrations of between 12.5 percent to 74.2 percent are reached.

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Section 6 - Apprisal of Employees of Hazards of Carbon Monoxide

(a) Each employee who receives significant exposure to carbon monoxide [see Section 3(b)] shall be apprised of all hazards, relevant symptoms, appropriate emergency procedures, and proper conditions and precautions for the safe use of CO or safe exposure to CO and shall be instructed as to the location of such information, which shall be kept on file as prescribed in paragraph (b) of this section and shall be readily accessible to all employees at each establishment where CO is involved in industrial processes and operations.

(b) Information as required in Appendix III shall be recorded on U.S. Department of Labor Form OSHA-20, "Material Safety Data Sheet," or on a similar form approved by the Occupational Safety and Health Administration, U.S. Department of Labor.

Section 7 - Work Practices

(a) Each container in which CO is stored shall be examined for leaks upon its arrival at the establishment or upon filling and shall be reexamined periodically at least every three months.

(b) Prior to transferring CO from a storage container, an inspection shall be conducted to detect any gas leaks in the transport system (e.g., cylinder seal with gas regulator, regulator apparatus, regulator seal with transport conduits, conduit system, etc.).

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Section 8 - Monitoring and Recordkeeping Requirements

(a) Employers shall monitor environmental exposure of employees toCO as follows:

(1) Personal exposure ("breathing zone") samples* shall be collected in accordance with procedures specified in Appendix I in all workplaces where employees are significantly exposed to CO [see Section 3(b)]. Samples will be collected and evaluated as both TWA and ceiling concentration values.

(2) Frequency of monitoring should be at least annually. It is recognized that more frequent monitoring may be indicated in certain circumstances depending upon the nature of the process, the rate of production, the effectiveness of control measurements, the time of day and seasonal variation, however, more frequent monitoring requirements cannot be recommended until there are extensive studies of specific operations in industry.

(3) Blood analysis for COHb, as specified in Appendix II, shall be performed on all persons employed in work areas when, in the judgment of the OSHA Industrial Hygienist, biologic standards are needed to evaluate borderline exposure to CO (see Chapter V).

(4) Determination of the CO concentration for borderline exposure, as judged by the OSHA Industrial Hygienist, shall be accomplished by continuous monitoring of the workplace environment. Such continuous monitoring shall be accomplished by means of monitoring equipment capable of determining the CO concentration in the workplace environment within 5 percent of the actual value.

^{*}Selected sampling of representative or higher risk workers

(5) Affected employees, or their representatives, shall be given a reasonable opportunity to observe any monitoring required by this section.

(b) Every employer shall maintain records of any personal or environmental monitoring required by this section. Records shall be maintained for a period of at least three years and shall be made available upon request to the Assistant Secretary of Labor for Occupational Safety and Health, the Director of the National Institute for Occupational Safety and Health, and to authorized representatives of either. Every employee and former employee shall have reasonable access to any record required to be maintained which indicates the employee's own exposure to CO.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were developed and prepared by the National Institute for Occupational Safety and Health (NIOSH) to meet the need for providing adequate protection for the safety and health of employees exposed to carbon monoxide. The necessary relevant data are made available in accordance with Section 20(a) of the Occupational Safety and Health Act of 1970 that requires the development of criteria by the Secretary of Health, Education, and Welfare on the basis of such research, demonstrations, and experiments and any other information available to him which will assure insofar as practicable that no employee will suffer diminished health, functional capacity, or life expectancy as a result of his work experience.

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultations with others, formalized a system for the development of criteria upon which standards can be established to protect the health of employees from exposure to hazardous chemical and physical agents. It should be emphasized that any criteria documentation for a recommended standard should enable management and labor to develop better engineering controls and more healthful work practices and should not be accepted as a final goal in itself.

In evaluating occupational hazards and setting priorities,¹ it was determined that the potential for exposure of employees at the workplace to CO was greater than that for any other chemical or physical agent. The significance of the CO dose-response relationship in man is attested furthermore by numerous research studies which have been documented in

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the scientific literature. In a recent conference on the biological effects of CO sponsored by the New York Academy of Sciences, the findings and views of scientists from the United States, Australia, England, France, and Denmark were presented.²

Background information for this report was obtained from many sources, including those directly cited and listed in the references. In addition there is a bibliography³ of nearly 1,000 references and abstracts on CO prepared by the U.S. Public Health Service as well as the National Air Pollution Control Administration report⁴ of March 1970 on CO exposure in the community.

These criteria for a recommended standard for CO are part of a continuing series of criteria being developed by NIOSH. The criteria and recommended standard apply only to those processes and operations involving the manufacture, emission or use of CO as applicable under the Occupational Safety and Health Act of 1970 (PL 91-596). The occupational safety and health aspects of CO exposure for workers engaged in mining and milling operations are covered by standards promulgated by the Bureau of Mines pursuant to authority granted by the Federal Metal and Nonmetallic Mine Safety Act (30 U.S.C. 725 <u>et seq</u>.). Relevant data, however, bearing on the safety and health hazards resulting from exposure to CO in mining and milling operations were considered in this document.

The criteria contained in this document were developed to assure that the recommended standard based thereon would (1) protect employees against both acute and chronic CO exposure, (2) be measurable by techniques that are valid, reproducible and available to industry and governmental agencies and (3) be attainable with existing technology.

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In 1969 the Committee on Effects of Atmospheric Contaminants on Human Health and Welfare, appointed by the Environmental Studies Board of the National Academy of Sciences, reported on the evaluation of current knowledge concerning the effects of CO on man.⁵ While this report deals primarily with the effects on man of exposure to CO from air pollution sources, it is pertinent to note the following statement in the Introduction: "...Today, the two main sources of carbon monoxide appear to be cigarette smoke and the internal combustion engine. And the subject of concern has changed from the acute effects of short-term exposure...to the lasting effects of long-term, low-level exposure, of a duration anywhere from a month to a lifetime, and in the range of CO concentrations that would produce 0.5-10% COHb." Thus, in the case of occupational exposures to CO, a worker's smoking habits must be taken into consideration when evaluating the environment. This factor has not been generally considered until the past few years. It should be emphasized that the above report raised many questions concerning the effects of low-level exposures to CO, and that Committee recommended many additional research studies in this area.

Although important evidence exists which indicates that subtle aberrations may occur in the central nervous system (CNS) during exposure to levels of CO lower than those of the recommended standard, the significance of these changes and their translation to effects upon employee safety and health is not entirely clear. The diversity of opinions and the conflicting experimental evidence existing in this area does not permit the clear-cut assessment of the scientific merit of such data or its extrapolation to the normal working population at this time. If reliable data become available which clearly demonstrate significant impairment of employee

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behavior during exposure to very low levels of CO (producing less than 5 percent COHb), then the criteria for the recommended standard will be reassessed on the basis of the additional evidence.

III. BIOLOGIC EFFECTS OF EXPOSURE TO CARBON MONOXIDE

Carbon monoxide (CO) is an odorless, colorless, tasteless gas which is an active reducing agent for chemicals at elevated temperatures, but is principally encountered as a waste product of incomplete combustion of carbonaceous material. A summary of the physical properties is presented in Table I. The best understood biologic effect of CO is its combination with hemoglobin (Hb) to form carboxyhemoglobin (COHb), thereby rendering the hemoglobin molecule less able to bind with oxygen. This action of CO results in more persons succumbing each year to acute CO poisoning than to any other single toxic agent, except alcohol.⁶

Extent of Exposure

With the single exception of carbon dioxide (CO₂), total emissions of CO each year exceed those of all other atmospheric pollutants combined. In 1968 it was estimated that 102 million tons of CO were released into the atmosphere by the major sources of emission.⁴ Over one-half of this amount (58 percent) was produced by the gasoline-powered internal combustion engine. Specified industrial processes accounted for approximately 10 percent of the total. A summation of CO emission estimates for 1968 by specific industrial processes is presented in Table II.

From Table II it can be observed that large amounts of CO are emitted from petroleum refineries, iron foundries, kraft pulp mills, sintering mills, lampblack plants and formaldehyde manufacturers. Major sources of CO production within the first four industries have been identified as the cupola in the iron foundry, the catalytic cracking units in the petroleum refineries, the lime kilns and the kraft recovery furnaces in the kraft paper mills, and the sintering of blast furnace feed in sintering plants.

Aside from the above major industrial processes which produce large quantities of CO, there are numerous operations (arc welding, automobile repair, traffic control, tunnel construction, etc.) where the occupational exposure for a worker to CO can be considerable. In fact any industrial process or operation where incomplete combustion of carbonaceous material occurs may easily be of consequence as concerns occupational exposure to CO. Historical Reports and Theoretical Considerations

Man's intimate association with carbon monoxide as a true environmental hazard began with his discovery of fire. Since that time his technological history has been one of advancement by means of incomplete combustion. The seriousness of exposure to high concentration of CO has been realized since the earliest medical writings. The Greeks and Romans used exposure to CO as a means of execution of criminals and committing suicide.⁷

Priestly discovered the chemical composition of CO in the late 18th century and in 1895 Haldane⁸ demonstrated the important relationship involving CO, hemoglobin and their saturated product, carboxyhemoglobin (COHb), on physiologic processes.

Since the time when Douglas and the Haldanes⁹ formulated the basic laws governing the interactions of CO and oxygen (0_2) with hemoglobin it has been understood that CO combines with the reduced hemoglobin molecule much more readily than does oxygen, when the two are simultaneously present in a breathing mixture. These investigators placed the affinity constant (M) for the equation:

 $\frac{[\text{COHb}]}{[0_2\text{Hb}]} = \frac{M \times P_{CO}}{P_{O_2}}$

within the range, 220 to 290 and later investigations have generally confirmed this range, although at a slightly lower level, under conditions of complete hemoglobin saturation by oxygen and CO.¹⁰⁻¹³ Briefly, the affinity constant may be expressed as the number of moles of oxygen which must be present with each mole of CO in order to maintain an equal saturation of hemoglobin. While CO actually combines less rapidly with reduced hemoglobin than does oxygen, the tenacity of the binding between CO and hemoglobin is some 200 to 300 times that of oxygen. This saturation of hemoglobin by either oxygen or CO occurs in four steps involving intermediates with four equilibrium constants:

$$Hb_{4} + X \stackrel{k'1}{k_{1}} XHb_{4} \qquad K_{1} = \frac{k'1}{k_{1}}$$

$$XHb_{4} + X \stackrel{k'2}{k_{2}} (X)_{2}Hb_{4} \qquad K_{2} = \frac{k'2}{k_{2}}$$

$$(X)_{2}Hb_{4} + X \stackrel{k'3}{k_{3}} (X)_{3}Hb_{4} \qquad K_{3} = \frac{k'3}{k_{3}}$$

$$(X)_{3}Hb_{4} + X \stackrel{k'4}{k_{4}} (X)_{4}Hb_{4} \qquad K_{4} = \frac{k'4}{k_{4}}$$

In the above equations, X represents either oxygen or CO with a different equilibrium constant for each equation. It has been determined that in both cases K_4 is much higher (18 to 50 times higher) than K_1 , K_2 , or K_3 because k'₄ is much greater than k_4 .⁴,¹⁴ Under these circumstances the last ligand to bind to hemoglobin (K_4 equation) dissociates much more readily than it binds.¹⁵ The differences between the four constants depend on intra-molecular forces occurring as a result of the interactions of each ligand with the others, or with other portions of the hemoglobin molecule. Hence, the effect is an allosteric one resulting in conformational changes in the hemoglobin molecule. These differences in reaction rates affect the dissociation of oxygen or CO from hemoglobin such that, as can be observed in Figure 1, the shapes of the respective dissociation curves are sigmoidal rather than parabolic, as is the case with myoglobin, which possesses only one heme group with a single dissociation constant.¹⁶ Likewise the dissociation curve for COHb-0 $_{2}^{\text{Hb}}$ tends to be parabolic, indicating the effect of CO upon the dissociation of the remaining O, molecules. Although the constant may be as high as 245 or as low as 135 depending upon, among other things, the blood pH and amount of reduced hemoglobin present, 17,18 the generally accepted figure of 210* is applicable only for human hemoglobin. 10 Each species has a particular value for the affinity constant because the composition of hemoglobin molecules varies between species.¹⁹ The M value for a species remains relatively constant, dependent on the physiological conditions mentioned above. Both Rodkey¹³ and Killick,²⁰ however, have reported individual variations in the value of M.

Because the tissue partial pressure of oxygen (P_{0_2}) (approximately 40 mm Hg in mixed venous blood) occurs at a steep portion of the curve, under normal physiologic conditions oxygen is rapidly dissociated from hemoglobin resulting in a tissue saturation which is maintained with a large oxyhemoglobin reserve near the lower end of the curve. This reserve is the result of the large value for K_4 , which permits dissociation only at the upper portion of curve under normal physiologic conditions.²¹

*Rodkey¹³ has recently placed this figure at 218.

The difference in the partial pressure of oxygen (P_{0_2}) between freshly oxygenated arterial blood $(P_{0_2} = 100 \text{ mm Hg})$ and mixed venous blood $(P_{0_2} = 40 \text{ mm Hg})$ represents a release to the tissues of approximately 5 milliliters $0_2/100$ milliliters blood.¹⁶ A shift of the steep portion of the oxyhemoglobin dissociation curve to the left would tend to change the release of oxygen to the tissues appreciably.

While the dissociation curve shifts to the right, allowing for a more efficient dissociation of oxygen to the peripheral tissues under conditions of reduced ambient oxygen tension (hypoxic hypoxia), just the opposite 4,16,19,21 situation occurs during exposure to CO (anemic hypoxia). The leftward shift during CO exposure occurs because of the much greater affinity of CO for hemoglobin and in spite of the fact that the amount of oxygen in physical solution in the blood remains near normal. The oxygen content of the blood is not only lowered during exposure to CO, but the shift of the oxyhemoglobin dissociation curve to the left decreases the amount of remaining oxygen that is made available to the tissues. Both mechanisms serve to effectively lower the tissue P_{0_2} and hence can create a generalized tissue hypoxia. Dinman has suggested that the great affinity of hemoglobin for CO was, evolutionarily speaking, of a definite survival advantage since this mechanism permits the expedient removal of endogenously-produced CO resulting from heme catabolism.

It has been demonstrated that following an initial exposure to CO, animals become less susceptible to subsequent exposure(s).⁴ On the other hand it has also been demonstrated that mice which survived one episode of exposure to a high concentration of CO succumbed during a subsequent exposure to the same concentration.²² If acclimatization to CO occurs, then it is

possible many of the physiologic mechanisms facilitating acclimatization would be similar to those which aid in acclimatizing the animal to hypoxia.^{16,23,24} Indeed, it has been demonstrated in animals that such similar acclimatory mechanisms as polycythemia and increased hematocrit and hemoglobin occur during both hypoxic hypoxia and CO-induced hypoxia. Whether there is a separate, distinct factor involved in the acclimatization of man to CO remains to be seen, although there is some evidence to the contrary.²²

Quite apart from acclimatization is the question of the existence and mechanism of chronic CO poisoning.²⁵ Some investigators believe that if this condition occurs it is the result of the accumulated effects of repeated acute episodes and not merely a continuous insult by low levels of CO.^{26,27}

Since complete acclimatization to ambient concentrations of CO may not be possible, biological alterations occurring during exposure to CO become suspect as indicators of possible deleterious effects. The same would still be true should acclimatization to CO occur. This reasoning has even led some investigators to believe that death resulting from acute CO intoxication may not be caused solely by simple asphyxia^{22,28-32} but also by some toxic effect exerted by CO per se.

Among the most subtle of known physiologic alterations are those which involve shifts in compartmental concentrations of trace metals. New techniques (e.g., atomic absorption and anodic stripping voltametry) now allow for the detection of very minute amounts of these important entities, and changes in their departmental concentrations during the course of various disease states, including chronic CO exposure, have been documented.^{33,34} Difficulties involved in determining the significance of findings and in the extrapolation of findings to the whole organism have,

so far, somewhat undermined the potential values of these techniques. However, the fact that most of the eight or ten essential trace metals participate, physiologically, either as co-factors or activators of enzymes underscores the importance of determining their aberrations <u>in vivo</u>. In fact, any condition precipitating changes in enzyme activity or concentration merits very close scrutiny, and the activity of several enzymes has been found to be altered during CO exposure.³⁵⁻³⁸

At the other end of the spectrum of alterations occurring in the animal organism as a result of exposure to CO are changes in behavioral patterns. There is evidence to suggest that certain behavioral changes induced in the whole animal via CO exposure are indications of subtle physiologic alterations occurring within the organism, the elaboration of which is beyond the detectable range of present physiologic techniques. Thus the work of several investigators has suggested that such quantities as time discrimination, ³⁹ visual vigilance, ⁴⁰ choice response tests, ³⁰ visual evoked responses, ^{41,42} and visual discrimination thresholds^{29,35} can be altered at levels of COHb below 5 percent. The results of these tests often must be evaluated in the light of very highly specific test conditions which may have included distractions that could have easily altered the responses. It is also possible that the motivational attitude of the experimental subject may have been sufficient to alter results.

Attempts to correlate behavioral changes with damage to the central nervous system (CNS) have produced conflicting results, although acute exposure to high concentrations of CO has consistently produced brain lesions. ⁴³ The general trend has been the finding of less severe CNS damage as the concentration of CO and length of exposure are decreased.

At CO concentrations of 100 ppm some investigators have found cerebral cortex damage in dogs, especially along the course of blood vessels, while other investigators have detected no direct damage but have discovered that the glial cells were mobilized, ⁴⁴ a condition which usually occurs only during the course of disease. It has been suggested, however, that CNS damage, when it does occur, may be secondary to cardiovascular damage. ⁴⁴

Although the concentration of myoglobin when compared to that of hemoglobin is small, nevertheless, it has been implicated by several investigators as an important factor during CO exposure 45,46 and hypoxia. 47Myoglobin has approximately 16 percent the oxygen-carrying capacity of an equal quantity of hemoglobin and accounts for only approximately 20 percent of the body's total CO capacity, but its existence as an extravascular carrier of oxygen prompted Wyman to compare the "translational diffusion" of oxygen into the cell via myoglobin with the pumping of oxyhemoglobin via the heart throughout the body. Exposure to CO may decrease the oxygencarrying capacity of myoglobin with the formation of carboxymyoglobin (COMb). which is analogous to the formation of COHb from hemoglobin. The affinity constant (M value in Haldane equation) for myoglobin, however, is only 40. compared with 210 for hemoglobin. This proposed mechanism of facilitated oxygen transport within the myocardium under normal conditions could lead to yet another deleterious consequence during CO exposure. Ayres 49 suggested that a state of oxygen debt might develop in cardiac muscle tissue where the myoglobin has become deoxygenated since, according to Wittenberg.⁵⁰ an estimated 50 to 90 percent of the oxygen reaching the muscle mitochondria during heavy work is carried by myoglobin.

As mentioned earlier in this report it has been confirmed that an endogenous source of CO exists as a product of heme catabolism. 51,52

When an α -methylene bridge in the heme portion of hemoglobin is broken during the catabolic process, a molecule of CO is released.⁵¹ It has been estimated that this production amounts to approximately 0.3 to 1.0 milliliter(ml)/hour with an additional 0.1 milliliter(ml)/hour resulting from a similar catabolic process involving other heme-containing compounds (e.g., myoglobin and cytochrome and catalase enzymes).^{6,53} This endogenous production of CO, which gives rise to approximately 0.5 to 0.8 percent COHb, would not be expected to be of important physiologic consequence <u>per se</u> since the hypothesized mechanism has evolved with man, but its removal would merit due consideration in a closed system such as a submarine or a space capsule. Also, in the determination of total CO exposure this quantity must be included as "base line" COHb.

