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BIOLOGICAL EFFECTS OF SHORT,
HIGH-LEVEL EXPOSURE TO GASES: CARBON MONOXIDE

PHASE REPORT

PREPARED BY

Thomas E. Nightingale, Ph.D.

June 1980

SUPPORTED BY

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-79-C-9086

Enviro Control, Inc.
One Central Plaza
11300 Rockville Pike
Rockville, Maryland 20852

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Environmental Protection Research Division
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Fort Detrick, Frederick, Maryland 21701

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) This report presents an analysis and synthesis of the available literature describing health and performance effects of exposure to carbon monoxide (CO). The US Army's concern is with high-level, short-term exposures that may exceed present threshold limit values of the American Conference of Governmental Industrial Hygienists (50 ppm as a TWA and a ceiling of 400 ppm for 15 minutes). The organs primarily affected by exposure to CO are the heart and brain, with effects caused by impaired oxygen delivery.			

During brief exposures to concentrations of up to 35,600 ppm, there was an electrocardiographic change suggestive of myocardial ischemia within 15 seconds after the start of exposure, although there were no changes in heart rate, blood pressure or blood chemistry values in young healthy subjects. The first subjective sign of CO toxicity will probably be a headache followed by an awareness of a pounding heartbeat; however, the great variation in tolerance precludes establishment of threshold values per se, although a carboxyhemoglobin (COHb) of 15 percent would probably not elicit these symptoms in most healthy subjects. Laboratory studies have shown a reduction in work capacity following CO exposure in humans. The basis for this lower work capacity has been investigated in both humans and animal models, which is compensated for by an increase in coronary blood flow in healthy subjects up to 9% COHb in man and 30% COHb in dogs. In subjects with occluded coronary arteries, arterial vasospasms or previous myocardial infarcts, compensatory changes are diminished. Data from fire fighters who are exposed to high levels of CO for short terms indicate possible long-term cardiovascular disease, consisting of myocardial ischemia and decreased ventricular wall motion which may relate to the high incidence of coronary mortality in fire fighters. Laboratory studies of fire fighters have shown an increased incidence of electrocardiographic changes during stress testing as well as some serum enzyme changes suggestive of myocardial damage in men who otherwise appear to be in good health. CO-related impairment of audiovisual performance and motor coordination has not been well defined. Most studies dealing with sensory and motor function have used low level CO exposures with exposure times of hours. Chronic and adaptive responses to CO have been studied in animals, but no model has shown consistent biochemical or pathological changes that could be extrapolated to man. Enhancement of atherosclerosis has been the most widely reported finding in animal studies, but recent work has shown that the evidence is not as clear cut as once thought. Nomograms to relate CO exposure levels and times have been developed, but factors such as exercise levels and cardiovascular and ventilatory function levels must be included in the model selected. These techniques will estimate increases in blood COHb values that must be added to the background COHb, which may be elevated, as in the case of cigarette smoke, or if the ambient air contains any measurable amount of CO.

EXECUTIVE SUMMARY

The overall purpose of this project is to characterize the biological responses of short, high-level exposures to four gases (ammonia, carbon monoxide, sulfur dioxide and the nitrogen oxides) associated with certain Army weapons systems. This report contains an analysis and synthesis of the available literature concerned with possible health and performance effects of exposure to carbon monoxide.

Carbon monoxide is generated by the combustion of ammunition propellants, from engine exhaust and from auxiliary generators. Soldiers may be exposed to combustion emissions during training with the various weapons systems or during combat. Armored vehicle crewmen may be especially vulnerable because of the closely confined and sometimes poorly ventilated space inside the vehicles and because of the proximity of personnel to the emission sources. Exposures may be above threshold limit values recommended by the American Conference of Governmental Industrial Hygienists and current industrial occupational standards, brief (1 hour or less) and repeated (1 to 6 times daily for periods of 1 to 14 days).

Threshold limit values for use in the workplace would appear to have limited application in this military setting; the basis for their selection is the protection of workers against nose and throat irritation and the minimization of complaints of discomfort among office workers and similarly uninured individuals. Selection of maximum allowable concentrations for use in the military should be based more appropriately on considerations of casualty prevention (i.e., immediate incapacitation or delayed health effects) to minimize effects that would impair operational efficiency. To this end, an effort has been made to identify threshold levels at which effects may be expected to occur, or applicable concentration-time relationships; the nature and extent of possible effects when such levels are exceeded; and gaps and inconsistencies in available data, which is the basis for identifying areas where follow-up research may be required.

The data on which this report is based were derived by the collection, critical review and evaluation of published literature and research reports. The main sources of information were the various computer data bases, especially MEDLINE and its back files, TOXLINE, TOXBACK, NTIS AND NIOSHTIC. Most of the data regarding physiological mechanisms that are affected by CO in both man and animals was found in reports of exposure to CO levels of 50 to 1000 ppm for periods of up to 2 hours. Audiovisual and motor coordination research was generally conducted with CO concentrations up to 500 ppm for periods up to 5 hours. The animals examined for delayed and adaptive response research were usually exposed to CO levels of up to 200 ppm for weeks of either continuous or intermittent exposure.

There are very few published reports of systematic human exposure to high levels of CO over short time intervals. This lack of data is due in part to the fact that CO is not detectable by the human senses, and that in healthy subjects the first sign of CO toxicity may be a headache or a sensation of a pounding heartbeat, neither of which is quantifiable in a research laboratory. A second reason for the lack of data is the fact that physiological and psychological testing is usually performed when parameters of interest are in a steady state, and the time to reach the steady state may vary from several minutes for a cardiovascular or pulmonary test to several hours to achieve steady state blood COHb levels.

An occupational group that fits the desired high-level, short-term intermittent CO exposure condition is fire fighters. While some data are available from this group, calculation of CO exposure levels is impossible for all practical purposes, since each fire is unique and the nature of the fire fighter's duties rules out many types of measurements that might provide data such as pre-exposure COHb levels, immediate post-exposure COHb levels, some estimation of ambient concentrations of CO and time of exposure to that level, maximum work capacity during exposure and longitudinal studies to determine CO exposure effects over time with periodic stress and clinical chemistry monitoring, including serum enzymes determinations. Some collected evidence indicates possible coronary problems such as coronary artery vasospasm and ventricular wall thickening and reduction of motion in fire fighters. These findings do not indicate if there is an exposure threshold or if these men are from a particularly susceptible subpopulation of fire fighters or from a group with a particular exposure history.