Cardiovascular Effects of CO

The critical importance of cardiovascular involvement during exposure to CO is becoming increasingly evident.^{6,28,49-60} While the brain has a higher requirement for oxygen than the heart, in contrast to the cerebral circulation the coronary circulation must supply an even increased amount of oxygen during periods of generalized tissue hypoxia; since under these circumstances the heart is forced to increase both its rate and its output in order to meet the normal oxygen demands of the body.⁴⁹ This increase in myocardial activity demands an increased oxygen supply to the myocardium which must be met by the coronary circulation. Under hypoxic conditions increased oxygen supply to the peripheral tissues can be accommodated by increased blood flow (via vascular dilatation) and/or increased oxygen extraction by the tissues. As mentioned earlier the peculiar dissociation characteristics of 0, Hb permits an oxygen reserve which is used at reduced

The myocardium under these circumstances appears only to increase P0. the flow of blood rather than to extract an additional amount of oxygen from the coronary circulation. While the peripheral tissues normally extract only 25 percent of the oxygen content of the perfusing arterial blood during resting conditions, the myocardium extracts 75 percent, thus leaving the mixed venous blood only 25 percent saturated. This mechanism has the overall effect of maintaining the myocardial oxygen tension at a higher level than would be present in other muscle tissue and thus insures a continual aerobic metabolism, even under hypoxic duress. In terms of oxygen tension, the mixed venous blood of the peripheral tissues is approximately 40 mm Hg while the mixed venous blood of the coronary circulation is only 20 mm Hg. In the presence of COHb (and the shift to the left of the oxyhemoglobin dissociation curve), however, the arterio-venous difference can only be maintained by an increased flow in the coronary circulation. In an individual with diminished coronary circulation because of coronary heart disease, however, this situation may result in a decrease in the mixed venous oxygen tension of the myocardium precipitated by an inability to maintain the normal arterio-venous gradient. This hypoxic effect is further enhanced, as mentioned above, by an increase in cardiac rate and output as a general response to peripheral tissue hypoxemia. A person with diminished coronary circulation caused by coronary heart disease, consequently, may be constantly near the point of myocardial tissue hypoxia.

Ayres⁴⁹ attempted to demonstrate the redox state of the myocardium during CO exposure via a biochemical assay procedure. His technique involved determination of extraction ratios in humans of pyruvate and lactate from perfusing coronary circulation following exposure to 50,000 ppm

of CO for 30 to 120 seconds. Glucose can be converted to pyruvate under anaerobic conditions via glycolysis, but the fate of pyruvate from that point depends largely on the redox state of the cell. With adequate oxygenation pyruvate will be converted to acetyl coenzyme A and from thence it can be oxidized via the citric acid cycle. If there is inadequate oxygenation, however, pyruvate will be converted to lactate, a terminal product in animal anaerobic metabolism, and both can be transported to the liver for oxidation, should the redox state of the liver be adequate. In Ayres' experiments, measurements were made of the extraction ratios of pyruvate and lactate by myocardial tissue from the coronary circulation of patients with coronary artery disease as well as with patients with noncoronary heart disease. Normally the myocardium extracts both of these metabolites from the coronary circulation for purposes of oxidation as mentioned above. When appreciable COHb (mean = 8.7 percent) was present, however, not only did the myocardium fail to extract either of these two substances, it actually produced both. The production of lactic acid in the myocardium at any time indicates the existence of a state of tissue hypoxia, and a prolonged state of hypoxia is detrimental to cell function with the possible consequence of cell death. When Ayres compared coronary blood flow in patients with coronary artery disease and in patients with noncoronary heart disease, he found that although extraction of pyruvate decreased in both groups, the coronary blood flow increased only in the patients with noncoronary heart disease. Although lactate was produced in the myocardium in both groups, this change from lactate extraction was statistically significant only in the patients with coronary artery disease.

Recent investigations have been reported by Adams, Erickson, and Stone 58 concerning the effects of low concentrations of COHb on coronary

blood flow, myocardial oxygen consumption and cardiac function in conscious dogs, breathing a 1500 ppm carbon monoxide air mixture through a tracheostomy. This exposure to CO increased the COHb slightly less than 1 percent per minute. At 5 percent COHb (control levels of COHb in the same animals were 1 percent) there was a significant increase in coronary blood flow of 13 percent. During the exposure to CO, there was a significant decrease in the arterio-venous difference in oxygen content across the heart and in myocardial oxygen consumption. The arterial oxygen content decreased, while the coronary venous oxygen content increased. Arterial and coronary sinus $P_{0,c}$ remained constant. Left atrial pressure decreased slightly, but there was no significant change in the left ventricular pressure or maximum left ventricular dP/dt. Myocardial oxygen consumption, which increases with hypoxic hypoxia, thus supporting the net increase in energy expenditure by the myocardium, results from an increase in coronary flow and a decrease in coronary sinus oxygen saturation, which compensates for the decrease in the quantity of oxygen available. As documented by the investigators, however, the coronary flow response during exposure to CO may not be adequate, since the oxygen consumption decreases. This phenomenon may be associated with the hyperbolic shift to the left of the oxyhemoglobin dissociation curve, resulting in an increase in the coronary venous saturation.

The interaction of CO and hypoxic hypoxia on coronary flow was studied in seven dogs using the same methods.⁵⁸ Coronary flow increased 38 percent during exposure to 10 percent oxygen. There was a 13 percent and 24 percent increase in coronary flow with 5 percent and 10 percent COHb, respectively. Exposure to 10 percent oxygen in the presence of 5 percent and 10 percent COHb, however, resulted in a 51 percent and 67 percent increase in coronary

flow, respectively. These results document the additive effect of CO and altitude hypoxia on coronary blood flow.

Lewey and Drabkin⁴⁴ exposed dogs to 100 ppm CO for 5 3/4 hours a day, six days a week for eleven weeks. The mean daily COHb levels were approximately 20 percent. Although no electroencephalographic (EEG) changes were noted by the investigators, the animals were observed to suffer from psychomotor disturbances and at autopsy, cerebral cortical damage, which tended to follow the course of blood vessels, was observed in all animals. In this study one animal, which had the posterior coronary artery ligated for some time prior to the study, demonstrated the most severe cerebral damage and also had severe myocardial alterations. The investigators suggested that "...an inadequate functioning heart increases the general risk in CO poisoning, and may be responsible for a higher degree of brain damage." Utilizing the same exposure regime as Lewey and Drabkin, ⁴⁴ Ehrich, Bellet, and Lewey⁶⁰ found electrocardiographic (EKG) alterations in dogs exposed to 100 ppm for eleven weeks, which produced a COHb of 21 percent.

When Lindenberg and co-workers³⁹ exposed fifteen dogs both continuously and intermittently to 50 ppm of CO for six weeks they observed pathologic EKG's in ten animals, pathology of the heart in seven animals and pathology of the brain in six animals.

Separate studies by Musselman²⁴ and Jones⁶¹ were conducted at 50 ppm CO and demonstrated no significant cardiovascular alterations occurring in various experimental animal species used in the experiments. Recently Theodore, O'Donnell, and Back⁶² exposed several species of animals to CO concentrations of 400 ppm CO for 71 days and then to 500 ppm CO for the 97 remaining days of a 168-day continuous exposure period. On gross examination of the CNS and the heart, none of the larger animals used in the

experiment (e.g., monkey, dog) demonstrated any changes. However, there was a marked increase in both hemoglobin concentration and RBC. The COHb levels reached 38 percent in the monkeys and 39 percent in the dogs. Although several species of animals were used by the investigators in the above experiments, only the canine was used in all investigations. It is very interesting in this regard, then, that when Ayres⁶³ acutely exposed canines and human CHD patients to concentrations of CO sufficient to produce significant myocardial changes, the lowest level of COHb at which such alterations were observed was only 6 percent in humans but was 25 percent in the dogs. It appears that the canine may be able to tolerate a much higher level of COHb than is the human before significant myocardial changes occur.

Jaffe⁶⁴ has emphasized the relationship between CO poisoning and an elevated titer of serum lactic dehydrogenase as an indicator of myocardial damage. He speculated that "...even 'normal' amounts of carbon monoxide may operate as the last straw in precipitating coronary attacks." When rats were exposed to 500 ppm CO for four hours Lassiter, Coleman, and Lawrence⁶⁵ observed a statistically significant aberration in the plasma lactic dehydrogenase isoenzyme distribution which was considered to be highly indicative of myocardial damage. The COHb level in the animals at termination of exposure was <40 percent.

The relationship between chronic cigarette smoking and increased risk of coronary heart disease (CHD) is undeniable, ⁶⁶ as is the fact that cigarette smoking causes increased exposure to CO. A CO concentration of 4 percent (40,000 ppm) in cigarette smoke, which will cause an alveolar concentration of 0.04 to 0.05 percent (400 to 500 ppm) will produce a COHb concentration $^{6,67-69}$ Goldsmith ⁷⁰ estimated that the cigarette smoker is exposed to 475 ppm of CO for approximately six minutes per cigarette.

In a review article on CO and human health, Goldsmith and Landaw⁷¹ stated that the COHb level in the one-pack-a-day cigarette smoker is 5.9 percent, which they say is a sufficient concentration to impose a serious health threat to persons with underlying vascular insufficiency. In another paper these two investigators used a regression analysis of expired air samples from 3,311 longshoremen and found a COHb of 6.8 percent in two-pack-a-day smokers and 1.2 percent COHb in nonsmokers. They believed that the high level in the nonsmokers, above the 0.5 to 0.8 percent normally present as a result of endogenous production, was accounted for by occupational exposure.

In a study by Kjeldsen⁵⁷ COHb levels of both smokers and nonsmokers were compared from 934'CHD-free" persons. The mean COHb was 0.4 percent for nonsmokers and 7.3 percent for cigarette smokers who inhaled. In addition, the mean level of COHb for all 416 smokers in the study, regardless of inhalation habits or number of cigarettes smoked, was 4.0 percent.

A similar study is presently being conducted to determine the range of COHb in the American public by Stewart and Peterson.⁷² The presently available data, from Milwaukee, has demonstrated that the mean COHb levels for nonsmokers is 1.33 ± 0.85 percent and for smokers is 4.47 ± 2.52 percent.

Pirnay and co-workers ⁷³ provided evidence, based on CO immobilization of 15 percent of hemoglobin, which they state confirms the hypothesis that there is a circulatory limitation upon maximal oxygen consumption and that decreases in maximal oxygen consumption seem to result from a reduction in oxygen transport capacity. This hypothesis has important implications for the cigarette smoker and nonsmoker alike who have CHD and who are occupationally exposed to CO. Based upon this data the imposition of mild to

moderate exercise upon such individuals during CO exposure could have very detrimental repercussions.

In an epidemiologic survey involving approximately 4,000 middle-aged males, who were kept under medical surveillance for 8 to 10 years, Doyle and co-workers⁷⁴ found that one-pack-a-day smokers had about a three-fold greater risk of myocardial infarction than did nonsmokers, or former smokers.

The finding that death rates for ex-smokers were no higher than for nonsmokers prompted Bartlett¹⁶ to state that the effect of cigarette smoking on this particular pattern is completely reversible when an individual ceases to smoke. He concluded that smoking caused a myocardial hypoxemia by some acute, reversible process, which was probably unrelated to the formation of hard, irreversible, atherosclerotic lesions and that CO would fit such an epidemiologic pattern very well. He further stated, however, that other components of cigarette smoke, including nicotine, may be responsible for this pattern and that the question, in his estimation, remained unsolved.

Astrup, Kjeldsen, and Wanstrup,⁷⁵ reporting on an investigation in progress in 1970 in which 1,000 randomly chosen individuals were examined for evidence of arteriosclerotic disease, demonstrated a clear relationship between this disease and high COHb levels after smoking. They further stated that it is very likely "...that it is the inhalation of CO in tobacco smoke that is, in part, responsible for the much higher risk of smokers to develop coronary heart disease and other obliterating arterial diseases in comparison to that of nonsmokers."

Chevalier, Krumholz, and Ross⁶⁷ found when the COHb of nonsmokers was increased, via CO exposure to 5 percent CO (50,000 ppm), such that their levels of COHb were the same as those observed in cigarette smokers (greater than 4 percent), that the nonsmokers developed an increased oxygen debt with

exercise and a reduced pulmonary diffusing capacity at rest. These findings were similar to those observed in smokers. The investigators implied that in persons with approximately 4 percent COHb the same amount of work is accomplished by means of increased metabolic rate. Or stated differently, a worker with approximately 4 percent COHb can maintain a particular level of activity only at the expense of an increase in metabolic rate.

Bartlett¹⁶ made a significant observation that CO in ambient air and CO from cigarette smoke are not additive as concerns their biologic effect because each represents an independent source of CO. He suggests that, because of this, smokers may be the least susceptible individuals to increases in COHb during exposure to low concentrations of CO since their levels of COHb, already high, would not be increased by the exposure. The author admitted, however, that the rate of excretion of CO for the cigarette smoker is decreased during ambient CO exposure and this would increase the longterm average COHb levels in the presence of ambient CO.

In evaluating the exposure of patients who have coronary heart disease with angina pectoris to CO sufficient to produce a COHb level of 5 percent, 21 Dinman²¹ stated that while a small additional decrease in the oxygen saturation of the blood brought about by mild exercise might be feasible, "...the degree of blood oxygen desaturation demanded with 10 percent COHb loading is rather severe."

Anderson and co-workers ⁷⁶ recently exposed normal young males and clinically normal middle-aged males to 100 ppm of CO for four hours which resulted in COHb levels at the end of that time of 5 to 9 percent. During exposure the two groups were subjected to 85 percent submaximal treadmill exercise testing while ECG monitoring and several cardiac function measurements were recorded. Statistical differences in the measured parameters

were observed only in the older group of subjects. The investigators stated that "...low-level CO exposure may augment the production of exerciseinduced myocardial ischemia in persons with preexisting subclinical heart disease, contribute to the development of myocardial dysfunction, and may lead to an increased incidence of arrhythmias in such persons." They further stated that these findings in clinically normal persons would be more pronounced in persons with overt ischemic heart disease (e.g., angina pectoris or myocardial infarction). The investigators further said that arrhythmias observed in the older group may explain the observations of Cohen, Deare, and Goldsmith⁷⁷ concerning the increased case fatality rates for persons with acute myocardial infarctions during periods of increased ambient levels of CO as well as explain the increased incidence of sudden death in smokers.

In a study conducted by Knelson,⁷⁸ seven patients with clinically diagnosed angina pectoris, who suffered daily from frequent angina pains, were exposed, at rest, to 50 ppm and to 100 ppm CO for separate four-hour periods. The patients, all cigarette smokers, refrained from smoking for eight to ten hours prior to being exposed to CO. The mean COHb prior to exposure was 1.32 ± 0.30 percent. Following four-hour exposure periods the mean COHb levels were 3.01 ± 0.34 percent in the patients exposed to 50 ppm CO and 4.65 ± 0.58 percent in those exposed to 100 ppm CO. Each patient served as his own control and was continuously monitored before, during and after a double-blind exposure period. Immediately after the exposure period each patient exercised on a treadmill and the time to angina pain and the duration of the pain were recorded. The investigator reported a statistically significant difference (p <0.01) in the time to onset of

pain in the patients exposed to 50 ppm for four hours. The same level of significance was also found for the patients exposed to 100 ppm although the differences of results between the two regimes were not significantly different. The other parameter measured, duration of pain, was statistically significant (p < 0.05) only for the patients exposed to 100 ppm CO. Again the differences of results between the lower and higher exposures were not significant. Knelson concluded, using this particular protocol of exposure, that patients with angina pectoris who were exposed to CO and then exercised experienced pain earlier and pain lasted longer, than when these same patients were exposed to ambient air.

An interesting set of data has been produced recently by Horvat and co-workers⁷⁹ concerning the effect of oxygen breathing on the threshold of angina pain in patients with confirmed coronary heart disease. The investigators first determined the angina threshold while the patients breathed air by increasing the heart rate via right atrial pacing. Patients were then, unknowingly, switched to 100 percent oxygen and the heart paced to the previously determined angina threshold. Angina pain did not occur in nine of eleven patients. Associated with this improvement was increased lactate extraction from an average of -17 ±15 to +18 ±10 percent (p <0.025). In four of six patients lactate production turned to lactate extraction, in six of seven patients S-T abnormalities in the EKG were improved as well as improvement in pulsus alternans in three of five patients.

These data present significant evidence that oxygen breathing permits the heart to do more work before coronary insufficiency develops. They also indicate the validity of the approach used by Knelson in determining

the time to onset of angina pain in patients exposed to CO. Each investigation, in fact, complements the other concerning the parameter of angina pectoris.

The important implications of these studies for the cigarette smoker with angina pectoris is all too clear. Thus, based on cardiovascular alterations which could prove to be of severe physiologic consequences for persons with CHD, a significant portion of who are in the worker population, it seems advisable that levels of COHb in excess of 5 percent should be avoided.

Neurophysiologic and Behavioral Effects of CO

The clinical effects on the central nervous system (CNS) of CO poisoning have been extensively reported. In general, increasing COHb levels result in a corresponding depression of the CNS showing a progression from slight headaches at 10-20 percent COHb, coma with intermittent convulsions at 50-60 percent, and death at 70 to 80 percent COHb. In contrast, the subclinical effects on the CNS of low level CO exposures are less well documented. This section will review the histopathological, neurophysiological, and behavioral effects of such low-level to moderate CO exposures, and evaluate the significance these findings may hold for occupational safety and health considerations.

Histopathological Effects

Lewey and Drabkin exposed six dogs to 100 ppm of carbon monoxide for 5 3/4 hours per day, six days per week, for a period of eleven weeks. The mean COHb level was found to be approximately 20 percent. The animals were sacrificed three months after the end of the exposure. Distinct histopathologic changes were found in the cerebral cortex and included infarction,

degenerative changes, formation of cysts, gliosis, perivascular infiltration, loss of myelin and softening of the white matter. The basal ganglia showed the severest damage with loss of cells and demyelinization. No changes were seen in the electroencephalogram (EEG) or in peripheral nerves. The question has been raised as to whether or not all the changes reported by Lewey and Drabkin were artifacts of post-mortem changes peculiar to dogs.

In contrast, Lindenberg and co-workers⁵⁹ exposed dogs to 100 ppm CO for twenty-four hours per day, seven days a week, for six weeks (1-1/2 times as much carbon monoxide as in the Lewey and Drabkin study). Lindenberg found areas of pathologic changes in the heart and the brain on histologic examination of the dog brains.

Musselman and co-workers²⁴ exposed dogs, rabbits and rats to 50 ppm of CO for three months. Gross histologic examination of the CNS revealed no histopathologic effects.

Shul'ga⁸⁰ exposed rats to 25-27 ppm of CO eight hours daily for ten weeks. Histologic examination of the brains of these animals revealed focal destruction of nerve cells in the cerebral cortex, abnormalities of the Purkinje cells with pyknosis of cells, and completely disintegrated nerve cells in the spinal cord. The results of Musselman are at variance with those of Shul'ga and are difficult to reconcile.

Neurophysiological Effects

Several studies have been reported concerning searches for subclinical effects of low levels of carbon monoxide exposure using such objective electrophysiological measures as spontaneous electroencephalograms (EEG), visual evoked responses (VER), sleep patterns, and conditioned electrocortical reflexes.

81 Dinman failed to observe any gross EEG changes in humans after their exposure to CO concentrations that produced about 27 percent COHb. Grudzinska⁸² examined the EEG's of sixty workers occupationally exposed to not more than 100 ppm of CO. A group of thirty workers not exposed to CO served as a control group. COHb levels in the exposed group averaged 7 percent and for the control group 3 percent. A higher proportion of flat, low-voltage tracings with diminished alpha rhythm was found in the EEG's of the exposed group (p <0.01). These data are difficult to interpret and include subjective assessments of "scanty alpha." The experimental design may not have been double blind. Sluijter described a decrease in the amplitude of alpha activity at COHb levels of 29 percent. In workers chronically exposed, with COHb levels of 10-20 percent, Zorn showed an instability in the fundamental frequencies in the EEG's of the workers. Lindenberg and co-workers, on the other hand, failed to show EEG changes in laboratory animals, except in the presence of high COHb levels that also produced marked cardiovascular alteration and severe brain damage.

Dinman⁸¹ suggested that analysis of spontaneous EEG records does not appear to promise consistent or reproducible results at low levels of CO exposure. However, it was pointed out that the EEG analyses could be improved by use of new computational methods unavailable at the time the reviewed studies were performed.

Another approach for assessing the effect of carbon monoxide on the CNS involves the use of photic stimulation and computer averaging of the resulting visual evoked responses (VER). The report of Xintaras and co-workers⁴¹ suggests that changes of the evoked photic response in the rat following exposure to 100 ppm of CO for two hours were analogous to

those effected by use of drugs known to depress the CNS. The COHb levels were not measured. By contrast, at levels of 22 percent and 37 percent COHb, analysis of human photic responses with similar techniques by Dinman⁸¹ did not reveal changes in VER latency or amplitude. Hosko,⁴² however, reported that COHb saturations greater than 20 percent effected two changes in the human VER. One was an increase in the amplitude of the 2-3-4 wave complex, a change also noted by Xintaras to occur in the rat VER.⁴¹ The second change noted by Hosko in the VER was a CO-induced negative-going shift involving late waves of the VER, which according to Hosko may be associated with general CNS depression. Rhythmic after-potential changes in the VER were also reported by Helmchen and Kunkel⁸⁵ following CO exposure.

Another approach to EEG measurement involves the analysis of a subject's sleep patterns. Sleep patterns are known to be extremely sensitive to changes in CNS conditions. The study of O'Donnell, Chikos, and Theodore⁸⁶ demonstrated changes in sleep patterns during the first three hours of CO exposure. The authors estimate that COHb concentration in the blood was probably not higher than 8 percent and possibly much lower. O'Donnell reported trends in his data that suggest a general reduction in nervous system activation, i.e., less light sleep, more deep sleep, and less mobility between stages of sleep. Johnson ⁸⁷ reported that rats exposed to 100 ppm of carbon monoxide for six hours per day for ten days exhibited a general decrease in the overall amplitude of visual evoked responses recorded during sleep.

That CO may cause extinction of conditioned reflexes was studied by ⁸⁰Shul'ga, who failed to demonstrate an effect on conditioned electrocortical reflexes in two subjects inhaling about 16-17 ppm CO. COHb levels were not reported.

Behavioral Effects of CO

The effects of CO on behavior have been researched by several investigators interested in the effects of CO on the CNS. Specific behavioral tests have involved measures of perception, psychomotor function, and cognitive ability. In the context used here, behavior is defined as the way a subject acts in response to a stimulus.

(a) Animal Studies

Goldberg and Chappell found evidence of a behavioral deficit for two-hour exposures to 200 ppm CO in the bar-pressing performance of trained rats. The behavioral tests utilized in separate controlled studies included the following: (a) the number of continuously reinforced bar presses made in one hour of testing, (b) the number of nonreinforced bar presses made in one hour, (c) the number of responses made in one hour when the probability of reinforcement was 30 percent. The effect of CO was to decrease the number of bar-pressing responses in all three behavioral tests. The maximum decrement was found to be 33 percent for continuously reinforced bar presses. No COHb determinations were obtained for the rats.

Beard and Wertneim³⁹ investigated the behavioral effects on rats of CO concentrations ranging from 100 to 1000 ppm. The behavioral test was a differential reinforcement of low rate of response (DRL) bar-pressing schedule. For this schedule the subject refrained from pressing the bar for a predetermined fixed time (the delay time) in order to receive a food reinforcement. The authors found that when the DRL delay time was 30 seconds, a 100 ppm CO exposure of eleven minutes duration effected a decrease in DRL response rate equal to two standard deviations below the control rate. When the DRL delay time was ten seconds, forty minutes of 100 ppm CO exposure

were required to achieve the same effect. No COHb measurements were obtained for the animals during CO exposure.

Back⁶² initiated in 1967 a series of experiments to ascertain the effects of continuous, long-term, low-level CO exposure on the behavior of adult rhesus monkeys. The study examined the effect of CO on operant avoidance behavior in monkeys utilizing both continuous and discrete avoidance tasks. The avoidance tasks required the subjects to press switches at selected times in order to avoid electrical shock. Continuous CO exposures ranging from 50 ppm for 105 days (mean COHb = 3.7 percent) to 400 ppm for seven days (mean COHb = 30.1 percent) produced no significant effect on avoidance behavior. Under these exposure conditions (i.e., 50 and 400 ppm) humans would be expected to reach COHb levels of 8.4 and 41 percent, respectively.

(b) Human Studies

One of the earliest studies to report a systematic investigation of the effects of CO on human behavior was conducted by Forbes, Dill, and DeSilva.⁸⁹ Eight normal men were given simple performance tests of reaction time, binocular vision, and hand-eye coordination that simulated tasks required of automobile driving. No performance decrements were observed, even though the COHb levels reached 45 percent. A later study concerning the effect of CO on automobile driving behavior was reported by Ray and Rockwell,⁹⁰ who investigated the effect on performance of COHb levels of O, 10, and 20 percent in three subjects. The subjects drove a specially instrumented automobile over a prescribed route while maintained at a constant COHb level. Performance tasks performed while driving included the following: estimation of ten-second time intervals, estimation of half-mile distances, taillight brightness discrimination, vehicle velocity detection, peripheral detection of an oil pressure warning light, and vehicle handling performance.

A COHb level of 10 percent was found to cause a decrease in mean time estimation and increases in distance estimation variance, mean and variance of response time for taillight discrimination, and mean and variance of velocity response times.

Several investigators have reported the effects of CO on brightness discrimination. McFarland and co-workers used a visual discriminometer to test effects of CO on visual thresholds of human male subjects ranging in age from 16 to 25 years. The subjects were required to indicate the lowest intensity of brief red light flashes that could be discerned when presented against an illuminated background. It was found that the visual threshold increased as COHb levels increased; an increase of 12 percent occurring at a COHb level of 5 percent. This finding was repeated by Halperin and co-workers in a subsequent report. The effect of CO on 40 brightness discrimination was also utilized by Horvath, Dahms, and O'Hanlon, who were interested in the effects of CO on vigilance. Ten male subjects were trained to discriminate one-second duration light pulses on the basis of stimulus brightness. The subjects were required to attend to the vigilance task for one hour. It was found that COHb level of 6.6 percent significantly impaired vigilance, causing a maximum decrement in performance of approximately 28 percent.

Schulte investigated in 49 male adults the effect of COHb levels ranging up to 20 percent on a variety of physiological and behavioral tests. The behavioral tests included the following: color stimulus response, letter stimulus, plural noun underlining, static steadiness, arithmetic test, and t-crossing test. No correlation was found between COHb levels and any of the physiological tests or reaction time on the simple choice

response tests. Effects of CO (significant at the 0.001 level) were observed on the following: number of errors in letter response, color response, arithmetic, and t-crossing tests; and increases in the time required to complete the arithmetic, t-crossing, and plural-noun underlining tests. Examination of Schulte's data indicates that these effects occur for COHb values as low as 5 percent.

Several reports exist concerning the effect of CO on timing (temporal) 39 behavior. Beard and Wertheim reported that exposure to CO concentrations between 50 and 250 ppm caused a progressive deterioration in the ability of eighteen subjects (young college students) to discriminate auditory stimuli on the basis of stimulus duration. The behavioral task consisted of presenting to the subject a "standard" tone of one-second duration, followed by a second tone which was varied randomly in eighteen steps between 0.675 and 1.325 seconds. The subject indicated by lever press his judgment of the second tone's duration. An impairment in time discrimination behavior was found for a ninety-minute 50 ppm exposure, which yields an estimated COHb value of 2.5 percent. In a later report Beard and Grandstaff described a study in which subjects were required to estimate in the absence of any external clues a specified length of time, which was either ten or thirty seconds. It was observed that an eighty-minute 50 ppm CO exposure impaired estimation of thirty-second lengths of time. A corresponding effect was not observed if the time interval to be estimated was ten seconds.

In contrast to the findings previously described concerning time discrimination and visual perception, other investigators have been unable to demonstrate comparable behavioral effects of CO. Stewart and Peterson⁹² could demonstrate no effect of an eight-hour 100 ppm CO exposure (which

produced COHb levels of 11-13 percent) on hand and foot reaction time, hand steadiness, coordination, orthorator visual tests, or a time estimationhand reaction time test. The latter test required the subject to estimate the duration of stimuli that persisted for 1, 3, or 5 seconds.

A series of investigations performed at Wright-Patterson Air Force Base, Ohio failed to demonstrate any effects of CO on human behavior under the test conditions. Theodore, O'Donnell, and Back⁶² and Mikulka, O'Donnell, and Heinig⁹³ exposed subjects to 0, 50, and 125 ppm CO for three hours, yielding mean COHb levels of 0.96, 2.98, and 6.64 percent respectively; they found no effect of CO on time estimation of ten-second intervals, performance on a critical instability tracking task, or tasks taken from the Pensacola Ataxia Battery. Three subjects were subsequently exposed to 250 ppm CO for three hours (mean COHb = 12.4 percent) with no effect on performance. O'Donnell, Chikos, and Theodore⁸⁶ found no effects in four subjects at COHb levels of 12.7 percent on critical flicker frequency, mental arithmetic, tracking, time estimation, and time discrimination. The results on tracking are in conflict with those of Trouton and Eysenck⁹⁴ who reported impairment in control precision and multiple limb coordination at COHb levels of approximately 5 percent.

Conflicting results have been reported concerning the effects of CO on critical flicker frequency (CFF) estimation. Lilienthal and Fugitt ³² found CFF impairment at COHb levels of 5-10 percent (at an altitude of 6000 feet). Vollmer, King, and Birren,⁹⁵ Guest, Duncan, and Lawther,⁹⁶ o'Donnell, Chikos, and Theodore⁸⁶ could demonstrate no effect of CO on CFF for COHb levels of 22, 10, and 12.7 percent respectively.

A review of the literature concerning the effects of CO on the CNS and behavior indicates a general lack of agreement concerning results. The behavioral data in particular reveal conflicting results when the data for a given behavioral measure, e.g., time estimation, from different studies 39,62,86,92,93 are compared. A number of possible explanations have been offered in an attempt to account for the variation in results. Possible considerations include the following: the lack of control of the motivational level of the subjects, certain physical and psychological aspects of the exposure test situation, the purity of the CO exposure gas, and the lack of control of experimenter bias (single blind versus double blind). Because of such factors, it is difficult to compare results from different laboratories, since no one study exactly replicates any other in terms of experimental design. It is felt that the findings of McFarland and Halperin concerning visual perception, Horvath concerning vigilance, Schulte 30 concerning cognitive function, Beard 39,91 concerning time discrimination, 90 Ray and Rockwell concerning driving behavior, and Trouton and Eysenck concerning limb coordination provide evidence for the behavioral effects of low-level CO exposures. These studies suggest a COHb level of 5 percent as a reasonable value in terms of providing the worker protection against adverse behavioral effects due to CO exposure.

Epidemiologic Studies

Many epidemiologic studies have been conducted which have related a source of CO with demonstrable biologic effects. A great many of such studies have been concerned with the gross physiologic effects and clinical symptoms associated with acute exposure to high concentrations of CO. The effects on humans of exposure at high concentrations of CO and the manifestation of

clinical symptoms resulting from such exposure episodes are quite predictable. It is generally understood that exposure to a particular concentration of CO will render inactive a portion of the oxygen-carrying capacity of the blood. This combination of CO with hemoglobin to form carboxyhemoglobin (COHb) is the best understood biologic activity of CO. The more subtle biologic effects of CO exposure which occur at lower concentrations have been detailed earlier in this chapter.

Several studies of epidemiologic importance have been conducted on occupationally-exposed individuals and are worthy of mention. In a survey conducted by Cohen and co-workers on border inspectors at the U.S.-Mexican border, they found significant increases in COHb in both smokers and nonsmokers which were correlated with high ambient CO concentrations. Concentrations of CO as high as 170 ppm for an hour were encountered in this study. Although COHb levels were not determined, individuals engaged in light to moderate activity during exposure at this concentration of CO for an hour could be expected to reach a COHb level of approximately 8 percent. In another study Cohen found a significant correlation between higher levels of ambient CO and the case fatality rate of individuals hospitalized with acute myocardial infarction. Ramsey found that parking garage employees experienced COHb levels in excess of 10 percent following a workday in which the CO concentration averaged almost 60 ppm. Ramsey stated that the occupational exposure in this study was more instrumental in producing the elevated COHb levels than was smoking. Breysse and Bovee, measured the COHb of workers exposed to CO emissions from the operation of gasolinepowered fork lift trucks and demonstrated elevated COHb levels in excess of 10 percent. These investigators stated that the cigarette smoking

habits of the workers made a significant contribution to their levels of COHb and that below CO concentrations of 50 ppm the contribution of smoking will be more important than that from the working environment. Likewise, Buchwald¹⁰⁰ has shown that cigarette smoke normally made a more significant contribution to COHb levels of garage and service station operators than did ambient CO concentrations.

101 A long-term mortality study of steelworkers by Lloyd and co-workers determined the specific mortality ratios (SMR) of observed deaths to expected deaths for 53 work areas within the steel industry. The 1953 study involved over 58,000 employees. Four of the 53 work areas (janitors, machine shops, mechanical maintenance assigned, and sheet finishing and shipping) demonstrated a statistically significant excess of deaths over those expected. One area, the carpenter shop, had a statistically significant deficit in mortality. Statistically significant excesses in deaths due to heart disease were found for janitors and mechanical maintenance assigned employees. The SMR for blast furnace workers, for deaths due to all causes, was 92. This indicated a slight deficit in the number of expected deaths. The same trend was found for open-hearth workers (SMR = 95) while coke plant workers had a slight increase (SMR = 104). Neither of the last two trends were statistically significant. All three of these areas are known to produce significant exposure to CO.

Lloyd and co-workers noted that while certain areas (e.g., janitors) had an excess of deaths due to heart disease, other areas had a deficit in this specific cause of mortality.

In attempting to determine why an apparent selection for health should have been more likely among steelworkers dying from heart disease, it was

suggested that such persons may have been more likely to migrate between work areas. Thus, employees exhibiting symptoms of cardiac insufficiency (e.g., shortness of breath) may move to less physically demanding jobs on their own. Similarly, employees with CHD who return to work following an attack are often returned to less physically demanding jobs (e.g., janitors and mechanical maintenance). As a result the investigators indicate that selection for health may have been more important than environmental factors in explaining the excess in mortality from heart disease among janitors and mechanical maintenance personnel. If this suggestion is correct, then the work areas from which those employees dying from heart disease migrated would not be expected to show similar increases in deaths from heart disease. For example, if these employees migrated from the areas aforementioned that produce significant exposure to CO, then those areas would be expected to have a lower SMR for heart disease. Although this rate for those areas was not published in the paper, because of statistical insignificance, the SMR for all deaths in those areas, as mentioned, did not demonstrate trends which were statistically significant.

Based upon this study, then, it would not seem possible either to infer or to deny that occupational exposure to CO at the three work places in question resulted in an excess of deaths due to heart disease.

More information is needed concerning daily exposure of workers, engaged in various levels of activity, to specific sources of CO within their working environment and the correlation of such information to both smoking habits and to nonoccupational exposure.

Regardless of CO source, however, the rate of CO excretion from the blood is dependent upon the concentration in the ambient air, and for smokers with elevated COHb levels who are occupationally exposed to CO, their excretion of CO will be proportionally delayed.

Because the recommended standard for occupational exposure to CO is designed to protect employees with CHD, it is necessary to characterize the extent of this disease among the general worker population.

Friedberg¹⁰² has defined CHD to represent clinical heart disease due to lesions of the coronary arteries. However, the term, CHD, is generally used to refer to the process of atherosclerosis of the coronary arteries leading to disturbances in the myocardial blood supply. It is in this latter context that the term applies in the criteria document.

It is an established fact that each year more persons in the U.S. die from CHD than from any other disease.¹⁰³ Coronary atherosclerotic heart disease is the most common form of cardiac disease in adults in the U.S.¹⁰⁴ During the Korean War autopsies performed on young soldiers, with an average age of twenty-two years, revealed that 77.3 percent had gross pathologic evidence of CHD.¹⁰⁴ A study¹⁰⁵ of autopsies in a stabilized population of 30,000 revealed that CHD was the cause of death in 40 percent of the males.

Friedberg states: 102

"The diagnosis of coronary (atherosclerotic) heart disease refers to clinical manifestations and not to the mere presence of atherosclerotic lesions. Extensive pathologic lesions may be present but cannot be diagnosed unless they produce overt clinical manifestations or are revealed by coronary angiography." In most cases the first clinical manifestation of CHD is expressed¹⁰⁶ either as the angina pectoris syndrome or as frank myocardial infarction.

According to the Framingham, Massachusetts, study conducted by the USPHS, CHD was first manifested in one-sixth of the cases of CHD as sudden death.

Brest¹⁰⁶ states that it has been estimated that in the U.S., more than 500,000 persons sustain silent infarctions each year. He further cites various prospective epidemiologic studies¹⁰⁶ which indicate that, annually, approximately 1 percent of all white middle-aged males in the U.S. will develop clinical CHD. He further stated that after age twenty it would be virtually impossible to delineate a control group "without atherosclerosis."

It is clearly evident from these statements that the general worker population in the U.S. is composed of a very significant number of persons with CHD. Since the detection of such persons in the absence of overt clinical symptoms is virtually impossible, it is necessary to assume that the average worker has asymptomatic CHD; especially when his first clinical symptom may be sudden death.

Correlation of Exposure and Effect

The signs and symptoms of acute CO poisoning are well known and easily recognized. These may include headache, nausea, vomiting, dizziness, drowsiness, and collapse. The gross clinical manifestations of CO poisoning at various levels of blood saturation have been well documented. The correlation of ambient CO concentrations with bodily uptake has been continuously studied since Douglas and the Haldanes first formulated the basic laws concerning the combination of CO and oxygen with hemoglobin. Although the correlation between exposure and effect is understood, at least in terms of symptomatology, in the case of acute exposure to high concentrations of CO, exposures to low concentrations of this gas, at and below 100 ppm, have often produced conflicting results.

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From the studies presented earlier in this chapter it is obvious that disagreement exists concerning the effects of CO on several biologic parameters as well as concerning the exposure conditions during which specific biologic aberrations occur. Often different investigators in attempting to repeat the work of others have failed to produce the same experimental results under supposedly identical exposure conditions. This has been true for epidemiologic, neurophysiologic, 41,44,59 cardiophysiologic 24,44,59,63,78 and behavioral studies. On such occasions it is necessary to examine very carefully the circumstances surrounding a particular set of experimental conditions. Thus, while several investigations have rendered conflicting data concerning alterations of the myocardium during exposure of animals to low concentrations of CO (50 ppm and 100 ppm), Ayres has shown that the dog (which was used in several of the above studies) may be less susceptible to CO than man. Hence, extreme care must be used in the extrapolation to man of any alterations observed in the canine myocardium during exposure to 50 ppm of CO. An eight-hour exposure to 50 ppm of CO would produce approximately 7.5 percent COHb in an individual engaged in light activity. Earlier work by Ayres in which he discovered that lactate was produced in the myocardium of patients with coronary artery disease during acute exposure to concentrations of CO sufficient to produce a COHb content of less than 9 percent provides metabolic evidence of myocardial hypoxia occurring under this regime. His finding that in patients with coronary artery disease the coronary blood flow did not increase at this level of COHb saturation, although it did increase in controls, serves to further underscore the possible consequences for an individual with coronary heart disease (CHD) who is carrying less than 9 percent COHb. Furthermore, it

must be emphasized that these coronary patients were at rest and were not subjected to exercise. The consequences of this additional stress were documented earlier in the study by Knelson.⁷⁸ His discovery that the time to onset of pain was diminished in cigarette smokers with angina pectoris during exercise immediately following exposure to 50 ppm of CO for four hours (average COHb of 3.0 percent), provides considerable evidence that workers with CHD, and particularly those with CHD who smoke, should not be exposed to concentrations of CO which will produce a level of COHb in excess of 5 percent.

Similarly, the effects of CO on behavior are not in complete agreement. As mentioned previously, several mechanisms have been suggested to possibly account for the differing results. These suggestions can be summarized by noting that no one study has completely replicated the experimental design of any previous study that indicated a behavioral impairment due to CO exposure. For this reason the reports by McFarland,²⁹ Halperin,³⁵Horvath,⁴⁰ Schulte,³⁰ Beard,^{39,91} Ray,⁹⁰ and Trouton⁹⁴ concerning the effect of CO on behaviors ranging from vigilance to cognitive function are sufficient to suggest possible safety hazards for the worker exposed to CO. A review of the above studies indicates that a value of 5 percent COHb should not be exceeded if these behavioral effects are to be avoided.

IV. ENVIRONMENTAL DATA

Information concerning environmental exposure to CO has been principally documented in the open literature concerned with air pollution. $^{2-5}$ Although CO has several valuable uses in industry (e.g., as a reducing agent), its presence in the industrial setting represents a source of pollution. In the first part of Chapter III it is pointed out that with the exception of carbon dioxide (CO₂), CO represents the largest single source of air pollution, and in Table II a summary of environmental pollution sources within industry is presented.