Published data do not indicate a threshold COHb that can be defined as an "effect" level, since headaches were reported to result when venous COHb levels were 9.1 and 10.2 percent (Stewart et al.⁴⁹), 20 percent (Apthorp et al.²) and 32, 36 and 37 percent on three occasions for the same subject (Haldane²³). However, firefighters who were also cigarette smokers had blood COHb values of up to 19 percent with no indication of being unable to perform their duties, and no headaches were noted.⁴⁹

Data regarding audiovisual and motor performance after CO exposure are not at all useful in establishing effect levels. Test conditions, CO exposure levels and times, parameters tested and presentation of findings of the reviewed papers were so diverse that no specific type of impairment and COHb level could be defined.

Studies conducted on exercising subjects in good health and those with a history of coronary disease indicate that the time to fatigue and/or to the onset of angina is shortened after CO exposures.

Consideration of special health problems, such as a particular tendency toward coronary artery vasospasm and ischemic ECG changes during stress testing, and limitation of CO exposures for pregnant females seem warranted based on the limited data available for these groups.

Equations to predict increases in blood COHb levels after exposure to a level of CO for a given time, with factors such as time between exposures taken into consideration, are valid only if factors such as exercise levels (with a concomitant increase in cardiovascular and respiratory function) are taken into account. It should be emphasized that equations such as the Coburn et al.¹⁶ will give data for increases above pre-existing levels. If a soldier who is a cigarette smoker enters an exposure to a level of CO with a background COHb of 10 percent, the CO exposure will be additive over short time intervals, due to the long time (3-4 hours) required to eliminate CO from the blood.

Relating the various factors that will influence COHb levels in the soldier is a complex matter which cannot be addressed completely with the available data base at this time. There are four areas that may be briefly reviewed to summarize the problem:

1. Background CO Levels - Ambient Air and Personal

Much of the published data was derived with subjects breathing purified air or oxygen, which produced a low initial COHb. Upon completion of testing, subjects returned to room air or a test gas with a low CO level. If ambient levels of CO are increased to any measurable level, there will be some impact on baseline COHb values. This problem extends to the smoking soldier, since smokers may have baseline COHb levels of 5 to 15 percent saturation. If a threshold level of 5 percent COHb were to be established, it is highly possible that most, if not all, smokers would exceed that level during most of their waking hours.

2. Exercise and Cardiopulmonary Changes

In the Coburn et al.¹⁶ and the models of Peterson and Stewart⁴³ and Stewart et al.⁴⁹, exercise is factored into the estimation of COHb, since ventilation and cardiovascular function increase with exercise levels. Pulmonary clearance in these models is assumed to be at steady-state levels, and while this is possible in laboratory studies, it is not probable in a field setting. One must consider the possibility that increased ventilation may accompany the increased activity associated with the onset of gun firing, and thus produce higher initial CO uptake values, while complications such as fatigue or the effects of CO and other inhaled gases may cause ventilation to decrease and thus slow CO clearance from the body.

3. Rate of COHb Uptake and Clearance

There is a large body of theory and speculation dealing with inhalation of high CO levels, but very limited data in man, especially in exercising man. The study by Stewart et al.⁴⁹ suggests that the rate of increase of COHb may be more important than peak levels, since two subjects experienced headaches at COHb levels of 9.1 and 11.6 percent, although these COHb levels are generally considered to be below subjective thresholds.

4. Individual Susceptibility

The wide range of COHb levels that produced headaches (9.1 to 37 percent) suggests a broad range of individual sensitivity, and that establishing an arbitrary threshold COHb as an effect level is unrealistic. While it is highly probable that most healthy young soldiers will not have an acute response to a short-term COHb of 15 percent, there is no way of knowing if arterial or myocardial changes will result at a later time. There is also no firm evidence that repeated exposures to CO will enhance disease processes, such as those reported in fire fighters, although the possibility cannot be excluded. Categories of subjects with increased susceptibility to CO effects include subjects with a tendency toward arterial vasospasms, a history of myocardial infarcts, anemia and the pregnant.

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I. INTRODUCTION AND BACKGROUND

The overall problem addressed by this project is the potential exposure of soldiers to carbon monoxide (CO) (from engine exhaust, auxiliary generators and explosives), ammonia (from explosives, especially those formulations containing nitroguanidine), oxides of nitrogen (from explosives), and oxides of sulfur (from explosives and engine exhaust). The exposures may be intense (above present threshold limit values of the American Conference of Industrial Hygienists, brief (1 hour or less), and repeated (1 to 6 times daily for periods of 1 to 14 days). Such exposures may occur during the training of soldiers with various weapons systems or during actual combat.

Threshold limit values (TLV) developed for use in the workplace would appear to have limited application in the various military situations under consideration. The present TLV for CO (50 ppm* as a time-weighted average (TWA) and a short-term exposure limit of 400 ppm for 15 minutes) was selected to protect workers against nose and throat irritation and to minimize complaints of discomfort among office workers and similar uninjured individuals. It would seem more appropriate to base selection of maximum allowable concentrations for use in the military upon considerations of casualty prevention (i.e., immediate incapacitation or delayed health effects) to minimize effects that will reduce operations efficiency.

This report presents an analysis and synthesis of the available literature concerned with possible health and performance effects of exposure to CO, specifically the possible immediate and reversible effects, mainly irritant, or single, short, high-level exposures and the delayed, reversible or irreversible effects of repeated exposures. An effort has been made to identify threshold levels at which effects may be expected to occur, or applicable concentration-time relationships; the nature and extent of effects when such levels are exceeded; and gaps and inconsistencies in available data, which is the basis for identifying areas where follow-on research may be required.

While exposure to emissions from ammunition propellants, including CO, may be encountered by soldiers in a variety of operational settings, the US Army's concern about the potentially deleterious effects of various air pollutants previously has focused on exposures in various armored vehicles. This focus of attention seems warranted, as armored crewmen may be especially vulnerable to the adverse effects of exposure to the toxicants in question because of the closely confined and sometimes poorly ventilated space inside the vehicles and because of the proximity of personnel to the emission sources.