Because the emission of CO is on so large a scale it becomes difficult to single out, identify and rank individual sources in order of importance as concerns occupational exposure. Indeed, as emphasized earlier in this report, the smoking habits of the worker have a tremendous bearing on his actual daily exposure to CO. The CO pollution from traffic to and from the place of employment likewise will affect his total daily exposure. Several studies concerning occupational exposure to CO are presented below.

In an early study (1928) Broomfield ¹⁰⁸ surveyed automobile repair shops in fourteen cities in the U.S. for CO concentrations. The average CO concentration of the twenty-seven facilities visited in the study was 210 ppm. Approximately 60 percent of the 102 samples at such facilities had concentrations of CO in excess of 100 ppm and 18 percent contained over 400 ppm. A nonsmoking individual engaged in light work (alveolar ventilation rate of 18 liters/min) and continuously exposed to these concentrations for four hours would be expected to have COHb levels approximately 23 percent (210 ppm), 13 percent (100 ppm) and 38 percent, respectively.

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A survey by Buchwald ¹⁰⁰ of COHb levels in Canadian garage and service station operators demonstrated, after six hours of exposure, that 60 percent of the smokers had COHb levels in excess of 5 percent as compared to less than 30 percent of the nonsmokers. In a nonexposed control group 50 percent of the smokers had COHb over 5 percent while in nonexposed controls there was a COHb range of 0-5 percent with a mean of 1.4 percent. Buchwald extrapolated the COHb levels in the smokers in both groups (exposed and unexposed) to relate to six-hour CO exposures of 80 ppm in the occupationally exposed group and 55 ppm in the nonexposed group. He suggested that the data in the study indicated cigarette smoking to be of greater significance to elevated COHb levels than automobile emissions.

A survey of employees in a parking garage prompted Ramsey ⁹⁸ to conclude that occupational exposure to CO was more instrumental than was smoking in the study in producing COHb levels. Ramsey found that three nonsmoking employees exposed to an average of 84 ppm of CO had an average end-of-day COHb level of greater than 11 percent. In the main portion of the study, nonsmoking exposed workers had an end of day mean COHb concentration of 7.3 percent compared to 9.3 percent for smokers. In a non-occupationally exposed control group, nonsmokers had end-of-day average COHb levels of 0.81 percent and smokers in this group registered 3.9 percent.

Breysse and Bovee ⁹⁹ conducted a survey of stevedores, gasoline-powered fork lift truck drivers and winch operators to determine their occupational exposure to CO. Using expired air breath samples the investigators found 5.7 percent of the approximately 700 COHb determinations were in excess of 10 percent and, after the workday, 7 percent of the stevedores and 18 percent of the lift truck operators had over 10 percent COHb. The obvious contribution of smoking upon the results of the study was demonstrated on "before

IV-2

work" COHb levels. Thirty percent of the smokers, but only 2 percent of the nonsmokers, exhibited COHb levels in excess of 5 percent.

Several reports¹⁰⁹ have concerned the exposure of inspectors to CO at U.S.-Mexican border-crossing stations. Although the hourly average CO concentrations fluctuated greatly in the studies (from 5 to 170 ppm in one study),⁹⁷ in the study by Cohen ⁹⁷ an hourly average CO concentration of 114 ppm was found during the evening shift. During this shift nonsmokers had an average 1.4 percent COHb before duty and 4.0 after duty while smokers had an average 3.8 percent COHb before duty and 7.6 afterward.

Sievers, Edwards and Murray¹¹⁰ in 1942 published the results of an in-depth medical study of men exposed to measured amounts of CO as workers in the Holland Tunnel for thirteen years. Although many parameters were measured, including examination for cardiac disease and neurologic disorders, it was concluded that the employees were in exceptionally good health and that there were no indications that CO or any other occupational exposure had influenced their state of health. The average CO concentration, which rarely exceeded 200 ppm, was 70 ppm. However, these employees were only exposed in the tunnel for two hours at a time, alternating two hours on an outside plaza where the CO concentration was "negligible." A nonsmoking individual engaged in light activity (alveolar ventilation rate of 18 liters/minute) could be expected to have a COHb level of approximately 6 percent at the termination of a continuous two-hour exposure period.

In a 1929 study of the COHb content of steel mill employees, Farmer and Crittenden¹¹¹ found an average 6 to 7 percent COHb saturation following an eight-hour workday. The COHb level at the beginning of the work shift, without regard to smoking habits, was approximately 2 percent and four out of fourteen employees had COHb levels greater than 10 percent.

IV-3

In a study on the COHb levels in British steelworkers, Jones and Walters ¹¹² found a 4.9 percent end-of-shift COHb saturation in nonsmoking blast furnace workers compared to 1.5 percent saturation in nonsmoking, unexposed controls. In heavy cigarette smokers the levels were 7.4 percent for blast furnace workers and 4.0 percent for controls. The range in values for the controls was 0.8 to 6.6 percent and in the blast furnace workers was 1.3-14.9 percent.

These studies indicate that while smokers definitely have higher COHb levels at the end of a workday, a significant portion of this is directly associated with their smoking habits. The studies also demonstrate that a significant portion of the work force is occupationally exposed to concentrations of CO sufficient to produce COHb levels of 5 percent and above in nonsmokers.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The former maximum allowable concentration (MAC) of 100 ppm for CO recommended by the American Standards Association (now American National Standards Institute) in 1945, was based principally on the work of Henderson and co-workers ¹¹³ published in 1921 and the often quoted work by Henderson and Haggard ¹¹⁴ published in 1943. Henderson and co-workers stated that when the concentration (ppm) x time (hrs) = 300, there was no perceptible effect; at 600, there was just a perceptible effect; at 900, there was headache and nausea; and at 1500 or more, the condition was dangerous to life. Stated differently, at 100 ppm a three-hour exposure produced no effect, but a six-hour exposure produced a perceptible effect and a nine-hour exposure caused headache and nausea.

In 1929 Sayers and co-workers ¹¹⁵ reported that in an experiment with six men who were exposed four to seven hours daily over a period of 68 days to 200 ppm CO, some of the more susceptible developed slight, but not discomforting symptoms after only two hours of exposure. After exposures for five to six hours COHb levels of 25 percent were reached.

Sievers and co-workers¹¹⁰ reported in 1942 that a group of 156 tunnel traffic officers exposed over a thirteen-year period to an average concentration of 70 ppm CO did not reveal any evidence of injury to health attributable to the exposure. It should be pointed out that these men worked two hours inside the tunnel and two hours outside for eight-hour shifts. The average CO concentration in the tunnel was 70 ppm and the average COHb was 5 percent. None of the usual symptoms (e.g., headache, nausea, anorexia, etc.) were observed.

It should be emphasized that these early and many other later investigators have stressed the fact that the effect of CO on man is enhanced by many environmental factors. These have included rate of exercise, high environmental temperatures, altitudes above 2000 feet, and simultaneous exposure to narcotic solvents.

The American Conference of Governmental Industrial Hygienists' (ACGIH) Committee on Threshold Limit Values recommended 100 ppm for CO in 1945, and in 1965 the conference recommended that the limit be reduced to 50 ppm, a value that was officially adopted by ACGIH in 1967. In recommending the lower value¹¹⁶ the Committee stated: "...for conditions of heavy labor, high temperatures of work 5000-8000 feet above sea level, the threshold limit value should be appropriately reduced to 25 ppm. No further benefit under any circumstances could be expected by reducing the level below 5 to 10 ppm since at this concentration one is practically in equilibrium with the normal blood level of around 1 percent COHb. The recommended TLV for CO of 50 ppm is thus based on an air concentration that should not result in blood CO levels above 10 percent, a level that is just below the development of signs of borderline effects." Since the "borderline effects" are not elaborated it is presumed that they are the clinical symptoms mentioned in the documentation (i.e., headache, fatigue and dizziness).

Mention should be made that the current MAC for CO in the U.S.S.R. and in Czechoslovakia is 18 ppm.¹¹⁷ Furthermore, the U.S. Navy established a limit for the average concentration of a continuous exposure to CO for prolonged submarine voyages at 25 ppm,¹¹⁸ and the National Aeronautics and Space Administration considers 15 ppm CO to be the maximum average concentration for space flights.¹¹⁹ This latter low level was selected because

of possible impairment of certain behaviors required of astronauts, a condition which could affect their performance during extended space flights.

The American Industrial Hygiene Association has recommended a community air quality guide for CO exposure of 20 ppm as an eight-hour average, which is stated to be equivalent to 3 percent COHb.¹²⁰ In addition a limit of 70 ppm has been recommended for a one-hour period, which is also stated to be equivalent to 3 percent COHb. The recommended limits are based on levels of CO concentration which will not exceed one-half of 5 to 6 percent COHb prior to tobacco consumption. It was considered that the recommended CO concentration would permit susceptibles with heart disease to obtain a timebased margin of safety prior to reaching the 5 to 10 percent COHb range.

From the viewpoint of health, limiting occupational exposure to CO to a TWA concentration which will produce no greater than 5 percent COHb may not provide a margin of safety for the employee with clinical symptoms of CHD, since Knelson has demonstrated that deleterious myocardial effects can occur at 3 to 5 percent COHb in patients with angina pectoris. However, limiting CO exposure to this level should protect the individual with asymptomatic CHD from developing clinical symptoms.

From the viewpoint of safety, limiting CO exposure to a concentration producing 5 percent COHb or less would appear to provide adequate protection for the worker against impairments in vigilance, coordination, timing behavior, visual perception, and certain cognitive functions.

Although the conditions by which a level of 5 percent COHb is reached in different individuals vary, dependent upon such parameters as activity, altitude, length of exposure, and CO concentration, as well as individual differences in the CO uptake, the nonsmoker who is engaged in sedentary

activity will approach this level in eight hours if continuously exposed to 35 ppm of CO.

Basis for Recommended Standard

The recommended standard is based upon the cardiovascular and behavioral evidence presented in Chapter III of this report which generally documents the initiation or enhancement of deleterious myocardial alterations in individuals with CHD who are exposed to CO concentrations sufficient to produce a COHb level greater than 5 percent. The work of Ayres and co-workers 49,63 demonstrating restricted coronary blood flow and myocardial lactate production under such circumstances and the recent studies of Knelson $\frac{18}{100}$ concerning CO exposure and exercise of patients with angina pectoris are germane to the recommended standard. Both investigations clearly demonstrate the potential hazards faced by workers with CHD who are exposed to CO of sufficient concentration to produce a COHb level in excess of 5 percent. The synergistic relationship imposed by chronic cigarette smoking and concomitant exposure to CO upon the enhancement of such detrimental myocardial alterations has been documented in a 1971 report to the Surgeon General on The Health Consequences of Smoking. Based on the available evidence, the imposition of a COHb level of 5 percent on an active worker with clinical or asymptomatic CHD is unwarranted.

The extrapolation of this level of COHb (5 percent) in an exposed worker to a meaningful ambient CO concentration in the workplace imposes certain difficulties. Primarily, air sampling methodology must rely on statistical techniques to achieve an eight-hour, time-weighted, integrated analysis. Secondly, the rate of activity of the worker will increase the exposure to CO by decreasing the length of time to COHb equilibrium and by

maintaining a higher COHb level in the active worker than in the sedentary worker who has not reached equilibrium. The significance of the first difficulty can be practically resolved by an air sampling protocol which will insure that sufficient quantities of such samples are taken to provide a reliable, statistical estimation of the proposed eight-hour standard. The activity factor can be practically minimized by the use of the Coburn¹²¹ equation which takes into consideration, among other parameters, the activity of the worker in terms of alveolar ventilation rate and pulmonary diffusion rate.

The recommended TWA standard of 35 ppm CO is based on a COHb level of 5 percent, which is the amount of COHb that an employee engaged in sedentary activity would be expected to approach in eight hours during continuous exposure. The ceiling concentration of 200 ppm is based upon the restriction of employee exposure to CO to transient excursions above 35 ppm which would not be expected to significantly alter his level of COHb.

The recommended standard does not take into consideration the smoking habits of the worker since the level of COHb in chronic cigarette smokers has generally been found to be in the 4 to 5 percent range prior to CO exposure.

The recommended standard is based on the utilization of the Coburn 121 to predict the mean COHb level of nonsmoking employees exposed to a known TWA concentration of CO for an eight-hour workday. The applicability of the equation for this purpose has been validated by a study of Peterson and Stewart 122 in which the COHb levels of sedentary young males exposed to known TWA concentrations of CO for known periods of time were accurately predicted by the equation.

The investigators commented on the results of the study by saying:

"The series of experiments just described is unique in that the nature of the exposures is similar to those most commonly encountered in home, industrial, and urban environments."

While the values assigned to several of the variables in the equation by the investiagtors were for sedentary individuals (e.g., alveolar ventilation rate of 6 liters/minute; CO pulmonary diffusion rate of 30 milliliters/minute/ mm Hg), it is recognized that the range of activities of employees in the workplace may vary considerably. Under such circumstances, however, when the recommended occupational exposure standard is based on the prediction of a COHb level by the use of a theoretical equation, it is necessary that the prior applicability of the equation be demonstrated.

For this reason, the values assigned by the investigators to the variables for alveolar ventilation rate (6 liters/minute) and CO pulmonary diffusion rate (30 milliliters/minute/mm Hg) were retained in determining the recommended standard.

The Coburn equation has recently been programmed by Roslinski* and the compiled data is presented in Appendix IV. It will be noted that the two variables relating activity to rate of CO uptake [i.e., alveolar ventilation rate (V_A) and CO pulmonary diffusion rate (D_L)] are instrumental in determining the COHb level at the termination of a particular period of exposure. For example, an eight-hour TWA exposure to CO at the recommended exposure standard of 35 ppm will produce 4.89 percent COHb when $V_A = 6$ liters/minute and $D_L = 30$ milliliters/minute/mm Hg. However, when $V_A = 30$ liters/minute and $D_L = 60$ milliliters/minute/mm Hg. It is incumbent upon the employer

^{*}Advisory Center for Toxicology National Academy of Sciences

Washington, D.C.

to recognize the effect that the level of activity has upon the uptake of CO and to judiciously evaluate the exposure of his employees and limit their activity accordingly. The data in Appendix IV have been included specifically for this purpose. In addition, the employer must give special consideration to limiting the activity of employees exposed to CO at high altitudes in order to compensate for the dual loss in oxygen-carrying capacity of the blood.

VI. COMPATIBILITY WITH AIR QUALITY STANDARDS

The Environmental Protection Agency (EPA), under provisions of the Clean Air Act (PL 91-604), promulgated national primary and secondary air quality standards on April 30, 1971. The primary and secondary standards for CO are:

"(a) 10 milligrams per cubic meter (9 ppm)--maximum eight-hour concentration not to be exceeded more than once per year.

(b) 40 milligrams per cubic meter (35 ppm)---maximum one-hour concentration not to be exceeded more than once per year." The EPA standard was based on criteria presented in "Air Quality for Carbon Monoxide" (35 F.R. 4768). The specific data upon which the EPA based the CO standard was primarily the work of Beard and Wertheim³⁹ who presented evidence that low levels of carboxyhemoglobin in human blood may be associated with impairment of ability to discriminate time intervals.

In promulgating this standard the Administrator of EPA made the following statement ¹²³ concerning comments raised about the evidence used to support the proposed standard:

"In the comments, serious questions were raised about the soundness of this evidence. Extensive consideration was given to this matter. The conclusions reached were that the evidence regarding impaired time-interval discrimination had not been refuted and that a less restrictive national standard for CO would therefore not provide the margin of safety which may be needed to protect the health of persons especially sensitive to the effects of elevated carboxyhemoglobin levels. The only change made in the national standards for CO was a modification of the 1-hour value. The revised standard affords protection from the same low levels of blood carboxyhemoglobin as a result of short-term exposure. The national standards for carbon monoxide, as set forth below, are intended to protect against the occurrence of carboxyhemoglobin levels above 2 percent. It is the Administrator's judgment that attainment of the national standards for carbon monoxide will provide an adequate safety margin for protection of public health and will protect against known and anticipated adverse effects on public welfare."

The air quality standard is designed to protect the population-at-large and takes into consideration 24-hour per day exposure of the very young, the very old, and the seriously ill. The evidence presented in this (NIOSH) criteria documentation supports the concept of the necessity of providing protection for that portion of the general worker population with coronary heart disease (CHD), who are especially sensitive to elevated levels of COHb.

Although the Administrator of EPA has stated above that the evidence concerning the impairment of time-interval discrimination at low levels of COHb, presumably as low as 2 percent, has not been refuted, neither has such evidence been confirmed.

- 1. Hosey, A.D. Priorities in Developing Criteria for "Breathing Air" Standards, J. Occup. Med., Vol. 12, pp. 43-46, 1970.
- Biological Effects of Carbon Monoxide. R.F. Coburn, Ed. Ann. N.Y. Acad. Sci., Vol. 174, 1970.
- Carbon Monoxide A Bibliography with Abstracts. Compiled by A.G. Cooper, U.S.P.H.S. Pub. No. 1503, 1966.
- 4. Air Quality Criteria for Carbon Monoxide. U.S. Dept. of HEW, NAPCA Pub. No. AP-62, Washington, D.C., 1970.
- 5. DuBois, A.B., Ed. Effects of Chronic Exposure to Low Levels of Carbon Monoxide on Human Health, Behavior, and Performance. National Academy of Sciences, National Academy of Engineering, Washington, D.C., 1969.
- Rose, E.F. Carbon Monoxide Intoxication and Poisoning, J. Iowa Med. Soc., Vol. 49, pp. 909-917, 1969.
- 7. Best, C.H. and N.B. Taylor. The Physiological Basis of Medical Practice. Eighth Edition, The Williams & Wilkins Company, 1966.
- Haldane, J. The Action of Carbonic Oxide on Man, J. Physiol. (London), Vol. 18, pp. 430-462, 1895.
- Douglas, C.G., J.S. Haldane, and J.B.S. Haldane. The Laws of Combination of Hemoglobin with Carbon Monoxide and Oxygen, J. Physiol., Vol. 44, pp. 275-304, 1912.
- Sendroy, Jr., J., S.H. Liu, and D.D. Von Slyke. The Gasometric Estimation of the Relative Affinity Constant for Carbon Monoxide in Whole Blood at 38°C., Am. J. Physiol., Vol. 90, pp. 511-512, 1929.
- Killick, E.M. The Acclimatization of the Human Subject to Atmospheres Containing Low Concentrations of Carbon Monoxide, J. Physiol., Vol. 87, pp. 41-55, 1936.
- Killick, E.M. The Nature of the Acclimatization Occurring During Repeated Exposure of the Human Subject to Atmospheres Containing Low Concentrations of Carbon Monoxide, J. Physiol., Vol. 107, pp. 27-44, 1948.
- Rodkey, F.L., J.D. O'Neal, and H.A. Collison. Oxygen and Carbon Monoxide Equilibria of Human Adult Hemoglobin at Atmospheric and Elevated Pressures, Blood, Vol. 33, pp. 57-65, 1969.

- Roughton, F.J.W. The Equilibrium Between Carbon Monoxide and Sheep Hemoglobin at Very High Percentage Saturations, J. Physiol., Vol. 126, pp. 359-383, 1954.
- 15. Gibson, Q.H. and F.J.W. Roughton. The Kinetics of Dissociation of the First Oxygen Molecule from Fully Saturated Oxygen Hemoglobin in Sheep Blood Solutions, Proc. Royal Soc., Vol. 143, pp. 310-334, 1955.
- Bartlett, Jr., D. Pathophysiology of Exposure to Low Concentrations of Carbon Monoxide, Arch. Environ. Health, Vol. 16, pp. 719-727, 1968.
- 17. Adair, G.S. The Hemoglobin System: VI. The Oxygen Dissociation Curve of Hemoglobin, J. Biol. Chem., Vol. 63, pp. 529-545, 1925.
- Allen, T.H. and W.S. Root. Partition of Carbon Monoxide and Oxygen Between Air and Whole Blood of Rats, Dogs and Men as Affected by Plasma pH, J. Appl. Physiol., Vol. 10, pp. 186-190, 1957.
- 19. Lilienthal, Jr., J.L. Carbon Monoxide, Pharmacol. Rev., Vol. 2, pp. 324-354, 1950.
- 20. Killick, E.M. Carbon Monoxide Anoxemia, Physiol. Rev., Vol. 20, pp. 313-344, 1940.
- 21. Dinman, B.D. Pathophysiologic Determinants of Community Air Quality Standards for Carbon Monoxide, J. Occup. Med., Vol. 10, pp. 446-456, 1968.
- Hirata, M., A. Hiok, and K. Hashimoto. Distribution of Death Rate in Acute Carbon Monoxide Intoxication in Mice, Tohoku J. Exp. Med., Vol. 97, pp. 67-73, 1969.
- Ramsey, J.M. The Time-Course of Hematological Response to Experimental Exposures of Carbon Monoxide, Arch. Environ. Health, Vol. 18, pp. 323-329, 1969.
- 24. Musselman, N.P., W.A. Groff, P.P. Yevich, F.T. Wilinski, M.H. Weeks, and F.W. Oberst. Continuous Exposure of Laboratory Animals to a Low Concentration of Carbon Monoxide, Aerospace Med., Vol. 30, pp. 524-529, 1959.
- 25. Grut, A. Chronic Carbon Monoxide Poisoning: A Study in Occupational Medicine. Munksgaard, Copenhagen, 1949.
- 26. Rossiter, F.S. Carbon Monoxide, Ind. Med., Vol. 11, pp. 586-589, 1942.

- 27. Zoru, O. and P.D. Druger. The Problem of Carbon Monoxide Poisoning, Ind. Med. Surgy., Vol. 29, pp. 580-581, 1960.
- Suzuki, T. Effects of Carbon Monoxide Inhalation on the Fine Structure of the Rat Heart Muscle, Tohoka J. Exp. Med., Vol. 97, pp. 197-211, 1969.
- McFarland, R.A., F.J.W. Roughton, M.H. Halperin, and J.I. Niven. Effects of CO and Altitude on Visual Thresholds, J. Aviation Med., Vol. 15, pp. 381-394, 1944.
- 30. Schulte, J.H. Effects of Mild Carbon Monoxide Intoxication, Arch. Environ. Health, Vol. 7, pp. 524-530, 1963.
- 31. Niden, A.H. and H. Schultz. The Ultrastructural Effects of Carbon Monoxide Inhalation on the Rat Lung, Virchows Arch. Path. Anat., Vol. 339, pp. 283-292, 1965.
- 32. Lilienthal, J.L. and C.H. Fugitt. The Effect of Low Concentrations of Carboxyhemoglobin on the Altitude Tolerance of Man, Am. J. Physiol., Vol. <u>145</u>, pp. 359-364, 1946.
- 33. Mazaleski, S.C., R.L. Coleman, R.C. Duncan, and C.A. Nau. Subcellular Trace <u>Metal Alterations</u> in Rats Exposed to 50 PPM of Carbon Monoxide, Am. Ind. Hyg. Assoc. J., Vol. 31, pp. 183-188, 1970.
- Pecora, L. Ferrous Therapy in Acute Carbon Monoxide Poisoning, Rass. Med. Ind., Vol. 33, pp. 352-353, 1964.
- Halperin, M.H., R.A. McFarland, J.I. Niven, and F.J.W. Roughton. The Time-Course of Effects of Carbon Monoxide on Visual Thresholds, J. Physiol., Vol. 146, pp. 583-593, 1959.
- Fati, S., R. Mole, and L. Pecora. Blood Enzyme Change During Carbon Monoxide Exposure, Folia Med., Vol. 43, pp. 1092-1097, 1960.
- 37. Coscia, G.C., G. Perrelli, P.C. Gaido, and F. Capellaro. The Behavior of Glutathione, Stable Glutathione, and Glucose-6-Phosphate-Dehydrogenase in Subjects Exposed to Chronic Inhalation of Carbon Monoxide, Rass. Med. Ind., Vol. 33, pp. 446-451, 1964.
- Rozera, G. and S. Fati. Acid and Alkaline Intra-Erythrocytic and Serous Phosphatases in Chronic Carbon Monoxide Poisoning, Folia Med., Vol. 42, pp. 1204-1214, 1959.
- 39. Beard, R.R. and G. Wertheim. Behavioral Impairment Associated with Small Doses of Carbon Monoxide, Am. J. Pub. Health, Vol. 57, pp. 2012-2022, 1967.

- 40. Horvath, S.M., T.E. Dahms, and J.F. O'Hanlon. Carbon Monoxide and Human Vigilance. Arch. Environ. Health, Vol. 23, pp. 343-347, 1972.
- 41. Xintaras, C., B.L. Johnson, C.E. Ulrich, R.E. Terrill, and M.F. Sobeki. Application of the Evoked Response Technique in Air Pollution Toxicology, Toxicol. Appl. Pharmacol., Vol. 8, pp. 77-87, 1966.
 - 42. Hosko, M.J. The Effect of Carbon Monoxide on the Visual Evoked Response in Man, Arch. Environ. Health, Vol. 21, pp. 174-180, 1970.
 - Bour, H. and I.M. Ledingham. Progress in Brain Research: Carbon Monoxide Poisoning. Elsevier Publishing Co., Amsterdam, Vol. 24, pp. 1-75, 1967.
 - Lewey, F.H. and D.L. Drabkin. Experimental Chronic Carbon Monoxide Poisoning in Dogs, Am. J. Med. Sci., Vol. 208, pp. 502-511, 1944.
 - Wyman, J. Facilitated Diffusion and the Possible Role of Myoglobin as a Transport Mechanism, J. Biol. Chem., Vol. 241, pp. 115-121, 1966.
 - 46. Wittenberg, J.B. The Molecular Mechanism of Hemoglobin-Facilitated Oxygen Diffusion, J. Biol. Chem., Vol. 241, pp. 104-114, 1966.
 - Reynafarje, B. Myoglobin Content and Enzymatic Activity of Muscle and Altitude Adaptation, J. Appl. Physiol., Vol. 17, pp. 301-305, 1962.
 - Rossi-Fanelli, A. and E. Antonini. Studies the Oxygen and Carbon-Monoxide Equilibrium of Human Myoglobin, Arch. Biochem. Biophys., Vol. 77, pp. 478-492, 1958.
 - 49. Ayres, S.M., H.S. Mueller, J.J. Gregory, S. Gianelli, Jr., and J.L. Penny. Systemic and Myocardial Hemodynamic Responses to Relatively Small Concentrations of Carboxyhemoglobin (COHb), Arch. Environ. Health, Vol. 18, pp. 699-704, 1969.
 - 50. Wittenberg, J.B. Myoglobin-Facilitated Diffusion of Oxygen, J. Gen. Physiol., Vol. 49, pp. 57-74, 1965.
 - 51. Lundwig, G.D. and W.S. Blakemore. Production of Carbon Monoxide by Hemin Oxidation, J. Clin. Invest., Vol. 36, p. 912, 1957.
 - 52. Coburn, R.F. Endogenous Carbon Monoxide Production and Body Carbon Monoxide Stores, Acta Med. Scandinav. (Suppl. 472), pp. 269-282, 1967.

- 53. Luomanmaki, K. Studies on the Metabolism of Carbon Monoxide, Ann. Med. Exp. Biol. Fennia (Suppl. 2), Vol. 44, pp. 1-55, 1966.
- Beck, H.G. and G.M. Suter. Role of Carbon Monoxide in the Causation of Myocardial Disease, J. Am. Med. Assoc., Vol. 110, pp. 1982-1988, 1938.
- 55. White, M.B. and M.B. Fredericks. Myocardial Necrosis: Diagnosis by Lactate Dehydrogenase Isoenzymes, J. Florida Med. Assoc., Vol. 52, pp. 881-884, 1965.
- 56. Goldsmith, J.P. Carbon Monoxide and Human Health, Science, Vol. 162, pp. 1352-1353, 1968.
- 57. Kjeldsen K. Smoking and Atherosclerosis. Investigations on the Significance of the Carbon Monoxide Content in Tobacco Smoke in Atherogenesis. Copenhagen, Munksgaard, 1969.
- 58. Adams, J.D., H.H. Erickson, and H.L. Stone. Coronary Hemodynamics and Myocardial Metabolic Response to Low Levels of Carboxyhemoglobin in the Conscious Dog, Am. J. Vet. Res., In Press.
- 59. Lindenberg, R., D. Levy, T. Preziosi, and M. Christensen. An Experimental Investigation in Animals of the Functional and Morphological Changes from Single and Repeated Exposures to Carbou Monoxide, Paper Presented at Meeting of the AIHA, Washington, D.C., 1962.
- Ehrich, W.E., A. Bellet, and F.H. Lewey. Cardiac Changes from Carbon Monoxide Poisoning, Am. J. Med. Sci., Vol. 208, pp. 511-523, 1944.
- 61. Jones, R.A., J.A. Strickland, J.A. Stunkard, and J. Siegel. Effects of Experimental Animals of Long-Term Inhalation Exposure to Carbon Monoxide, Toxicol. Appl. Pharmacol., Vol. 19, pp. 46-53, 1971.
- 62. Theodore, J., R.D. O'Donnell, and K.C. Back. Toxicological Evaluation of Carbon Monoxide in Humans and Other Mammalian Species, J. Occup. Med., Vol. 13, pp. 242-255, 1971.
- Ayres, S.M., S. Giannelli, and H. Mueller. Effects of Low Concentrations of Carbon Monoxide, Ann. N.Y. Acad. Sci., Vol. 174, pp. 268-293, 1970.
- 64. Jaffe, N. Role of Carbon Monoxide in Coronary Disorders, New Eng. J. Med., Vol. 278, p. 111, 1968.

site DV RI Coleman and CH Lawrence My

- 65. Lassiter, D.V., R.L. Coleman, and C.H. Lawrence. Myocardial Damage Resulting From CO Exposure as Detected by Changes in Plasma Lactic Dehydrogenase Isoenzymes, Paper Presented at Am. Ind. Hyg. Conference, San Francisco, Calif., May 17, 1972.
- 66. <u>The Health Consequences of Smoking</u>. A Report to the Surgeon General: 1971. DHEW Pub. No. (HSM) 71-7513, 1971.
- 67. Chevalier, R.B., R.A. Krumholz, and J.C. Ross. Reaction of Non-Smokers to Carbon Monoxide Inhalation. Cardiopulmonary Responses at Rest and During Exercise, J. Am. Med. Assoc., Vol. 198, pp. 1061-1064, 1966.
- 68. Judd, H.J. Levels of Carbon Monoxide Recorded on Aircraft Flight Decks, Aerospace Med., Vol. 42, pp. 344-348, 1971.
- Osborne, J.S., S. Adamek, and M.E. Hobbs. Some Components of the Gas Phase of Cigarette Smoke, Anal. Chem., Vol. 28, pp. 211-215, 1957.
- Goldsmith, J.R., J. Terzaghi, and J.D. Hackney. Evaluation of Fluctuating Carbon Monoxide Poisoning, Arch. Environ. Health, Vol. 7, pp. 647-663, 1963.
- Goldsmith, J.R. and S.A. Landaw. Carbon Monoxide and Human Health, Science, Vol. 162, pp. 1352-1353, 1968.
- 72. Research Study to Determine the Range of Carboxyhemoglobin in Various Segments of the American Population. Annual Report, Submitted to Coordinating Research Council and The Environmental Protection Agency by Dept. of Environmental Medicine, Medical College of Wisconsin, Project No. CRC APRAC CAPM 8-68, MCOW-ENVM-COHb-71-1, 1971.
- 73. Pirnay, F., J. Dujardin, R. Deroanne, and J.M. Petit. Muscular Exercise During Intoxication by Carbon Monoxide, J. Appl. Physiol., Vol. 34, pp. 573-575, 1971.
- 74. Doyle, J.T., T.R. Dawber, W.B. Kannel, S.H. Kinch, and H.A. Kahn. The Relationship of Cigarette Smoking to Heart Disease: The Second Report of the Combined Experience of the Albany, N.Y. and Framingham, Mass. Studies, J. Am. Med. Assoc., Vol. 190, pp. 886-890, 1964.
- 75. Astrup, P., K. Kjeldsen, and J. Wanstrup. Effects of Carbon Monoxide Exposure on the Arterial Walls, Ann. N.Y. Acad. Sci., Vol. 174, pp. 294-300, 1970.
- 76. Anderson, E.W., J. Strauch, J. Knelson, and N. Fortuin. Effects of Carbon Monxoide (CO) on Exercise Electrocardiogram (ECG) and Systolic Time Intervals (STI), Circulation (Suppl. II), Vol. 44, p. II-135, 1971.

- 77. Cohen, S.I., M. Deare, and J.R. Goldsmith. Carbon Monoxide and Survival from Myocardial Infarction, Arch. Environ. Health, Vol. 19, pp. 510-517, 1969.
- 78. Knelson, J.H. Cardiovascular Effects During Low Level CO Exposure, Paper Presented to the Committee on Motor Vehicle Emissions, NAS-NRC, Washington, D.C., February 10, 1972.
- 79. Horvat, M., S. Yoshida, R. Prakash, H.S. Marcus, H.J.C. Swan, and W. Ganz. Effect of Oxygen Breathing on Pacing-Induced Angina Pectoris and Other Manifestations of Coronary Insufficiency, Circulation, Vol. 45, pp. 837-844, 1972.
- 80. Shul'ga, T.M. New Data for Hygienic Evaluation of Carbon Monoxide in <u>Atmospheric Air</u>, U.S.S.R. Literature, Vol. 9, pp. 73-81, 1964.
- 81. Dinman, B.D. Review of Electroencephalographic Data. National Academy of Science Report, Effects of Chronic Exposure to Low Levels of Carbon Monoxide on Human Health, Behavior, and Performance, pp. 29-31, 1969.
- Grudzinska, B. and L. Pecora. Electroencephalographic Patterns in Cases of Chronic Exposure to Carbon Monoxide in Air, Folia Med., Vol. 3, pp. 493-515, 1963.
- Sluijter, M.E. The Treatment of Carbon Monoxide Poisoning by Administration of Oxygen at High Atmospheric Pressure, Progr. Brain Res., Vol. 24, pp. 123-182, 1967.
- Zorn, H. Zur Diagnostik der chronischen Kohlenoxydvergiftung, Rass. Med. Ind., Vol. 33, pp. 325-329, 1967.
- 85. Helmchen, H. and H. Kunkel. Befunde zur rhythmischen Nachschwankung bei optisch ausgelosten Reizantworten (evoked responses) in EEG des Menchen, Arch. Phychiat. Nervenkr., Vol. 205, pp. 397-408, 1964.
- O'Donnell, R.D., P. Chikos, and J. Theodore. Effect of Carbon Monoxide Exposure on Human Sleep and Psychomotor Performance, J. Appl. Physiol., Vol. 31, pp. 513-518, 1971.
- Johnson, B.L. and C. Xintaras. Influence of Carbon Monoxide on Visual Evoked Potentials Utilizing Signal Analysis Methods, Proc. Ann. Conf. Engineering in Medicine and Biology, Vol. 21, p. 54.5, 1968.
- Goldberg, H.D. and M.N. Chappell. Behavioral Measure of Effect of Carbon Monoxide on Rats, Arch. Environ. Health, Vol. 14, pp. 671-677, 1967.

VII-7

- 89. Forbes, W.H., D.B. Dill, and H. DeSilva. The Influence of Moderate Carbon Monoxide Poisoning Upon the Ability to Drive Automobiles, J. Ind. Hyg. Toxicol., Vol. 19, pp. 598-603, 1937.
- 90. Ray, A.M. and T.H. Rockwell. An Exploratory Study of Automobile Driving Performance under the Influence of Low Levels of Carboxyhemoglobin. Ann. N.Y. Acad. Sci., Vol. 174, pp. 396-408, 1970.
- 91. Beard, R.R. and N.W. Grandstaff. Behavioral Responses to Small Doses of Carbon Monoxide, Proc. Ann. Conf. on Environ. Toxicol., Vol. 1, pp. 93-105, 1970.
- 92. Stewart, R.L. and M.R. Peterson. Experimental Human Exposure to Carbon Monoxide, Arch. Environ. Health, Vol. 21, pp. 154-164, 1970.
- 93. Mikulka, P., R. O'Donnell, and P. Heinig. The Effect of Carbon Monoxide on Human Performance, Ann. N.Y. Acad. Sci., Vol. 174, pp. 409-420, 1970.
- 94. Trouton, D. and H.J. Eysenck. The Effects of Drugs on Behavior. Handbook of Abnormal Psychology, H.J. Eysenck, Ed. Basic Books, Inc., New York, 1961.
- 95. Vollmer, E.P., B.G. King, and J.E. Birren. The Effects of Carbon Monoxide on Three Types of Performance at Simulated Altitudes of 10,000 and 15,000 feet, J. Exptl. Psychol., Vol. 36, pp. 244-251, 1946.
- 96. Guest, A.D.L., C. Duncan, and P.J. Lawther. Carbon Monoxide and Phenobarbitone: A Comparison of Effects on Auditory Flutter Fusion Threshold and Critical Flicker Fusion Threshold, Ergonomics, Vol. 13, pp. 587-594, 1970.
- 97. Cohen, S.I., G. Dorion, J.R. Goldsmith, and S. Permutt. Carbon Monoxide Uptake by Inspectors at a United States-Mexico Border Station, Arch. Environ. Health, Vol. 22, pp. 47-54, 1971.
- 98. Ramsey, J.M. Carboxyhemoglobinemia in Parking Garage Employees, Arch. Environ. Health, Vol. 15, pp. 580-588, 1967.
- 99. Breysse, P.A. and H.H. Bovee. Use of Expired Air-Carbon Monoxide for Carboxyhemoglobin Determinations in Evaluating Carbon Monoxide Exposures Resulting from the Operation of Gasoline Fork Lift Trucks in Holds of Ships, Am. Ind. Hyg. Assoc. J., Vol. 30, pp. 477-483, 1969.
- 100. Buchwald, H. Exposure of Garage and Service Station Operatives to Carbon Monoxide: A Survey Based on Carboxyhemoglobin Levels, Am. Ind. Hyg. Assoc. J., pp. 570-575, 1968.

- 101. Lloyd, J.W., F.E. Lundin, C.K. Redmond, and P.B. Geiser. Long-Term Mortality Study of Steelworkers, J. Occup. Med., Vol. 5, pp. 151-157, 1970.
- 102. Friedberg, C.K. Diseases of the Heart. Third Edition, W.B. Saunders Co., Philadelphia, pp. 643-705, 1966.
- 103. <u>The Health Consequences of Smoking</u>. A Report to the Surgeon General: 1972. DHEW Pub. No. (HSM) 72-7516, 1972.
- 104. Eros, W.F., R.H. Holmes, and J. Beyer. Coronary Disease Among United States Soldiers Killed in Action in Korea, J. Am. Med. Assoc., Vol. 152, pp. 1090-1093, 1953.
- 105. Spiekerman, R.E., J.T. Brandenburg, R.W.P. Achor, and J.E. Edwards. The Spectrum of Coronary Heart Disease in a Community of 30,000. A Clinicopathologic Study, Circulation, Vol. 25, pp. 57-65, 1962.
- 106. Brest, A.N. and J.H. Moyer. Cardiovascular Disorders. F.A. Davis Co., Philadelphia, Vol. 2, pp. 657-665, 1968.
- 107. Dawber, T.R. and W.B. Kannel. Susceptibility to Coronary Heart Disease, Mod. Concepts Cardiovasc. Dis., Vol. 30, pp. 671-679, 1961.
- 108. Broomfield, J.J. and H.S. Isbell. The Problem of Automobile Exhaust Gas in Streets and Repair Shops of Large Cities, Public Health Reports, Vol. 43, pp. 750-765, 1928.
- 109. Lynch, J.R. and C.M. Humphreys. Heat Stress and Carbon Monoxide Exposure at Mexican Border Crossing Stations, U.S. Dept. of HEW, Pub. No. TR-27, Cincinnati, 1965.
- 110. Sievers, R.F., T.L. Edwards, A.L. Murray, and H.H. Schrenk. Effects of Exposure to Known Concentrations of CO, J. Am. Med. Assoc., Vol. 118, pp. 585-588, 1942.
- 111. Farmer, C.J. and P.J. Crittenden. A Study of the Carbon Monoxide Content of the Blood of Steel Mill Operatives*, J. Ind. Hyg., Vol. 11, pp. 329-335, 1929.
- 112. Jones, J.G. and D.H. Walters. A Study of Carboxyhemoglobin Levels in Employees at an Integrated Steelworks, Ann. Occup. Hyg., Vol. 5, pp. 221-230, 1962.
- 113. Henderson, Y., H.W. Haggard, M.C. Teague, A.L. Prince, and R.M. Wunderlich. Physiological Effects of Automobile Exhaust Gases and Standards of Exposure for Brief Periods, J. Ind. Hyg. and Toxicol., Vol. 3, pp. 79-137, 1921.