*Throughout the remainder of the report, concentrations are expressed as parts per million (ppm). To convert ppm to mg/m³, multiply ppm by 1.10. This constant is derived by dividing the molecular weight of CO (28.01 g) by the volume that 1 mole of gas would occupy at 25°C (298°K) and 1 atmosphere of pressure, multiplied by 10³/m³ (to convert to m³ units).

One of the first attempts by the Army to resolve the problem of exposures to engine exhaust and ammunition propellant emissions dates back to 1943. The stated purpose of the 1943 reports was "...to determine the extent of the hazard from fumes released by firing of the weapons in the M4A4E1 tank with 105 mm howitzer and in the M7 tank." The sources of toxic gas production and accumulation considered were the weapons systems, especially with respect to their construction and placement within the tank. The reports provide insights into the overall nature and potential severity of the problem of toxic gases in armored vehicles. The main findings were:

- In general, the atmospheric conditions inside the tanks were completely unsatisfactory.
- The blood of crew members showed dangerous levels of carboxy-hemoglobin (COHb).
- Sufficient ammonia was present to cause considerable eye and nose irritation.
- The greater the workload of a crew member the greater the respiratory rate and the level of COHb in the blood.
- The turret machine gun proved especially dangerous. In one study, the blood COHb increased at an alarming rate to 23 percent in only 9 minutes, and the concentrations of CO and ammonia proved so intense that operation of the weapon was considered extremely difficult and unreliable. In the second study, the testing had to be discontinued early because of the immediate danger to the crew. Further, the ammonia levels were so extreme that turret crew members were unable to execute their normal tasks effectively.
- The unsatisfactory performance of certain crew members was due to the trapping of these gases by poor gun placement and mounting and inadequate ventilation.

II. APPROACH TO THE PROBLEM

The approach to the work involved the following major tasks:

- The identification of information sources
- The preliminary screening of information before acquisition
- The assessment of the availability of sufficient literature to perform remaining work elements
- The acquisition of the literature
- The critical review of documents for scientific validity
- The evaluation of biologic response data in terms of performance and health effects, both immediate and delayed, and reversible and irreversible.

The main sources of information were the various computer data bases, especially MEDLINE and its backfiles, TOXLINE, TOXBACK, NTIS and NTOSHIC. The computer search was performed by first selecting key terms describing substance and exposure. Only articles containing one or more terms from each of three sets of keywords were retrieved. Due to the paucity of relevant articles produced by this first attempt, the search method was revised. The second search eliminated all exposure level limiters and included only terms and synonyms for substance and biological effects. Again, only articles containing one or more terms from both sets were retrieved by the computer.

All materials yielded by the search of the data bases were screened by the Principal Investigator to identify articles apparently relevant to the study. The screening was based on the content of article abstracts (when available) and on the presence of keywords in article titles. Full-text copies of all apparently relevant articles were then secured for critical review and evaluation. In addition to confirming the relevance of the material to the present study, the critical review determined the adequacy and appropriateness of the experimental design, the accuracy and validity of the statistical analyses performed, and the correctness of the conclusions in light of the data analysis.

Upon completion of the search of the data bases and the screening of materials yielded by the search, it was apparent there were very few documents on short, high-level exposures to CO in either animals or man. Review of the references listed in key articles and other basic sources confirmed that the search had identified nearly all documents of any potential value to the project. The relative paucity of data on CO as well as the absence of reports of serious adverse effects under anticipated conditions of exposure, resulted in an early decision to terminate further searching, and to prepare a report based on review and analysis of the literature already collected. This does not mean there are significant

omissions of articles bearing directly on the problem of short, high-level exposures to CO (as far as can be ascertained, all such key articles have been included); but rather, not all of the available literature of possible peripheral interest has been collected and reviewed (e.g., reports of accidental human exposures to unmeasured concentrations, probably in the range of several thousand parts per million).

The report is divided into the following sections:

- "Summary of Effects and Conclusions," which presents the main findings of the literature review in summary fashion and identifies significant gaps and inconsistencies.
- "Discussion" of the data presented in the literature, leading to the main findings, gaps and inconsistencies.
- A section on "Suggested Follow-on Work," in which possible additional research is proposed to fill major gaps in the information or to resolve discrepancies.
- "Literature Review and Analysis" (attached as Appendix A), which is a presentation of the purpose, methods and findings of each key article, followed by a critical analysis, as appropriate, of the experimental design, statistical methods, and the correctness of the conclusions.

III. SUMMARY OF EFFECTS AND CONCLUSIONS

Laboratory investigations into the acute effects of CO have not revealed any specific toxicity of CO other than its impairment of oxygen delivery and utilization. Studies in humans have generally used levels from 25 to 1000 ppm and either short (30 seconds) or long (up to 24 hours) exposures to produce blood COHb levels of up to 20 percent, which were then correlated with measured parameters of interest. There have been very few reports of high CO levels being administered to humans. Three studies in the literature involved self-administration, with peak COHb values of 34 to 56 percent.^{2,23,26}

Animal studies have used low CO levels in an attempt to produce COHb values of 3 to 10 percent as would be found in human smokers⁵⁷, or high levels (up to 65 percent COHb) to define physiological limits of cardiac function^{1,44} or cerebral blood flow.¹⁸

One occupational group that fits the desired criteria of repeated short-term, high level exposure to CO is fire fighters. While CO levels as high as 3000 ppm have been measured at fires,¹⁰ the fact that each fire is unique, with different CO levels in each room of a structure, makes quantifying total CO dose difficult. However, since some programs have begun to examine fire fighters during testing programs as well as during working sessions, useful data are appearing in the literature.

A. Immediate Effects

Because CO is a colorless, tasteless and odorless gas, the first subjective sign of intoxication in a healthy subject may be a headache when blood COHb levels reach 10 to 20 percent saturation.^{2,23,26,49} If the exposure continues, symptoms may progress to dizziness, nausea, a feeling of weakness, mental confusion, impaired vision and an awareness of palpitations and breathing difficulties prior to collapsing.²³ Individual differences and the subjective nature of symptoms such as headaches have made it difficult to quantify CO responses precisely, since one subject may have a headache at a COHb of 20 percent and another at a COHb of 38.5 percent.²

If a person performs exercise or work during CO inhalation, the maximum worktime before exhaustion will be reduced, depending both on COHb and exercise levels.^{19,20,60} Subjects with a prior history of myocardial damage can be expected to show signs of anginal pain in a shorter time and after less exertion than would be the case while breathing pure air.³

Animal studies have shown that coronary^{12,64} and cerebral^{51,55} blood supply were increased when COHb levels increased. It is interesting to note that both dogs and goats used in these investigations were able to increase blood flows to these critical organs up to the point of 30 percent COHb, which is also the level at which man has been found to experience physiological difficulties.^{2,23}

While numerous studies of audiovisual and motor coordination have been conducted, there is no consensus of which test is most relevant to the issue of mental impairment due to CO. A recent review by Laties and Merigan³² concluded that our knowledge of CO effects as a function of subject task and exposure parameters in man are quite tentative.