- 114. Henderson, Y. and H.W. Haggard. Noxious Gases and the Principles of Respiration Influencing Their Action. Reinhold Publishing Co., New York, Second Edition, 1943.
- 115. Sayers, R.R., W.P. Yant, E. Levy, and W.B. Fulton. Effects of Repeatedly Daily Exposures of Several Hours to Small Amounts of Automobile Exhaust Gases, U.S.P.H.S. Bull. No. 186, 1929.
- 116. Documentation of the Threshold Limit Values for Substances in the Work Room Air, ACGIH, Third Edition, 1971.
- 117. Trevethick, R.A., and J.A. Adam. A Review of Industrial Hygiene Standards and Their Application, Trans. Soc. Occup. Med., Vol. 19, pp. 112-117, 1969.
- 118. Submarine Atmosphere Habitability Data Book. Bur. Ships, Navy Department, <u>Navships</u> 250-649-1, Sept. 1962.
- 119. Nelson, N., Ed. Atmospheric Contaminants in Spacecraft. Space Science Board, NAS-NRC, Oct. 1968.
- 120. Community Air Quality Guide for CO, Am. Ind. Hyg. Assoc. J., Vol. 30, pp. 322-325, 1969.
- 121. Coburn, R.F., R.E. Forster, and P.B. Kane. Considerations of the Physiological Variables That Determine the Blood Carboxyhemoglobin Concentration in Man, J. Clin. Invest., Vol. 44, pp. 1899-1910, 1965.
- 122. Stewart, R.L. and M.R. Peterson. Experimental Human Exposure to Carbon Monoxide, Arch. Environ. Health, Vol. 21, pp. 165-171, 1970.
- 123. . Title 42, Chapter IV, Part 410, Federal Register, Vol. 36, No. 84, April 30, 1971.
- 124. Maehly, A.C. in Methods of Forensic Sciences. F. Lindquist, Ed. Vol. 1, Wiley (Interscience), New York, pp. 539-545, 1962.
- 125. Feldstein, M. Methods for the Determination of Carbon Monoxide. A. Stolman, Ed. Progress in Chemical Toxicology, Vol. 3, Academic Press, New York, pp. 99-119, 1967.
- 126. Amenta, J.S. in Standard Methods in Clinical Chemistry. D. Deligson, Ed. Vol. 4, Academic Press, New York, pp. 31-36, 1963.
- 127. Harper, Jr., P.V. A New Spectrophotometric Method for the Determination of Carbon Monoxide in the Blood, J. Physiol., Vol. 163, pp. 212-217, 1952.
- 128. Klendshoj, N.C., M. Feldstein, and A.L. Sprague. The Spectrophotometric Determination of Carbon Monoxide, J. Biol. Chem., Vol. 183, pp. 297-303, 1950.

129. Van Slyke, D.D. and J.M. Neill. Determination of Bases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem., Vol. 61, pp. 523-584, 1924.

VII. APPENDIX I

SAMPLING AND ANALYSIS OF CARBON MONOXIDE (CO)

Air Sampling Methods

Worker exposure to CO shall be measured with a portable, direct reading, hopcalite-type carbon monoxide meter calibrated against known concentrations of CO, or with gas detector tube units certified under Title 42 of the Code of Federal Regulations, Part 84. Samples shall be collected from the worker's breathing zone and a sufficient number shall be collected at random intervals throughout the workday so that a statistically accurate determination of compliance may be made as outlined in the following section.

Principles for Air Sampling for Carbon Monoxide (CO)

The characteristic manner in which CO proceeds from the pulmonary alveolar spaces, through the blood capillary membrane "barrier," into the plasma, through the red blood cell membrane, ultimately to combine with hemoglobin imposes certain requirements for air sampling if proper determination of compliance with the recommended standard is to be made. The rate of CO diffusion from the lung to hemoglobin depends upon the partition coefficient for CO between alveolar air and pulmonary blood. The magnitude of this coefficient is such as to delay transfer of CO to the circulating hemoglobin (Hb). This time delay makes it essential in any estimation of the carboxyhemoglobin level to know how long the exposure was experienced as well as the CO concentration during the exposure. Reference to Figure 2 shows that a continuous exposure of over eight hours' duration is required to attain maximum combination of CO with hemoglobin at the recommended standard of 35 ppm.

VIII-1

The sampling and analytical procedures recommended below will provide the necessary data to determine compliance with the recommended standard.

The methodology and equipment utilized to collect and analyze samples to determine concentrations of CO in the air or concentration of COHb in the exposed worker shall be subjected to a proficiency and/or calibration test program conducted by NIOSH or by another agency of the federal government under agreement with NIOSH for certification for such determinations. Determination of Compliance

The following procedure shall be used to determine compliance with the eight-hour, time-weighted average standard based on a small number of instantaneous (grab) samples collected at random intervals during the workday.

Given: the results of <u>n</u> samples with a mean <u>m</u> and a range (difference between least and greatest) <u>r</u>. If, for from 3 to 10 samples, <u>m</u> is greater than the total of:

A. The standard

B. The percentage of systematic instrument error multiplied times the standard

C. $\frac{t \times r}{n}$

then the true average concentration exceeds the standard (p <0.05). The value of <u>t</u> is taken from the following table:

<u>n</u> (number of samples)	<u>t</u> (student's "t" test value)
3	2.35
4	2.13
5	2.01
6	1.94
7	1.89
8	1.86
9	1.83
10	1.81

VIII-2

For a large number of samples the procedure given in Section 3-2.2.1 of National Bureau of Standards (NBS) handbook 91 shall be followed.

IX. APPENDIX II

ANALYSIS OF CARBOXYHEMOGLOBIN (COHb)

Analytical Methodology

An extensive review of the methodology covering the determination of carbon monoxide has been prepared by Maehly. ¹²⁴ In an updating review of this area published in 1967, Feldstein¹²⁵ presents a critical review of procedures for the analysis of samples of combustion effluents, air, exhaled breath and blood. The methods involved range from sophisticated analytical procedures to less complicated colorimetric and gravimetric techniques.

Because carboxyhemoglobin constitutes the toxic product formed during carbon monoxide intoxication, and because the carboxyhemoglobin formed is quite stable, the analyst is presented with the opportunity of directly evaluating the toxic agent. In so doing, two facts are established: (1) proof that an exposure has occurred, and (2) quantitative proof the exposure has produced a particular toxic concentration in the body. Diffusion, chromatographic and gasometric methods all involve liberation of carbon monoxide from hemoglobin and either gasometric transfer operations or secondary titrations which are technically difficult for the microliter gas volumes involved. This limitation is even more critical when the effects of temperature and pressure on gas volumes are considered. Careful evaluation of the methods for direct measurement of carboxyhemoglobin has been reviewed in detail. Of these methods, three are considered to be feasible for consideration as the recommended method.

(a) The colorimetric method of Amenta¹²⁶ uses small blood samples and measures the absorbance of an ammonia-hemolyzed sample at three wave-length

settings on the spectrophotometer: 560, 575, and 498 nm. In calculating the results, the absorbance of the mixture at 498 nm (an isosbestic point) is the denominator in the equation for oxyhemoglobin, carboxyhemoglobin, and the unknown. This mathematical manipulation gives a value corrected for the total hemoglobin concentration (i.e., the R factor). The values $(R_{0_2} = 1.097, R_{C0} = 0.057)$ are then used for calculating percentage COHb by the ratio R_{0_2} - R_X/R_{0_2} - R_{C0} x100 = percentage COHb. The relatively small absorbance difference observed with this method reduces its precision and accuracy, especially in the low COHb range (ca. 10 percent).

(b) The method of Harper ¹²⁷ involves hemolysis of blood by distilled water, addition of a buffer (pH 7.2) and reduction of oxyhemoglobin by sodium hydrosulfite. The reduced hemoglobin is then converted to methemoglobin by the addition of potassium ferricyanide. The carboxyhemoglobin is converted to methemoglobin at a slower rate than reduced hemoglobin; therefore, the carboxyhemoglobin can be measured before appreciable conversion to methemoglobin takes place. The method requires a careful control of timed manipulations to obtain reproducible results.

(c) The method of Klendshoj, Feldstein and Sprague¹²⁸ is similar to and was published before Harper's method. In this method the oxyhemoglobin is reduced by the sodium hydrosulfite following hemolysis in dilute ammonia solution. The absorbances at 555 and 480 nm are compared to a diluted ammonia blank, and the percentage COHb is obtained from a previously constructed calibration curve. The absorbance difference between reduced hemoglobin and COHb represents a total difference 1.21 absorbance units. Methemoglobin does not interfere in the determination but the method cannot be used with hemolyzed samples. The precision and accuracy of the method are comparable

with the Van Slyke gasometric method.¹²⁹ The sensitivity of the method is sufficient to detect 2 percent COHb with quantitative accuracy.

The method of Klendshoj, Feldstein and Sprague is recommended as the method of choice because it measures the physiologically active form of carbon monoxide directly with excellent sensitivity and accuracy in the area of biologic interest. In addition, it is a method free of difficult manipulations and does not require extraordinary laboratory equipment to obtain a precise and quantitative result.

Procedure

(a) Cleaning of glassware. All glassware shall be free of scratches and of any material that could potentially cause hemolysis. Rinsing in deionized water is usually sufficient.

(b) Collection and shipping of samples. Blood shall be collected using oxalated (or EDTA) evacuated test tubes. Blood for CO determination shall be drawn from a vein without stasis and shall be refrigerated immediately after collecting the sample. Samples shall be analyzed within 96 hours after collection. Samples may be shipped provided they reach the destination within 48 hours and are refrigerated upon arrival.

(c) Analysis of samples. One (1) ml of the oxalated blood is transferred to a 100 ml graduated flask and made up to volume with 0.4 percent ammonia. Three (3) ml of this solution is placed in a cuvette, ten (10) ml of sodium hydrosulfite is added, and read at once at 555 and 480 nm against 0.4 percent ammonia as a blank. The value of D555/D480 is calculated and the percentage of COHb is read from a prepared standard concentration-quotient curve.

Calibration and Standards

(a) Determination of Quotient D555/D480 for HbCO and reduced hemoglobin. Ten (10) ml of oxalated blood (or pooled samples) from sources

known not to have been exposed to carbon monoxide are obtained. Five (5) ml are placed in each of two 250 ml separatory funnels. The air in one separatory funnel (A) is displaced with pure oxygen and tightly stoppered. The air in the second separatory funnel (B) is displaced with carbon monoxide and tightly stoppered. The two separatory funnels are rotated gently for 1/2 hour to ensure saturation with oxygen and CO respectively. A one (1) ml portion is diluted to 100 ml with 0.4 percent ammonia and analyzed according to procedure in Section (c) above. The quotient D555/D480 for reduced oxyhemoglobin should be approximately 3.15 ± 0.05 and for "reduced" carboxyhemoglobin 1.94 ± 0.05 . Transfer and dilution should be performed as quickly as possible to avoid changes in the oxyhemoglobin concentrations.

(b) A calibration curve is constructed by mixing the following volumes of the blood from separatory funnels (A) and (B) from Section (a) and then performing an analysis as outlined in Section (c) above.

<u>(A)</u>	<u>(B)</u>	Percent COHb
1	0	0
0.9	0.1	10
0.8	0.2	20
0.5	0.5	50

A calibration curve of the percent COHb vs. the quotient D555/D480 is then plotted in linear fashion. Although the curve does not give a linear presentation over this range, readings between increments will give values correct to ±2 percent of the amount present.

Calculations

Concentrations shall be read directly from the curve or calculated from the following best fit formula of the curve:

Conc. COHb(percent) = mx + b

where <u>m</u> and <u>b</u> are determined by regression analysis of the ratios D555/D480 for all calibration standards and <u>x</u> is the sample D555/D480 ratio.

Apparatus

(a) Spectrophotometer with a band pass of 5 nm or less (2 nm is preferable)

- (b) 1 cm path length cuvettes, volume 3 ml
- (c) 1 ml pipettes
- (d) 100 ml graduated cylinders
- (e) 1000 ml volumetric flask
- (f) Spatula capable of transferring 10 mg solid reagent
- (g) 250 ml separatory funnels

(h) Evacuated test tubes (10 ml) containing approximately 250 mg potassium oxalate

Reagents

(a) Cylinder of pure oxygen (medical or aviators breathing grade specification)

(b) Cylinder of pure carbon monoxide (certified 99 percent purity)

(c) Purified analytical grade sodium hydrosulfite (Na S $_{2}^{0}$) (Sodium Dithionite)

(d) Concentrated ammonia (28%)

(e) 0.4% ammonia solution. Dilute 15 ml of conc. $NH_3(28\%)$ to

1 liter

Principle of the Method

Oxyhemoglobin in oxalated blood is completely reduced in the presence of small amounts of sodium hydrosulfite, whereas carboxyhemoglobin is not affected. The spectral absorbance curves of oxyhemoglobin (0_2Hb) and carboxyhemoglobin (COHb) are different. The ratio of the absorbance at 555 nm and 480 nm is directly proportional to the percent COHb in the blood.

Range and Sensitivity

For 1 ml of oxalated blood the range is 0 to 100 percent saturation COHb. Sensitivity is 0.5 percent saturation.

Interferences

Hemolyzed blood contains pigments arising from the breakdown of hemoglobin and will cause interference in the method. Bile pigments may also interfere. Precision and Accuracy

The difference in concentrations obtained by this procedure and compared to results obtained on the same samples analyzed by the Van Slyke method are not significant at the 5 percent level [t-Value = 1.81 (14 deg. of Freedom)]. The average difference is 0.47 percent with a standard error of the mean of 0.26.

Advantages and Disadvantages of the Method

(a) The method is relatively fast, can be automated quite easily, requires few reagents, extensive training is not required, and does not require expensive analytical instruments nor reagents to obtain acceptable results.

(b) The hydrosulfite reagent is not very stable. Care must be exercised in collecting and storing the blood to prevent hemolysis. Pure air (or oxygen) and carbon monoxide gas must be available to prepare calibration standards. Interferences with the spectral absorption of COHb are possible, as aforementioned, especially if hemolysis occurs.

X. APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to any tank or other device which contains or emits carbon monoxide shall be provided in the appropriate section of the Material Safety Data Sheet or approved form. If a specific item of information is inapplicable (i.e., flash point) initials "n.a." not applicable should be inserted.

(i) The produce designation in the upper left hand corner of both front and back to facilitate filing and retrieval. Print in upper case letters in as large print possible.

(ii) Section I. Name and Source.

(A) The name, address and telephone number of the manufacturer or supplier of the product.

(B) The trade name and synonyms for a mixture of chemicals, a basic structural material, or for a process material; and the trade name and synonyms, chemical name and synonyms, chemical family, and formula for a single chemical.

(iii) Section II. Hazardous Ingredients.

(A) Chemical or widely recognized common name of all hazardous ingredients

(B) The approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range of maximum amount, i.e., 10-20 percent V; 10 percent max. W.

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(C) Basis for toxicity of each hazardous material (e.g., established OSHA standard), in appropriate units and/or LD_{50} , showing amount and mode of exposure and species or LC_{50} showing concentration, duration and species.

(iv) Section III. Physical Data.

(A) Physical properties of the total product including boiling point and melting point in degrees Fahrenheit; vapor pressure, in millimeters of mercury, vapor density of gas or vapor (air = 1), solubility in water, in parts per hundred parts of water by weight; specific gravity (water = 1); percentage volatile (indicate if by weight or volume) at 70° Fahrenheit; evaporation rate for liquids (indicate whether butyl acetate or ether = 1); and appearance and odor.

(v) Section IV. Fire and Explosion Hazard Data.

(A) Fire and explosion hazard data about a single chemical or a mixture of chemicals, including flash point, in degrees Fahrenheit; flammable limits, in percent by volume in air; suitable extinguishing media or agents; special fire-fighting procedures; and unusual fire and explosion hazard information.

(vi) Section V. Health Hazard Data.

(A) Toxic level for total compound or mixture, relevant symptoms of exposure, skin and eye irritation properties, principal routes of absorption, effects of chronic (long-term) exposure and emergency and first-aid procedures.

(vii) Section VI. Reactivity Data.

(A) Chemical stability, incompatibility, hazardous decomposition products, and hazardous polymerization.

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(viii) Section VII. Spill or Leak Procedures.

(A) Detailed procedures to be followed with emphasis on precautions to be taken in cleaning up and safe disposal of materials leaked or spilled. This includes proper labeling and disposal of containers containing residues, contaminated absorbants, etc.

(ix) Section VIII. Special Protection Information.

(A) Requirements for personal protective equipment, such as respirators, eye protection and protective clothing, and ventilation, such as local exhaust (at site of product use or application), general, or other special types.

(x) Section IX. Special Precautions.

(A) Any other general precautionary information, such as personal protective equipment for exposure to the thermal decomposition products listed in Section VI, and to particulates formed by abrading a dry coating, such as by a power sanding disc.

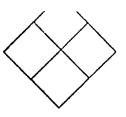
(xi) The signature of the responsible person filling out the data sheet, his address, and the date on which it is filled out.

(xii) The NFPA 704M numerical hazard ratings as defined in Section (c)(5) following. The entry shall be made immediately to the right of the heading, "Material Safety Data Sheet" at the top of the page and within a diamond symbol preprinted on the forms.

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DATA SHEET

Form Approved Budget Bureau No. Approval Expires Form No. OSHA



	TION I SOURCE A	ND NOMENCLATUR	Y					
MANUFACTURER'S NAME	EME	EMERGENCY TELEPHONE NO.						
ADDRESS (Number, Street	, City, State, Zl	P Code)	1					
TRADE NAME AND SYNONYMS			CHE	MICAL FAM	IILY			
CHEMICAL NAME AND SYNON	YMS		FOF	MULA				
SECT								
BASIC MATERIAL	APPROXIMATE OR MAXIMUM	ESTABLISHED OSHA	I	^{.D} 50	LC	50		
DASIC MAIENIAL	% WT. OR VOL.	STANDARD	ORAL	PERCUT.	SPECIES	CONC.		
		DATA	I		I	1		
BOILING POINT	ION III PHYSICAL °F.	VAPOR PRESSUE	 ?E			mm Hg.		
MELTING POINT	°F.	VAPOR DENSITY (Air=1)						
•SPECIFIC GRAVITY (H20=1		EVAPORATION RATE (=1)						
	······································							
SOLUBILITY IN WATER	Pts/100 pts h ₂ 0	VOLATILE		% VOI	•	/ WC.		
AND ODOR								
	ION IV FIRE AND	D EXPLOSION HAD						
FLASH POINT				LAMMABLE) UPPI	ER		
METHOD USED				LIMITS	LOWI	ER		
EXTINGUISHING MEDIA								
SPECIAL FIRE FIGHTING PROCEDURES								
UNUSUAL FIRE AND EXPLOSION HAZARDS		X-4			<u></u>			

SECTION V HEALTH HAZARD DATA

TOXIC LEVEL

CARCINOGENIC

PRINCIPAL ROUTES OF ABSORBTION SKIN AND EYE IRRITATION

RELEVANT SYMPTOMS OF EXPOSURE

EFFECTS OF CHRONIC EXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

SECTION-VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

INCOMPATIBILITY (Materials to Avoid)

HAZARDOUS DECOMPOSITION PRODUCTS

SECTION VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IN CASE MATERIAL IS RELEASED OR SPILLED

WASTE DISPOSAL METHOD

SECTION VIII SPECIAL PROTECTION INFORMATION

SPECIAL	RESPIRATOR
MECHANICAL (General)	GLOVES
VENTILATION REQUIREMENTS LOCAL EXHAUST	PROTECTIVE EQUIPMENT (Specify Types) EYE

OTHER PROTECTIVE EQUIPMENT

SECTION IX SPECIAL PRECAUTIONS

PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE

OTHER PRECAUTIONS

Signature

Address

Date

XI. APPENDIX IV CO EXPOSURE DATA

The exposure data contained in this appendix result from programming the equation introduced by Coburn 121 that relates environmental CO exposure to bodily uptake. The Coburn equation:

$$\frac{[\text{COHb}]P_{CO_2}}{[O_2\text{Hb}]M} - V_{CO} \left[\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{V_A} \right] - P_{I_{CO}} = -e^{-\frac{P_{CO_2}t}{MV_b[O_2\text{Hb}]\frac{1}{D_L} + \frac{713}{V_A}}} = -e^{-\frac{P_{CO_2}t}{MV_b[O_2\text{Hb}]\frac{1}{D_L} + \frac{713}{V_A}}}$$

has been rearranged for programming as follows:

CO in air (ppm) =
$$\frac{1316 \left[(AC - V_{CO}B + a (V_{CO}B - AD) \right]}{1 - a}$$
Where A =
$$\frac{P_{C} - O_{2}}{M[O_{2}H_{b}]}$$
B =
$$\frac{1}{D_{L}} + \frac{P_{L}}{V_{A}}$$
C =
$$[COHb]_{t} = COHb \text{ concentration (ml CO/ml blood) at time t.}$$
D =
$$[COHb]_{0} = \text{"background" COHb (ml CO/ml blood) at time = 0.}$$
V_{CO} = Rate of endogenous CO production (ml/min)

$$-\frac{tA}{VbB}$$
Q = blood volume
P_C - O_{2} = PO_{2} \text{ in capillaries (mm Hg)}
$$[O_{2}Hb] = \text{ oxyhemoglobin conc. (ml/ml blood)}$$
M =
$$CO/O_{2} \text{ affinity for Hb}$$

$$\begin{split} & D_L = \text{diffusion rate of CO through lungs (ml/min/mm Hg)} \\ & P_L = \text{dry barometric pressure in lungs (mm Hg)} \\ & V_A = \text{ventilation rate (ml/min)} \\ & \underline{\text{Assumptions (Constants)}} \\ & D = 0.0015; (0.75\%) \\ & V_{CO} = 0.007 \text{ ml/min} \\ & V_b = 5500 \text{ ml} \\ & P_C = o_2 = 100 \text{ mm Hg} \\ & [O_2\text{Hb}] = 0.2 \text{ ml/ml blood} \\ & M = 218 \\ & P_L = 713 \text{ mm Hg} \end{split}$$

Assumptions (Variables)

		Sedentary	Light Work	Heavy Work
DL	=	30	40	60
V _A	*	6,000	18,000	30,000

Based upon the above assumptions, the predicted environmental CO values and lengths of exposure necessary to reach 5 percent COHb for various combinations of pulmonary diffusion rate (D_L) and alveolar ventilation rate (V_A) are given on the following pages.