B. Delayed and Adaptive Responses

The role of CO in chronic disease processes such as coronary and atherosclerotic disease is suggested by data from two human populations - smokers and fire fighters. While the US Army is concerned with repeated high-level, short-term exposures, the nature of CO binding to hemoglobin and its subsequent elimination over a course of several hours may represent a prolonged challenge to the body.⁶¹ This effect may become important when these short-term exposures are superimposed on blood COHb levels of up to 10 percent as found in smokers.⁵⁷

Epidemiological and clinical data from fire fighters indicate that they have the highest occupational incidence of heart disease.¹⁰ While their exposure conditions in regard to time would appear similar to those envisioned by the US Army for soldiers in a crew compartment, the inhaled smoke products could be significantly different. In addition to determining CO levels in fires,¹⁰ other investigators have studied blood thiocyanate levels, which are largely attributable to smoke inhalation.^{33,52}

While the workscope for this literature review did not specify any particular subpopulation that should be identified, there is a high potential risk for the pregnant female. The 1979 edition of the Surgeon General's Report on Smoking and Health⁵⁷ includes an extensive review on maternal-fetal interactions of the smoking mother. One of the data sets indicates that fetal COHb levels are 10-15 percent higher than maternal levels. Considering the fact that maternal smoking has been reported to be associated with decreased infant weight and increased number of abortions, stillbirths, and deaths during the neonatal and postnatal periods, caution in limiting exposures to CO and other toxicants would seem justified, even though CO per se has not been conclusively proven to be the cause of the fetal problems.³⁴

C. Conclusions

Published data suggests that headaches and a decreased ability to perform physical tasks will be the first symptoms of CO inhalation in healthy soldiers. There is no clear pattern of audiovisual or motor coordination thresholds for COHb, and the literature regarding delayed and adaptive responses to inhalation of high CO levels is defined only for fire fighters.

Establishing a threshold for CO exposure must acknowledge background CO levels inhaled as well as COHb levels due to smoking, the fact that cardiopulmonary function is actually a set of very labile parameters

that are constantly changing, the possibility that rates of CO uptake and washout may be more important than peak COHb levels attained, and that individual susceptibility may invalidate any established guidelines.

A series of calculations were performed with the Coburn-Forster-Kane equation¹⁶ to predict peak COHb levels in a simulated battle scenario (Appendix C). While these calculations are illustrative for steady state levels, they do not fully demonstrate the impact of short-term, high-level CO exposures during physical exertion. These factors are better shown by calculations based on the work of Stewart et al.,⁴⁹ which relate inhaled CO levels (in ppm) to ventilation rates (in liters per minute) during fluctuating CO concentrations. In the following table, changes in blood COHb per minute are shown as a function of CO level inhaled and ventilation rates ranging from quiet breathing (5 liters per minute) to strenuous activity while sitting (30 liters per minute) and severe exercise (60 liters per minute).

CO (ppm)	ΔCOHb Ltr V	V (Ltrs/min)			
		5	15	30	60
50	0.0023	0.012	0.035	0.069	0.14
100	0.0043	0.022	0.066	0.13	0.26
200	0.009	0.045	0.135	0.27	0.54
500	0.023	0.115	0.345	0.69	1.38
1000	0.043	0.215	0.645	1.29	2.58
2000	0.09	0.45	1.35	2.70	5.40
3000	0.14	0.70	2.10	4.20	8.40
4000	0.18	0.90	2.70	5.40	10.80
5000	0.23	1.15	3.45	6.90	13.8
6000	0.27	1.35	4.05	8.10	16.2

These data indicate that exposure to 6000 ppm CO for 1 minute would elevate venous blood COHb by 8.10 percent during strenuous activity. For longer exposures there would be proportional increases which would of course, be superimposed on pre-existing COHb levels. It thus becomes very evident that short-term high level CO exposures coupled with physical exertion do pose a potential risk for exposed subjects.

IV. DISCUSSION

A. Exposure Limits

In 1973 the National Institute for Occupational Safety and Health (NIOSH) recommended an 8-hour TWA standard of 35 ppm. This standard was based on the concentration of CO that would cause the blood COHb level of nonsmoking employees engaged in sedentary activity to approach 5 percent during 8 hours of continuous exposure. This standard was developed with the aide of the Coburn-Forster-Kane equation.¹⁶ A 5 percent COHb level was selected on the basis of cardiovascular and behavioral evidence. It was acknowledged that subjects with clinical symptoms of coronary heart disease may not experience an adequate margin of protection with 5 percent COHb, but it was felt that limiting CO exposure to this level should protect the individual with asymptomatic coronary heart disease from developing clinical symptoms.

In 1971, the Environmental Protection Agency (EPA), under the provisions of the Clean Air Act (PL 91-604) set an air quality standard of 9 ppm CO as a maximum 8-hour concentration not to be exceeded more than once per year and a maximum one-hour standard of 35 ppm not to be exceeded more than once per year. These standards, based primarily upon the work of Beard and Wertheim,¹¹ were designed to keep blood COHb levels below 2 percent for nonsmokers.

In 1973, the National Research Council prepared for the EPA a recommended "Guide for Short Term Exposures of the Public to Air Pollutants." The Short-term Public Limit (StPL) was designed to maintain COHb below 2 percent for nonsmokers engaged in light work and below 3 percent for heavier exercise. These standards were selected so that the public should not experience any risk to health with CO exposure and persons with pre-existing coronary heart disease should not experience significant myocardial change.

Recommended Short-term Public Limits for CO

10 min/90 ppm
30 min/35 ppm
60 min/25 ppm
4 to 5 hr/day/3 to 4 days/month/15 ppm

Recommended standards for Public Emergency Limits (PEL) were also prepared. This standard envisions possible temporary discomfort, which is reversible, and that no injury will result from the exposure. Persons with myocardial disease are expected to be the most susceptible. These PEL values were selected to prevent COHb levels from exceeding 5 percent during light work and 6 percent during heavy work, and to produce COHb levels less than 3 percent for persons at rest.