D_{L}	V _A	CO	Time	сонь
(ml/min/mm Hg)	(ml/min)	(ppm)	(min)	
30.0	6000.0	35.0	10.0	0.907
0.00	1	U•CC	30.0	1.208
			60.0	1.629
			90.0	2.016
	1		120.0	2.371
			180.0	2.996
			240.0	3.521
			300.0	3,960
			360.0	4.328
			420.0	4.635
	Ţ		480.0	4.891
	1		1440.0	6.185
	10000.0		10.0	0.977
			30.0	1.404
			60.0	1,982
			90.0	2.492
			120.0	2.943
			180.0 240 .0	3.692
			300.0	4.268 4.712
			360.0	5.053
			420.0	5.315
			480.0	5.517
4	+		1440.0	6.224
40.0	18000.0		10.0	1.112
1	1		30.0	1.770
			60.0	2.606
			90.0	3.288
			120.0	3.842
			180.0	4.663
			240.0	5.193
			300.0	5,539
			360.0	5.765
			420.0	5,913
Ļ			480.0	6.010
60.0	30000.0		1440.0	6.208
00.0	30000.0		10.0 30.0	1.317 2.291
			60.0	3,409
			90.0	4.210
			120.0	4.781
		ļ	180.0	5.490
			240.0	5.837
			300.0	6.012
]		360.0	6.102
			420.0	6.148
			480.0	6.172
¥	Y	¥	1440.0	6.199

$^{\mathrm{D}}\mathrm{L}$	VA	Time	CO
(ml/min/mm Hg)	(ml/min)	(min)	(ppm)
30.00	4000.00	10.0	1085.96
30.00	4000.00	20.0	549.99
30.00	4000.00	30.0	371.36
30.00	4000.00	46.0	282.07
30.00	4000.00	50.0	228.50
30.00	4000.00	60.0	192.81
30.00	4000.00	90.0	133.37
30.09	4000.00	120.0	103.71
30.00	4000.00	150.0	85.95
30.00	4000.00	180.0	74.16
30.00	4000.00	210.0	65.76
30.00	4000.00	240.0	59.50
30.00	4000.00	270.0	54.65
30.00	4000.00	300.0	50.79
30.00	4000.00	330.0	47.65
30.00	4000.00	360.0	45.06
30.00	4000.00	390.0	42.88
30.00	4000.00	420.0	41.03
30.00	4000.00	450.0	39.43
30.00	4000.00	480.0	38.06
30.00	5000.00	10.0	905.67
30.00	5000.00	20.0	460.02
30.00	5060.00	30.0	311.51
30.00	5000.00	40.0	237.27
30.00	5000.00	50.0	192.75
30.00	5000.00	60.0	163.08
30.00	5000.00	90.ú	113.70
30.00	5000.00	120.0	89.07
30.00	5000.00	150.0	74.36
30.00	5000.00	180.0	64.59
30.00	5000.00	210.0	57.65
30.00	5000.00	240.0	52.48
30.00	5000.00	270.0	48.49
30.00	5000.00	300.0	45.32
30.00	5000.00	330.0	42.76
30.00	5000.00	360.0	40.64
30.00	5000.00	390.0	38.87
30.00	5000.00	420.0	37.37
30.00	5000.00	450.0	36.08
30.00	5000.00	480.0	34.97

D_{L}	v _A	Time	CO
(m1/min/mm Hg)	(ml/min)	(min)	(ppm)
30.00	6000.00	16.0	785.48
30.00	6000.00	20.0	400.05
30.00	6000.00	30.0	271.61
30.00	6000.00	40.0	207.41
30.00	6000.00	50.0	168.92
30.00	6000.00	60.0	143.27
30.00	6000.00	90.0	100.60
30.00	6000.00	120.0	79.35
30.00	6000.00	150.0	66.65
30.00	6000.00	180.0	58.25
30.00	6000.00	210.0	52.28
30.00	6000.00	240.0	47.85
30.00	6000.00	270.0	44.44
30.00	6000.00	300.0	41.74
30.00	6000.00	330.0	39.56
30.00	6000.00	360.0	37.76
30.00	6000.00	390.0	36.26
30.00	6000.00	420.0	35.00
30.00	6000.00	450.0	33.93
30.00	6000.00	480.0	33.00
30.00	7000.00	10.0	699.63
30.00	7900.00	20.0	357.21
30.00	7000.00	30.0	243.11
30.00	7000.00	40.0	186.09
30.00	7006.00	50.0	151.91
30.00	7000.00	60.0	129.13
30.00	7000.00	90.0	91.26
30.00	7000.00	120.0	72.41
30.00	7000.00	150.0	61.18
30.00	7000.00	180.0	53.74
30.00	7000.00	210.0	48.48
30.00	7000.00	240.0	44.58
34.00	7000.00	270.0	41.58
30.00	7000.00	300.0	39.22
30.00	7000.00	33Û.Û	37.32
30.00	7000.00	36 0 .0	35.75
30.00	7000.00	390.0	34.46
30.00	7000.00	420.0	33.37
30.00	7000.00	450.0	32.45
30.00	7000.00	480.0	31.66

DL	VA	Time	CO
(ml/min/mm Hg)	(ml/min)	(min)	(ppm)
30.00	8000.00	10.0	635.25
30.00	8000.00	20.0	325.09
30.00	8000.00	30.0	221.75
30.00	8000.00	40.0	170.11
30.00	66.5008	56.0	139.15
30.00	8000.00	60.0	118.54
30.00	8000.00	96.0	84.27
30.00	8000.00	120.0	67.23
30.00	8000.00	150.0	57.08
30.00	8000.00	180.0	50.39
30.00	8000.00	210.0	45.66
30.00	8000.00	240.0	42.16
30.00	8000.00	270.0	39.47
30.00	8000.00	300.0	37.36
30.00	8000.00	330.0	35.67
30.00	8000.00	360.0	34.29
30.00	8000.00	390. 0	33.14
30.00	8000.00	420.0	32.19
30.00	8000.00	450. 0	31.38
30.00	8000.00	480.0	30.69
30.00	9000.00	10.0	585.17
30.00	9000.00	20.0	300.10
30.00	9000.00	30.0	205.13
30.00	9000.00	40.0	157.68
30.00	9000.00	50.0	129.24
30.00	9000.00	6 0. Ŭ	110.30
30.00	900.00	90 . 0	78.84
30.00	9000.00	120.0	63.21
30.00	9000.00	150.0	53.92
30.00	9000.00	180.0	47.79
30.00	9000.00	210.0	43.48
30.00	9000.00	240.0	40.29
30.00	9000.00	270.0	37.86
30.00	9000.00	300.0	35.95
30.00	9000.00	330.0	34.42
30.00	9000.00	360.0	33.18
30.00	9000.00	390.0	32.15
30.00	9000.00	420.0	31.30
30.00	9000.00	450.0	30.58
30.00	9000.00	480.0	29.98

D _L	V _A	Time	CO
(ml/min/mm Hg)	(mĺ/min)	(min)	(ppm)
30.00	10600.00	19.0	545.11
30.00	10000.00	20.0	280.12
30.00	10000.00	30.0	191.84
30.00	10000.00	40.0	147.74
30.00	10000.00	50.0	121.31
30.00	10000.00	60.0	103.72
30.00	10000.00	90.0	74.50
30.00	10000.00	120.0	60.00
30.00	10000.00	150.0	51.39
30.00	10000.00	180.0	45.73
30.00	10000.00	210.0	41.75
30.00	10000.00	240.0	38.82
30.00	10000.00	270.0	36.58
30.00	10000.00	300.0	34.83
30.08	10000.00	330.0	33.44
30.00	10006.00	360.0	32.31
30.00	10000.00	390.0	31.39
30.00	10000.00	420.0	30.62
30.00	10000.00	450.0	29.98
30.00	10000.00	480.0	29.43
30.00	11000.00	10.0	512.33
30.00	11000.00	20.0	263.77
30.00	11000.00	30.0	180.97
30.00	11000.00	40.0	139.61
30.00	11000.00	50.0	114.83
30.00	11000.00	60.0	98.33
30.00	11000.00	90.0	70.95
36.00	11000.00	120.0	57.39
30.00	11000.00	150.0	49.34
30.00	11000.00	180.0	44.06
30.00	11000.00	210.0	40.35
30.00	11000.00	240.0	37.62
30.00	11000.00	270.0	35.55
30.00	11000.00	300.0	33.94
30.00	11000.00	330.0	32.66
30.00	11000.00	360.0	31.62
30.00	11000.00	390.0	30.78
30.00	11000.00	420.0	30.08
30.00	11000.00	450.0	29.50
30.00	11000.00	480.0	29.01

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DL	v _A	Time	CO
(ml/min/mm Hg)		(min)	(ppm)
30.00	12000.00	10.0	485.02
30.00	12000.00	20.0	250.14
30.00	12000.00	30.0	171.91
30.00	12000.00	40.0	132.84
30.00	12000.00	50.0	109.43
30.00	12000.00	60.0	93.85
30.00	12000.00	90.0	68.01
30.00	12000.00	120.0	55.21
30.00	12000.00	150.0	47.64
30.00	12000.00	180.0	42.67
30.00	12000.00	210.0	39.19
30.00	12000.00	240.0	36.64
30.00	12000.00	270.0	34.71
30.00	12000.00	300.0	33.21
30.00	12000.00	330.0	32.02
30.00	12000.00	360.0	31.97
30.00	12000.00	3 90. 0	30.29
30.00	12000.00	420.0	29.65
30.00	12000.00	450.0	29.12
30.00	12000.00	480.0	28.67
30.00	13000.00	10.0	461.91
30.00	13000.00	20.0	238.62
30.00	13000.00	30.0	164.25
30.00	13000.00	40.0	127.11
30.00	13000.00	50.0	104.86
30.00	13000.00	60.0	90.06
30.00	13000.00	90.0	65.52
30.00	13000.00	120.0	53.38
30.00	13000.00	150.0	46.20
30.00	13000.00	186.0	41.50
30.00	13000.00	210.0	38.22
30.00	13000.00	240.0	35.82
30.00	13000.00	270.0	34.01
30.00	13000.00	300.0	32.60
30.00	13000.00	330.0	31.49
30.00	13000.00	360.0	33.61
30.00	13000.00	390.0	29.89
30.00	13000.00	420.0	29.29
30.00	13000.00	450.0	28.81
30.00	13000.00	480.0	28.40

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CO	(mdd)	42.1	28.7	57.6	2.2	00.9	6.8	3.9	1.8	4.9	0.5	7.4	35.13	3.4	2.0	1.0	0.2	9.5	0.6	8.5	
Time	(min)	10.0	3	•	ਂ	0	5	5	់	50.	80.	10.	240.0	70.	.00	30.	60.	90.	20.	450.0	480.0
v_{A}	(ml/min)	14000.00	0.00	0000	0.	.000	•	14000.00	•	•	•		14000.00	۰	14000.00	.00	14000.00	14000.00	14000.00	14000.00	14600.00
DL	(ml/min/mm Hg)	•	30.00	•	٠	•	•		30.00	•	•		30.00	•	õ	•	0.	õ	30.00	٠	30.00

7.7	80.	14000.00	40.00
8. C	50.	٠	٠
8.4	20.	00.	40.03
8 • 8	390.0	•	40.00
9. 4	60.		•
0.1			٠
1.0	00		•
2.1	73.		٠
3.6	f 0.		•
5.6	10.		٠
8.4	80.		•
2.3	50.		٠
8.4	120.0	14000.00	40.00
8.8	•		٠
9.9	•		٠
2.6			٠
11.7	40.0		•
43.7	٠	٠	٠
207.72			40.00
6•65	10.0	14000.00	40.00

6-IX

$^{\mathrm{D}}\mathrm{L}$	VA	Time	CO
(ml/min/mm Hg)	(ml/min)	(min)	(ppm)
30.00	15000.00	10.0	424.93
30.00	15000.00	20.0	220.18
30.00	15000.00	30.0	151.99
30.00	15000.00	40.0	117.95
30.00	15000.00	50.0	97.56
30.00	15000.00	60.0	84.00
36.00	15000.00	90.0	61.54
30.00	15000.00	120.0	50.45
30.00	15000.00	150.0	43.92
30.00 30.00	15000.00	180.0 210.0	39.66
30.00	15000.00	240.0	36.69 34.53
30.00	15000.00	270.0	32.91
30.00	15000.00	300.0	31.66
30.00	15000.00	330.0	30.68
30.00	15000.00	360.0	29.90
30.00	15000.00	390.0	29.27
30.00	15000.00	420.0	28.76
30.00	15000.00	450.0	28.34
30.00	15000.00	480.0	28.00
40.00	15000.00	10.0	382.80
40.00	15000.00	20.0	199.17
40.00	15000.00	30.0	138.03
40.00	15000.00	40.0	107.51
40.00	15000.00	50.0	89.25
40.00	15000.00	60.0	77.11
40.00	15000.00	90.0	57.03
40.00 40.00	15000.00	120.0	47.15
40.00	15000.00	150.0 180.0	41.35 37.58
40.00	15000.00	210.0	34.98
40.00	15000.00	240.0	33.10
40.00	15000.00	270.0	31.70
40.00	15000.00	300.0	30.63
40.00	15000.00	330.0	29.80
40.00	15000.00	360.0	29.14
40.00	15000.00	390.0	28.62
40.00	15000.00	420.0	28.20
40.00	15006.00	450.0	27.86
40.00	15000.00	480.0	27.59

D_{L}	VA	Time	CO
(ml/min/mm Hg)		(min)	(ppm)
30.00	16000.00	10.0	409.91
30.00	16000.00	20.0	212.69
30.00	16000.00	30.0	147.01
30.00	16000.00	40.0	114.23
30.00	16000.00	50.0	94.60
30.00	16000.00	60.0	81.54
30.00	16000.00	90.0	59.93
30.00	16000.03	120.0	49.27
30.00	16000.00	150.0	43.00
30.00	16000.00	186.0	38.91
30.00	16000.00	210.0 240.0	36.07 34.01
30.00 30.00	16000.00	270.0	32.47
30.00	16000.00	300.0	31.28
30.00	16000.00	330.0	30.36
30.00	16000.00	360.0	29.62
30.00	16000.00	390.0	29.03
30.00	16000.00	420.0	28.55
30.00	16000.00	450.0	28.16
30.00	16000.00	480.0	27.85
()))	1/003 00	10.5	2/7 70
40.00	16000.00	10.0	367.78
40.00 40.00	16000.00	20.0 30.0	191.68 133.05
40.00	16000.00	40.0	103.80
40.00	16000.00	50.0	86.29
40.00	16000.00	60.0	74.66
40.00	16000.00	90.0	55.42
40.00	16000.00	120.0	45.98
40.00	16000.00	150.0	40.44
40.00	16000.00	180.0	36.86
40.00	16000.00	210.0	34.38
40.00	16000.00	240.0	32.60
40.00	16000.00	270.0	31.28
40.00	16000.00	300.0	30.27
40.00	16000.00	330.0	29.50
40.00	16000.00	360.0	28.89
40.00	16000.00	390.0	28.40
40.00	16000.00	420.0	28.02
40.00	16000.00	450.0	27.71
40.00	16000.00	480.0	27.46

•	•	•	÷.	•	•	0.00	•	•	•	•	•	•	•	•	•0	•	•	•	•	
000.0	000.0	000.0	000.0	0.0008	8000.0	18000.00	8000.0	8000.0	8000.0	8000.0	8000.0	8000.0	8000.0	8000.0	8000.0	8000.0	8000.0	8000.0	0.0008	
80.	50.	20.	•00	60.	30.	300.0	70.	40.	10.	•08	50.	20.	90.	Ċ	•	•	0	•	•	
7.2	7.4	7.7	0*8	8.4	:9 •0	29.71	0.6	1.7	نّ 4 • ٽ	ັນ • 6	6.8	4.0	2.7	0.5	1.3	7.6	24.7	9.2	42.7	

444444444444444

XI-12

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17000.00 17000.00 17000.00 17000.00 17000.00 17000.00 17000.00 17000.00 17000.00 17000.00 17000.00 17000.00 17000.00 17000.00	V _A (m1/mj
44433332221111 85226336341852965434321 85263636656666666666 80666666666666666666666666	, nin
128 128 128 128 128 128 128 128 128 128	CO (ppr

4444444444444 000000000000000000000000	000000
200000.00 2000000.00 2000000.00 2000000.00 2000000.00 2000000.00 2000000.00000.000 2000000.000000.000 2000000.00000000	
4 4 5 0 • 0 4 8 0 • 0 4 8 0 • 0 4 8 0 • 0 4 8 0 • 0 6 0 • 0 6	000000
50.64 37.64 314.76 31.17 29.264 28.66 28.66 27.82 27.82 27.53 27.12	1 1 N 8 9 N • • • • • • • •

XI-13

44444444444444444444444444444444444444	D _L (m1/min/mm Hg)
	V _A (m1/min)
4800.00 480	Tíme (mín)
332.21 173.94 79.20 38.32 39.20 39.20 39.20 39.20 31.43 32.27 30.33 28.32 28.32 28.32 28.43 27.62 27.53	CO (ppm)