Recommended Public Emergency Limits

10 min/275 ppm
30 min/100 ppm
60 min/60 ppm

B. Physiological Response and Alterations in Work Capacity

Laboratory investigations of the effects of CO have focused on those physiological indices associated with impaired oxygen delivery, because it has been generally believed since the time of Haldane (1895)²³ that CO itself does not produce any acute toxic manifestations. This belief has been reinforced by numerous later studies in humans such as one that showed only a headache occurred after brief, high-level exposures.⁴⁹

There are no measurable effects of CO on resting man until headaches or a noticeable pounding heartbeat are noted.⁴⁹ These signs may occur at venous COHb levels as low as 10 percent. These findings are not unexpected, since the two organs with the most critical oxygen needs are the brain and heart. To obtain data relating CO exposure and function, investigators have developed protocols in which measurable indices can be monitored before, during and after interventions such as exercise.

1. Cardiovascular Studies

A reduction of oxygen delivery to the heart will be noticed most quickly in a person who has a pre-existing impairment of the coronary vasculature. Aronow and Isbell³ conducted a study of low-level CO exposure in such a population who had previously been shown to have at least a 50 percent narrowing of at least one major coronary vessel. The criterion for assessing the degree of impairment was the time to onset of angina while the subjects were exercising on a bicycle ergometer at a constant load. The patients were continually monitored for electrocardiographic (ECG) data; their blood pressure was recorded prior to exercising and as soon as exercise was stopped. Venous blood samples were taken prior to and after inhaling either air or 50 ppm CO in air for 2 hours. Each patient performed the exercise protocol four times, twice with air breathing as controls, once after breathing purified air and once after inhaling the CO mixture. The time to onset of angina was very repeatable, with averages of 223.0, 224.3 and 226.7 seconds for the ten patients breathing air for three trials. When CO was inhaled to produce an average COHb of 2.68 percent, the time to onset of angina fell significantly to 187.6 seconds ($p < 0.001$). The authors also noted that the ECG indicator of ischemia, the S-T segment depression, generally appeared earlier and was deeper, although no quantitation was done on this parameter. Blood pressures and heart rates at rest after either air or CO inhalation were not different, but after exercise and CO inhalation, both heart rates and systolic blood pressure were lower ($p < 0.001$) at onset of angina in patients who had inhaled CO. This study clearly shows impaired work performance in this susceptible population after inhaling CO.

Similar studies have been performed in normal healthy subjects. A volume of data has been collected and the final conclusion is the same as in cardiac patients, i.e., exercise performance is limited by CO. These studies have used criteria such as time to exhaustion, with exercise

rates adjusted for each individual to either produce a peak heart rate or a predetermined level of oxygen uptake for a control test and then repeat that exercise level after inhaling CO.

Eklom and Huot¹⁹ used workloads that would exhaust well-trained physical education students in 5 to 6 minutes. An objective measure of maximum workload was that of reaching a plateau level in maximum oxygen uptake ($\dot{V}O_2$ max) as determined by analysis of expired air volume and oxygen content. Lower levels of exercise were based on either 20 or 70 percent of $\dot{V}O_2$ max. With the subjects performing at submaximal and maximal exercise levels after breathing air or CO sufficient to produce COHb levels from 4.8 to 21.2 percent saturation, the authors were able to demonstrate relationships between maximum oxygen uptake and maximum worktime that could be related to blood COHb by the equations:

$$\text{Percent decrease in } \dot{V}O_2 \text{ max} = -0.19 + 1.17 \text{ COHb}$$

$$\text{Percent decrease in maximal worktime} = 15.8 + 1.82 \text{ COHb}$$

These equations provide a means of predicting the degree of impaired physical performance to be expected at a particular COHb level, but they do not give any insight as to the type of limiting factors, such as cardiac, ventilatory, metabolic etc.

A later study from this same laboratory was conducted by examining hemodynamic factors during high and low oxygen states while exercising.²⁰ High oxygen levels were produced by administering 50 percent O_2 , while low oxygen levels were produced by having the subjects breathe an unspecified level of CO for 15 minutes. Resulting COHb values were 12.8 to 15.8 percent. Maximal oxygen consumption ($\dot{V}O_2$ max) and physical performance, as shown by time to exhaustion, were both changed in parallel with inhaled oxygen levels. During maximal exercise at elevated COHb, $\dot{V}O_2$ max was reduced by 14.2 percent, maximum cardiac output (Q max) fell by 6.1 percent and stroke volume fell by 5.4 percent, while maximum heart rate, arterial blood pressure and pulmonary ventilation remained unchanged (when compared to similar data during air breathing). Average COHb levels during these observations were 13.3 percent. These data indicate that the performance limitation in both this and the previous study was due to cardiovascular and not pulmonary factors.

In a study designed to compare the effects of gradual increases of COHb as would occur by inhaling 75 or 100 ppm CO for 15 minutes with rapid increases in COHb resulting from inhaling a bolus of unspecified volume and CO concentration, followed by a maintenance level of CO amounting to 17.5 or 23.6 ppm, Horvath et al.²⁸ also collected data regarding exercise and oxygen consumption. There were no differences in final COHb levels between the two methods of administration, with upper COHb values of 4.25 to 4.30 percent. The authors found that $\dot{V}O_2$ max and exercise time were reduced when COHb was over 4.0 percent. To define this relationship, the authors note that the equation

$$\dot{V}O_2 \text{ max} = 2.2 + 0.91 \text{ COHb}$$

fits the observed values at over 4 percent COHb. These investigators concluded that the method of producing elevated COHb levels was not critically different in so far as final COHb levels, and that this lack of difference may have been due to the fact that the CO levels administered were relatively low, at least when compared to those used by Stewart et al.⁴⁹ in which CO concentrations of up to 35,600 ppm were inhaled for 1.5 minutes.