D	VA	Time	СО
(m1/min/mm Hg)	(m1/min)	(min)	(ppm)
50.00	20000.00	10.0	297.45
50.00	20000.00	20.0	156.62
50.00	20000.00	30.0	109.77
50.00	20000.00	40.0	86.42
50.00	20000.00	50.0	72.47
50.00	20000.00	60.0	63.21
50.00	20000.00	90.0	47.98
50.00	20000.00	120.0 150.0	40.57
50.00 50.00	20000.00 20000.00	180.0	36.28 33.55
50.00	20000.00	210.0	31.70
50.00	20000.00	240.0	30.40
50.00	20000.00	270.0	29.46
50.00	20000.00	300.0	28.76
50.00	20000.00	330.0	28.24
50.00	20000.00	360.0	27.84
50.00	20000.00	390.0	27.53
50.00	20000.00	420.0	27.30
50.00	20000.00	450.0	27.11
50.00	20000.00	480.0	26.97
40.00	21000.00	10.0	314.14
46.00	21000.00	20.0	164.94
40.00	21000.00	30.0	115.29
40.00	21000.00	40.0	90.54
40.00	21000.00	50.0	75.74
40.00	21000.00	60.0	65.92
40.00	21000.00	90.0	49.73
40.00	21000.00	120.0	41.84
40.00	21000.00	150.0	37.25
40.00	21000.00	180.0	34.32
40.00	21000.00	210.0	32.32
40.00	21000.00	240.0	30.90
40.00	21000.00	270.0	29.87
40.00	21000.00	300.0	29.10
40.00	21000.00	330.0	28.51
40.00	21000.00	360.0	28.06
40.00	21000.00	390.0	27.71
40.00	21000.00	420.0	27.44
40.00	21000.00	450.0	27.23
40.00	21000.00	480.0	27.07

D_L	٧ _A	Time	CO
(ml/min/mm Hg)	(ml/min)	(min)	(ppm)
50.00	21600.00	10.0	288.87
50.00	21000.00	20.0	152.34
50.00	21000.00	30.0	106.93
50.00	21000.00	40.0	84.30
50.00	21009.00	50.0	70.78
50.00	21000.00	60.0	61.82
50.00	21000.00	90.0	47.08
50.00	21000.00	120.0	39.92
50.00	21000.00	150.0	35.79
50.00	21000.00	180.0	33.16
50.00	21000.00	210.0	31.39
50.0 0	21000.00	240.0	30.15
50.00	21000.00	270.0	29.26
50.00	21000.00	300.0	28.59
50.00	21000.00	330.0	28.10
50.00	21000.00	360.0	27.73
50.00	21000.00	390.0	27.44
50.00	21000.00	420.0	27.22
50.00	21000.00	450.0	27.06
50.00	21000.00	480.0	26.93
40.00	22000.00	10.0	306-34
40.00	22000.00	20.0	161.05
40.00	22000.00	30.0	112.71
40.00	22000.00	40.0	88.61
40.00	22000.00	50.0	74.21
40.00	22000.00	60.0	64.66
40.00	22000.00	90.0	48.91
40.00	22000.00	120.0	41.24
40.00	22000.00	150.0	36.80
40.00	22000.00	180.0	33.96
40.00	22000.00	210.0	32.03
40.00 40.00	22000.00 22000.00	240.0 270.0	30.67 29.67
40.00	22000.00	300.0	28.94
40.00	22000.00	330.0	28.38
40.00	22000.00	360.0	27.95
40.00	22000.00	390.0	27.63
40.00	22000.00	420.0	27.37
40.00	22000.00	450.0	27.17
40.00	22000.00	480.0	27.02

DL	V _A	Time	CO
(m1/min/mm Hg)	(ml/min)	(min)	(ppm)
50.00	22000.00	10.0	281.07
50.00	22000.00	20.0	148.46
50.00	22000.00	30.0	104.35
50.00	22000.00	4C.Û	82.38
50.00	22000.00	50.0	69.26
50.00	22000.00	60.0	60.56
50.00	22000.00	90.0	46.26
50.00	22000.00	120.0	39.33
50.00	22000.00	150.0	35.34
50.00	22000.00	180.0	32.82
50.00	22000.00	210.0	31.12
50.00	22000.00	240.0	29.93
50.00	22000.00	270.0	29 .07
50.00	22000.00	306.0	28.45
50.00	22000.00	330.0	27.98
50.00	22000.00	360.0	27.63
50.00	22000.00	39 0. ŭ	27.37
50.00	22000.00	420.0	27.16
56.00	22000.00	45ů.0	27.01
50.00	22000.00	480.0	26.89
40.00	23000.00	10.0	299.22
40.60	23000.00	20.0	157.50
40.00	23000.00	36.0	110.36
40.00	23000.00	40.0	86.86
40.00	23000.00	50.0	72.81
40.00	23000.00	60.Ŭ	63.50
40.00	23000.00	90.0	48.16
40.00	23000.00	120.0	40.70
40.00	23000.00	150.ů	36.38
40.00	23000.00	180.0	33.63
40.00	23000.00	210.0	31.77
40.00	23000.00	240.0	30.45
40.00	23000.00	270.0	29.50
40.00	23000.00	300.0	28 .79
40.00	23000.00	330.0	28.26
40.00	23000.00	360.0	27.86
40.00	23000.00	390.0	27.55
40.00	23000.00	420.0	27.31
40.00	23000.00	450.0	27.12
40.00	23000.00	48 0 ∙0	26.98

DL	v _A	Time	CO
(m1/min/mm Hg)	(ml/min)	(min)	(ppm)
50.00	23000.00	10.0	273.95
50.00	23000.00	20.0	144.91
50.00	23000.00	30.0	102.00
50.00	23000.00	40.0	80.63
50.00	23000.00	50.0	67.86
50.00	23000.00	60.0	59.41
50.00 50.00	23000.00	90.0 120.0	45.52 38.80
50.00	23000.00	150.0	34.94
50.00	23000.00	180.0	32.50
50.00	23000.00	210.0	30.87
50.00	23000.00	240.0	29.73
50.00	23000.00	270.0	28.91
50.00	23000.00	300.0	28.32
50.00	23000.00	330.0	27.88
50.00	23000.00	360.0	27.55
50.00	23000.00	390.0	27.30
56.00	23000.00	420.0	27.11
50.00	23000.00	450.0	26.97
50.00	23000.00	480.0	26.86
40.00	24000.00	10.0	292.69
40.00	24000.00	20.0	154.25
40.00	24000.00	30.0	108.20
40.00	24000.00	40.0	85.25
40.00	24006.00	50.0	71.53
40.00	24000.00	60.0	62.44
40.00	24000.00	96.0	47.48
40.00 40.00	24000.00	120.0	49.21
40.00	24000.00	150.0 180.0	36.01
40.00	24000.00	210.0	33.34 31.53
40.00	24000.00	240.0	30.26
40.00	24000.00	270.0	29.35
40.00	24000.00	300.0	28.67
40.00	24000.00	336.0	28.16
40.00	24000.00	360.0	27.78
40.00	24000.00	390.0	27.48
40.00	24000.00	420.0	27.26
40.00	24000.00	450.0	27.08
40.00	24000.00	480.0	26.95

D _{T.}	VA	Time	CO
(m1/min/mm Hg)	(ml/min)	(min)	(ppm)
50.00	24000.00	10.0	267.42
50.00	24000.00	26.0	141.66
50.00	24000.00	30. 0	99.84
50.00	24000.00	40.0	79.02
50.00	24000.00	50.0	66.59
50.00	24000.00	66.0	58.35
50.00	24000.00	90.0	44.84
50.00	24000.00	120.0	38.31
50.00	24000.00	150.0	34.57
50.00	24000.00	180.0	32.22
50.00	24000.00	210.0	30.64
50.00	24000.00	240.0	29.55
50.00	24000.00	270.0	28.77
50.00	24000.00	300.0	28.20
50.00	24000.00	330.0	27.79
50.00	24000.00	360.0	27.48
50.00	24000.00	390.0	27.24
50.00	24000.00	420.0	27.07
50.00	24000.00	456.0	26.93
50.00	24000.00	480.0	26.83
40.00	25000.00	10.0	286.68
40.00	25000.00	20.0	151.25
40.00	25000.00	30.0	106.21
40.00	25000.00	40.0	83.76
40.00	25000.00	50.0	70.36
40.00	25000.00	60.0	61.47
40.00	25000.00	90.0	46.85
40.00	25000.00	120.0	39.76
40.00	25000.00	150.0	35.66
40.00	25000.00	180.0	33.07
40.00	25000.00	210.0	31.32
40.00	25000.00	240.0	30.09
40.00	25000.00	270.0	29.20
40.00	25000.00	300.0	28.55
40.00	25000.00	330.0	28.07
40.00	25000.00	360.0	27.70
40.00	25000.00	390.0	27.42
40.00	25000.00	420.0	27.21
40.00	25000.00	450.0	27.04
40.00	25000.00	480.0	26.92

DL	VA	Time	CO
(ml/min/mm Hg)	(m1/min)	(min)	(ppm)
50.00	25000.00	10.0	261.41
50.00	25000.00	20.0	138.66
50.00	25000.00	30.0	97.86
50.00	25000.00	40.ů	77.54
50.00	25000.00	50.0	65.41
50.00	25000.00	60.0	57.38
50.00	25000.00	90.0	44.22
50.00	25000.00	120.0	37.87
50.00	25000.00	150.0	34.24
50.00	25006.00	180.0	31.96
50.00	25000.00	210.0	30.44
50.00	25000.00	240.0	29.39
50.00	25000.00	270.0	28.64
50.00	25000.00	300.0	28.10
50.00	25000.00	330.0	27.70
50.00	25000.00	360.0	27.41
50.00	25000.00	390.0	27.19
50.00	25000.00	420.0	27.03
50.00 50.00	25000.00	450.0 480.0	26.90
50.00	25000.00	400.0	26.81
50.00	26600.00	16.0	255.87
50.00	26000.00	20.0	135.90
50.00	26000.00	30.0	96.03
50.00	26000.00	40.0	76.18
50.00	26000.00	50.0	64.33
50.00	26000.00	60.0	56.49
50.00	26000.00	90.0	43.64
50.00	26000.00	120.0	37.46
50.00	26000.00	150.0	33.93
50.00	26000.00	180.0	31.72
50.00	26000.00	216.0	30.25
50.00 50.00	26000.00	240.0 270.0	29.24
50.00	26000.00	300.0	28.52
50.00	26000.00	330.0	28.01
50.00	26000.00	360.0	27.63 27.35
50.00	26000.00	390.0	27.15
50.00	26000.00	420.0	26.99
50.00	26000.00	450.0	26.88
50.00	26000.00	480.0	26.79
~~~~			£ 0 • 1 )

D	VA	Time	CO
(ml/min/mm Hg		<b>(</b> min)	(ppm)
50.00	27000.00	10.0	250.74
50 <b>.</b> 00	27000.00	20.0	133.35
50.00	27000.00	30.0	94.33
50.00	27000.00	40.0	74.91
50.00	27000.00	50.0	63.33
50.00	27000.00	60.0	55.66
50.00	27000.00	90.0	43.11
50.00	27000.00	120.0	37.08
50.00	27000.00	150.0	33.65
50.00	27060.00	180.0	31.50
50.00	27000.00	210.0	30.08
50.00	27000.00	246.0	29.10
50.00 50.00	27000.00 27000.00	270.0 300.0	28.42
50.00	27000.00	330.0	27.92 27.57
50.00	27060.00	360.0	27.30
50.00	27000.00	390.0	27.11
50.00	27000.00	420.0	26.97
50.00	27000.00	450.0	26.86
50.00	27000.00	480.0	26.78
50.00	28000.00	10.0	245.97
50.00	28000.00	2 <b>0.</b> 0	130.97
50.00	28000.00	30.0	92.76
50.00	28000.00	40.0	73.74
50.00	28000.00	50.0	62.40
50.00	28000.00	60.0	54.90
50.00	28000.00	90.0	42.62
50.00	28000.00	120.0	36.73
50.00	28000.00	150.0	33.39
50.00 50.00	28000.00 28000.00	180.0 210.0	31.30
50.00	28000.00		29.92
50.00	28000.00	240.0 270.0	28.98
50.00	28000.00	300.0	28.32 2 <b>7.85</b>
50.00	28000.00	330.0	27.51
50.00	28000.00	360.0	27.26
50.00	28000.00	390.0	27.07
50.00	28000.00	420.0	26.94
50.00	28000.00	450.0	26.84
50.00	28000.00	480.0	26.76

D	VA	Time	СО
(m1/min/mm Hg)		(min)	(ppm)
( 0)	•		
50.00	29000.00	10.0	241.53
50.00	29000.00	20.0	128.76
50.00	29000.00	30.0	91.30
50.00	29000.00	40.0	72.65
50.00	29000.00	50.0	61.54
50.00	29000.00	60.0	54.19
50.00	29000.00	90.0	42.17
50.00	29000.00	120.0	36.41
50.00	29000.00	150.0	33.15
50.00	29000.00	180.0	31.12
50.00	29000.00	210.0	29.78
50.00	29000.00	240.0	28.87
50.00	29000.00	270.0	28.23
50.00	29000.00	300.0	27.78
50.00	29000.00	330.0	27.45
50.00	29000.00	360.0	27.22
50.00	29000.00	390.0	27.04
50.00	29000.00	420.0	26.92
50.00	29000.00	450.0	26.82
50.00	29000.00	480.0	26.75
50.00	30000.00	10.0	237.39
50.00	30000.00	20.0	126.70
50.00	30000.00	30.0	89.93
50.00	30000.00	40.0	71.63
50.00	30000.00	50.0	60.73
50.00	30000.00	60.0	53.52
50.00	30000.00	90.0	41.74
50.00	30000.00	120.0	36.11
50.00	30000.00	150.0	32.92
50.00	30000.00	180.0	30.95
50.00	30000.00	210.0	29.65
50.00	30000.00	240.0	28.77
50.00	30000.00	270.0	28.15
50.00	30000.00	300.0	27.72
50.00	30000.00	330.0	27.41
50.00	30000.00	360.0	27.18
50.00	30000.00	390.0	27.02
50.00	30000.00	420.0	26.90
50.00	30000.00	450.0	26.81
50.00	30000.00	480.0	26.74

## TABLE II

Emissions,					
Source	10 ⁶ tons/yr	Emission factor			
Industrial processes					
Foundries					
Controlled (with afterburners)	0.2	10 1b CO/ton of charge			
Uncontrolled	3.1	250 lb CO/ton of charge			
Petroleum Refineries		-			
Fluid catalytic crackers	2.0	13.7 lb CO/bbl of fresh feed			
Fluid coking	0.2	30 lb CO/bbl of fresh feed			
Moving-bed catalytic crackers	0.2	3.8 1b CO/bb1 of fresh feed			
Kraft pulp mills	2.6	215 1b CO/ton of product			
Carbon black					
Furnace	0.30	560 lb CO/ton of product			
Channel	0.05 ^d	-			
Thermal	0.01	47 lb CO/ton of product			
Steel mills		-			
Beehive coke ovens	0.02	4.5% of exhaust gas by volume			
Basic oxygen furnaces	0.1	3.2% of exhaust gas by volume			
Sintering	2.4	500 ft ³ /ton			
Formaldehyde	0.03	100 lb CO/ton of product			

## CARBON MONOXIDE EMISSION ESTIMATES - 1968⁴

## TABLE I

## PHYSICAL CHARACTERISTICS OF CO4

28.01 Molecular weight Melting point -207°C -192°C Boiling point Specific gravity relative to air 0.968 Density 1.25 g/liter At 0°C, 760 mm Hg At 25°C, 760 mm Hg 1.15 g/liter Explosive limits in air 12.5 to 74.2% (volume) Solubility^a At 0°C 3,54 m1/100 m1 water 2.14 m1/100 m1 water At 25°C Conversion factors  $1 \text{ mg/m}^3 = 0.800 \text{ ppm}$   $1 \text{ ppm} = 1.250 \text{ mg/m}^3$   $1 \text{ mg/m}^3 = 0.874 \text{ ppm}$ At 0°C, 760 mm Hg At 25°C, 760 mm Hg  $1 \text{ ppm} = 1.145 \text{ mg/m}^3$ 

^aVolume of CO indicated is at 0°C, 760 mm Hg.

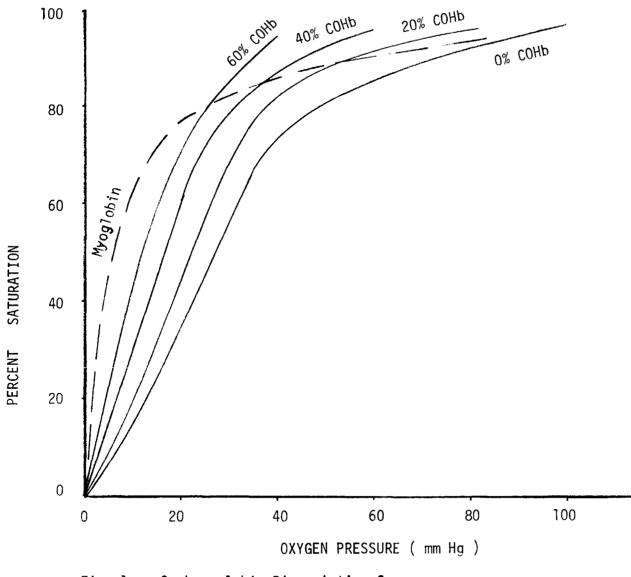
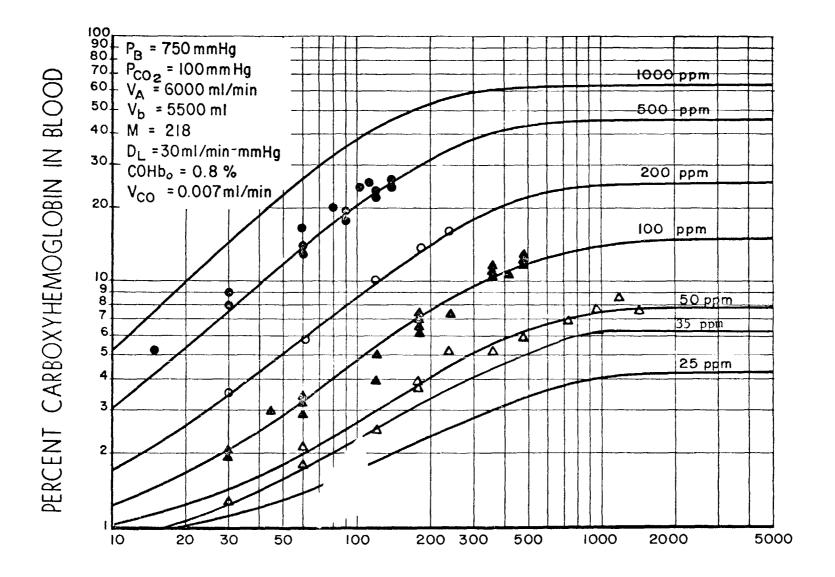


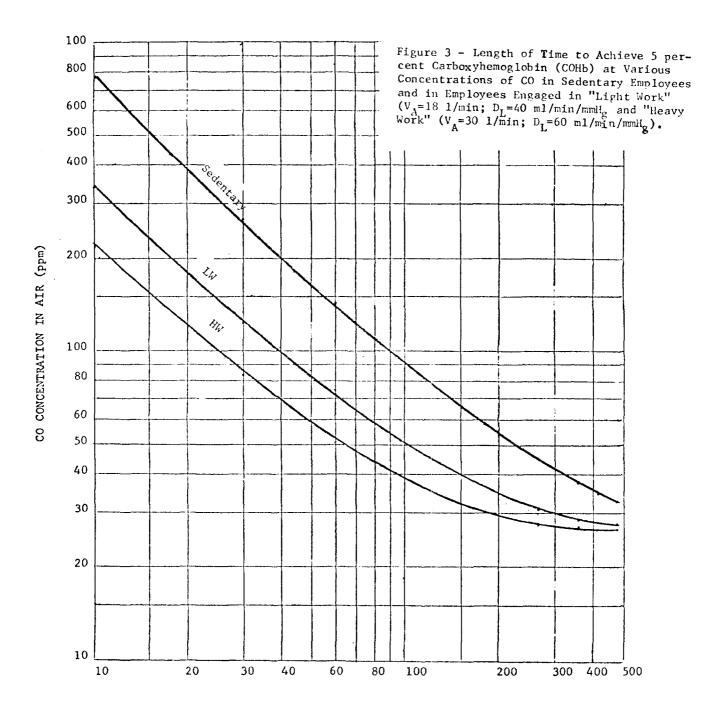
Fig 1 -- Oxyhemoglobin Dissociation Curve







EXPOSURE DURATION, MINUTES Stewart, R. D., et al: Experimental Human Exposure to Carbon Monoxide. <u>Arch. Environ. Health.</u> 21:154-164, 1970.



DURATION OF EXPOSURE (MINUTES)