While Horvath et al.²⁸ were concerned with low COHb levels up to 4 percent, Vogel and Gleser⁵³ conducted measurements of cardiovascular and oxygen delivery mechanisms at COHb levels up to 18-20 percent saturation. They also used a booster dose of CO amounting to 10,000 to 12,000 ppm in a total volume of 40 liters, which the subject inhaled over an estimated period of several minutes, followed by a maintenance level of 225 ppm CO for the remainder of the trial. CO again had no effect on resting heart rate, blood pressure, cardiac output or minute ventilatory volume. At submaximal exercise levels, no changes were noted in $\dot{V}O_2$ max because the increased cardiac output compensated for the lower tissue oxygen extraction. However, at maximal exercise levels, cardiac output and mixed venous oxygen content were the same for both air breathing and CO inhalation, so that the result was a fall in $\dot{V}O_2$ max. This study demonstrates the lack of chemoreceptor-initiated sympathetic activity in resting subjects inhaling CO. It also shows that CO itself is not a chemoreceptor stimulant or depressant, since heart rate and cardiac output responses to severe exercise were the same in normoxia and CO inhalation.

A report of coronary blood flow measurements in humans exposed to 50,000 ppm CO for 30 to 120 seconds indicates that with COHb levels from 7.86 to 9.0 percent, coronary blood flow increased sufficiently to maintain oxygen supply in spite of the reduced oxygen content of the arterial blood supply.⁵ Unfortunately, no mention is made of the clinical status of these subjects, although they were noted to be in the laboratory for diagnostic cardiac catheterization.

A similar study was performed in conscious dogs that had been instrumented for coronary artery flow, left ventricular and arterial blood pressure, and collection of blood from the left atrium and coronary sinus.⁶⁴ After control measurements, CO was administered at 1000 ppm for 45 to 60 minutes to lower arterial oxygen saturation by approximately 30 percent. No change was noted in arterial blood pressure, left ventricular contractility or ECG waveform. Myocardial oxygen consumption was maintained at control levels throughout the study by a 100 percent increase in coronary blood flow and decreased coronary artery resistance (52 percent).

These two studies indicate that in a normal heart, increased blood flow is adequate to maintain oxygenation to a COHb level of 9 percent in man and 30 percent in dogs. However, in hearts with limited flow or a previous history of myocardial damage, this is probably not true. This

question was addressed in a study by Becker and Haak.¹² In dogs that had experimental myocardial infarcts produced by ligation of a coronary artery, a series of pressure and flow measurements were made along with electrocardiograms made by a unipolar lead placed on the surface of the heart at some 10 to 15 locations. Control measurements were made; the dogs were then given a volume of 10 liters of a mixture of 5000 ppm CO in air over an estimated 3-4 minutes, and the measurements were repeated. This stepwise procedure was repeated five times to produce COHb values of 4.9, 8.9, 11.3, 14.2 and 17.0 percent. There were no changes in cardiac output, aortic root pressure, mean left atrial pressure, left ventricular ejection time or heart rate. Blood flow to the non-ischemic area of the myocardium increased with CO exposure, while the infarcted portion showed greater changes in S-T segment alterations, suggesting flow limitations plus oxygen reductions can severely impair a previously ischemic area, although a possible neurogenic mechanism has been proposed to maintain oxygen availability during stress.^{1,64}

2. Cerebral Blood Flow

Studies of cerebral flow and physiological function related to CO inhalation are few in number. Paulson *et al.*⁴² measured cerebral blood flow in humans who were undergoing diagnostic angiograms. After the patients inhaled a volume of 5000 ppm CO in air equal to one-fifth to one-fourth of their body weight in kilograms, measurements were repeated and then the patients inhaled another volume of CO and a third set of measurements was conducted. Average increases of COHb were reported as 8 and 20 percent. Cerebral blood flow was reported to increase by 26 percent at the COHb level of 20 percent, while the calculated cerebral metabolic rate of oxygen (CMRO₂) was unchanged. Cerebral blood flow at 8 percent COHb was reported to have changed in the same pattern as the higher COHb, but to a lesser extent. The authors conclude that a highly efficient mechanism maintains the brain's oxygen supply.

A more detailed study of cerebral blood flow, blood pressure and oxygen consumption as a function of blood COHb levels was conducted in dogs.⁵⁵ In a total of 13 dogs, comparisons were made between low oxygen conditions produced by administering O₂-N₂ mixtures and various levels of CO to produce equivalent reductions in arterial oxygen content. Comparisons were thus made between control levels of 17.5 volume percent oxygen and 16.0, 14.0, 8.0 and 4.0 volume percent for the O₂-N₂ mixtures and COHb levels of 0, 11, 30, 51 and 75 percent. At the elevated levels of COHb, cerebral blood flow increased to 110, 154, 196, and 232 percent of control, while blood pressure tended to decrease only slightly to the point of 30 percent COHb saturation in the blood. These data indicate that cerebral vascular resistance decreased to 86 percent of control at 11 percent COHb and to 63 percent of control at 30 percent COHb, and still further to 47 and 30 percent respectively at COHb's of 51 and 75 percent. Cerebral oxygen consumption was maintained up to blood levels of 30 percent COHb, but at COHb levels of 51 and 75 percent, it was significantly reduced. In a second series of 10 dogs, these investigators examined cerebral blood flow at levels up to 50 percent COHb, with a concerted effort to define blood flows at lower levels. They found that up to a COHb of 30 percent, cerebral blood flow

TABLE 1

Summary of Physiological Response and Altered Work Capacity Studies

CO Administered		Peak COHb (%)	Subject	Parameter and Results	Reference
Level (ppm)	Time (min)				
50	120	2.68	Man-Exercising	Time to onset of angina decreased from 223-226 sec to 187 sec with CO inhalation.	13
Unspecified	15	21.2	Man-Exercising	Maximum O_2 consumption and maximum work-time both decreased with CO.	19
Unspecified	15	15.8	Man-Exercising	Cardiopulmonary function measured during exercise. Maximum cardiac output fell with CO. Blood pressure, heart rate and pulmonary ventilation not affected by CO.	20
75-100	15	4.3	Man-Exercising	Maximum O_2 consumption decreased with CO.	23
12,000 + 225	Unspecified + up to 8	20.0	Man-Exercising	Maximum O_2 consumption decreased with CO.	60
50,000	2	9.0	Man-Resting	Coronary blood flow increased with CO.	5
1000	60	30 (estimated)	Dogs	Coronary blood flow increased and coronary arterial resistance decreased with CO. Blood pressure, ventricular contractility ECG and myocardial O_2 consumption all unchanged by CO.	64
5000	3-4	17.0	Dogs	ECG changes pronounced in ischemic and infarcted areas of heart with CO.	12
5000	12-15 (Estimated)	20.0	Man-Resting	Cerebral blood flow increased in proportion to blood COHb.	42
Unspecified		75.0	Dogs	Cerebral blood flow increased and cerebral vascular resistance decreased proportionately up to 30% COHb to maintain O_2 delivery. At 51 and 75% COHb, blood flow could not maintain O_2 delivery.	55
10,000	11	65.4	Goats	Cerebral blood flow increased to maintain O_2 delivery up to 30% COHb. Beyond that level, oxygen consumption fell.	18

increased proportionately and at that cerebral O₂ consumption was unchanged. Above 30 percent COHb, cerebral blood flow increased out of proportion to the decreased O₂ carrying capacity, but the brain was no longer able to maintain constant oxygen consumption.

Almost identical findings were reported by Doblar et al. for similar studies conducted in goats.¹⁸

Both of these investigators found that cerebral blood flow increased immediately, as soon as COHb began to rise, and the increase was adequate to compensate for the decrease in O₂ content up to a level of 30 percent COHb.

C. Audiovisual and Motor Coordination Effects

Since Haldane reported that his hearing and vision were markedly impaired during exposures to carbon monoxide,²³ numerous investigators have sought the definitive test to demonstrate specific types of impairment. Thus, there are almost as many tests and test conditions as there are investigators. Laties and Merigan³² have conducted an extensive review of the literature and have organized the published work into categories:

- Vision and audition
- Motor behavior
- Tracking, coordination and driving
- Time discrimination
- Vigilance

While these categories appear to define psychometric parameters in a broad sense, differences in methods of CO administration, both in regard to levels administered and duration of CO administration, make it difficult to compare findings. For example, Benignus et al.¹³ and Christensen et al.¹⁵ examined the possibility of CO impairment of visual discrimination during vigilance. The first investigators used CO levels of either 100 or 200 ppm for 3.3 hours, while the latter used 114 ppm for 2 hours. COHb values of 4.61 and 12.62 percent were reported by Benignus et al. while Christensen et al. found COHb levels of 4.7 percent. Both sets of investigators concluded that there was no CO-related impairment, at least in terms of this particular task, even though peak blood COHb levels were considerably different.

An additional problem in this area of research is the relevance of a particular task to the overall question of quantifying impaired visual, auditory or mental function. What is the significance of discriminating between brighter or dimmer light flashes or being able to decide if two audible tones are presented at the same time intervals? To avoid this

TABLE 2
Summary of Audiovisual and Motor Coordination Studies

CO Administered		Peak COHb (%)	Subject	Parameter and Results	Reference
Level (ppm)	Time (min)				
500	300	20	Man	Time estimation, time discrimination and hand reflexes. Only the ability to discriminate between paired tones was lowered at COHb from 4 to 16%	50
1000	1440	31.8	Man	Reaction time, driving, hand steadiness, visual acuity, audiogram, time estimation. Fatigue of hands and hand reaction times increased at 28% COHb. Headaches reported at COHb levels of 13 to 15.0 and upward to 23.0%.	48
Unspecified		19.7	Man	Brightness discrimination was impaired at all COHb levels from 4.5%. Effects attributed to CO were sometimes less than day to day changes.	24
195	180	13.3	Man (Smokers and Nonsmokers)	Night vision, eye movement and reading showed no CO effect. Blood COHb of nonsmokers was up to 9.0 and that of smokers up to 13.3%.	35
950	45	12.1	Man	Depth perception, brightness, reaction time and critical flicker-fusion were tested. Only reaction time increased in proportion to COHb levels.	46
150	540	12.7	Man	Mental arithmetic, time estimation, tracking, monitoring were all unaffected by CO.	40
250	180	12.37	Man	Tracking, time estimation and a series of equilibrium tests were all unaffected by CO.	39
Unspecified		8.3	Man	Auditory time discrimination was unaffected by CO.	63
200	200	12.6	Man	Visual discrimination and vigilance showed some decrement in low level CO trials (100 ppm), but these were not consistent and did not occur at higher levels.	13
Unspecified		7.0	Man (Smokers and Nonsmokers)	Driving skills including reaction time, visual acuity, night vision, hand steadiness and depth perception. Care, self-criticism and impaired judgment resulted from COHb increases of 3.4%.	62
150	140	7.81	Man	Auditory time discrimination was not affected by CO	41
114	125	4.7	Man	Visual discrimination and vigilance were not affected by CO.	15
250	150	Not Determined	Man	Auditory time discrimination deteriorated at all CO levels in a proportional manner.	11
111	150	6.6	Man	Visual vigilance deteriorated when blood COHb values of 4.4 to 6.6 were attained.	27

question, some investigators have used complex forms of behavior such as driving ability or specific tasks such as steering, braking and maintaining a particular distance between vehicles.^{48,51} Even this type of research is not without problems though; results of one study led the authors to conclude that increases of COHb levels by 3.4 percent showed a deterioration in driving skills, even though the differences were small and inconsistent.⁶³

In terms of the needs of the US Army, there is probably no one test that will reveal all the parameters important to the soldier exposed to high-level, short-term and intermittent episodes of CO; instead a battery of tests will need to be assembled, since the selective action of CO on particular segments of the brain³⁸ suggests that localized metabolic changes may be induced within the central nervous system³⁷ and that several areas of mental performance may have to be tested at one time. It may be necessary for a panel of clinical psychologists to conduct a series of tests in a population such as fire fighters to determine what parameters are indicative of impaired mental function, and if these parameters can be tested in a realistic setting in a reasonable time.

Some studies have involved subjects in test booths for extended periods of time.⁵⁰ While it may be necessary for some visual tests to be performed after dark adaptation has occurred, performance in testing situations would be expected to decrease after a long exposure session.¹⁵

Of the parameters tested, those of interest to the US Army would most likely involve vision and reaction time,^{35,46} visual vigilance,²³ visual discrimination during vigilance,^{13,15} brightness difference discrimination,^{24,46} auditory vigilance,²¹ driving ability,^{48,63} and the combined tasks such as mental arithmetic, time estimation, tracking, monitoring and visual tasks.^{39,40}

D. Immediate Health Effects

There has not been a great increase in our awareness of the immediate health effects of CO inhalation since Haldane's work in 1895.²³ The headaches that Haldane described still continue to be noted, with the only change being the COHb level at which they are noticed.^{48,49} Two healthy resting males reported headaches at COHb levels of 9.1 and 10.2 percent,⁴⁹ while exercising males noted headaches at 20 percent COHb,² and still other sedentary males developed headaches at 15 to 17 percent COHb.⁴⁸ These findings demonstrate the high degree of variability in subjective reports of this nature. Among the factors that probably lead to these variations are those related to exposure conditions, such as the rate of increase in CO and other inhalants that may be present outside of the laboratory setting, and personal factors such as pain threshold, general physical condition and motivations.

TABLE 3
Summary of Immediate Health Effects Studies

CO Administered Level (ppm)	Time (min)	Peak COH (%)	Subject	Parameter and Results	Reference
4100	240	56	Man (Resting and Exercising)	Report of symptoms during several CO exposures. Exercise increased number and severity of symptoms. Audiovisual and coordination difficulties were intermittent. Headaches occurred at COHb of 32, 36 and 37% on 3 occasions.	23
35,600 10,000	3/4 10	16.5	Man (Resting)	Blood pressure, heart rate, ECG, ventilation visual evoked responses were measured during CO exposures. Headaches occurred in 2 subjects (COHb's of 9.1 and 11.6%). Slight depression in ECG (S-T segments) of one subject.	49
Unspecified		51.3	Man (Exercising)	Cardiopulmonary monitoring to point of fatigue while exercising. Headache reported by 1 subject at COHb of 20%. No other symptoms with peak COHb's of 51.3, 37.5, 26.4 and 28.5%.	2
1000	60	38	Man (Resting)	No symptoms reported up to COHb levels of 14-22% in some subjects while others reported headaches at COHb's of 16-22%.	26

The severity of the headache may vary from annoying one subject to virtually incapacitating another because of nausea or ataxia. Physical activity may intensify the headache.²⁶ High levels of COHb may lead to loss of consciousness and death. The upper limit at which death occurs has been reported to vary from 48 to 95 percent.³⁴

E. Delayed and Adaptive Responses

We are aware of no published reports dealing with delayed responses to single or even repeated high-level CO exposures other than the evidence from fire fighter statistics.⁶ These data show that coronary heart disease is the largest single cause of death in firemen. While it is acknowledged that there are numerous other substances that may be inhaled at a fire,^{33,44,52} the most consistent toxicant is CO.

There is a large body of scientific literature dealing with atherosclerotic disease and inhaled cigarette smoke. While this literature is not directly related to the concerns of this report, evidence such as that from fire fighters, which indicates an additive effect⁴⁵ for smoke inhalation from cigarette and occupational sources, suggests that this possibility should be considered. Smoke from a cigarette may contain up to 40,000 ppm of CO in an inhaled volume estimated at approximately 350 ml, and is capable of producing venous COHb levels of 3 to 10 percent, depending on inhalation patterns, type of cigarette and the number smoked per day.⁵⁷

Numerous reports from animal studies on the effects of CO on vascular lesions^{4,31} or myocardial ultrastructural changes^{53,54} have been published, but some more recent evidence suggests that these findings should be reexamined^{29,30} since the evidence is not as clear-cut as once thought: conflicting results in early animal studies that reportedly showed a CO effect on vascular may have been due to several factors, including small numbers of animals per test condition, species susceptibility, use of dietary cholesterol to produce hypercholesterolemia and the lack of objective methodology in evaluating suspected microscopic lesions.

Data presented by Longo³⁴ dealing with maternal and fetal COHb levels raise an issue that should be reviewed. While short-term, high-level exposures to CO may not be life threatening to a young male soldier, there appears to be a possibility that a fetus carried by a female soldier may be at a considerably higher risk for two reasons. First, fetal blood appears to have a slightly greater affinity for CO than does maternal blood. The reasons for this are not clear at this time. Second, tissue oxygenation of the fetus is in a less favorable situation than the mother because oxygen moves according to mass concentration or pressure gradients, and if oxygen is reduced in maternal blood, fetal levels of oxygen will be reduced. Longo presented data for a maternal COHb of 10 percent that would decrease the 50 percent hemoglobin saturation (P_{50}) from 26.5 to 21 mm Hg in maternal blood, and decrease fetal blood P_{50} from 20 to 15.5 mm Hg. He noted that

TABLE 4
Summary of Delayed and Adaptive Response Studies

CO Administered Level (ppm)	Time (min)	Peak COHb (%)	Subject	Parameter & Results	Reference
Unknown		Varied	Human (Females)	Review article and original data relating maternal CO inhalation with fetal morbidity and mortality.	34
Unknown		Varied	Human	Statistical report of fire fighters' deaths. Forty five percent of firemen deaths in line of duty were due to heart attacks. Atherosclerosis was present in every case.	6
1900 210	300 6 wks	39	Rabbits	No histological change in lungs or pulmonary arteries related to CO.	29
250	2 wks	20.6	Monkeys	Histological changes in coronary arteries with accumulation of lipids intracellularly.	53
Unspecified		30	Rabbits	Gross and microscopic lesions in low O ₂ and CO exposed animals were similar, with endothelial and subintimal changes and subintimal edema.	4
180	2880	18	Rabbits	Some ultrastructural changes in myocardium after exposure to 100 ppm CO for 8 hours or longer (COHb 8-9%).	54
180	2 wks	18	Rabbits	Some histological and gross lesions such as arterial plaques, subendothelial fragmentation, edema with widening of subendothelial spaces.	31
40,000	Repeated	15+	Humans	Higher incidence of atherosclerosis and coronary heart disease.	57

changes of this magnitude may affect tissue oxygenation and the maintenance of an adequate intracellular oxygen tension for normal enzymatic processes.

F. Fire Fighters - A Relevant Occupational Exposure

During their normal duties, fire fighters are exposed to high levels of CO for short durations, in an intermittent fashion. While levels, duration and frequency of exposure are extremely variable, data obtained from studies of firemen themselves provide some insight regarding COHb levels and physiological measurements of CO effects obtained in the laboratory.⁵¹

There have not been many attempts to measure levels of CO and other toxic substances in structural fires, since there are so many variables that each fire must be considered unique. In 25 fires in the city of Los Angeles, Barnard and Weber¹⁰ reported CO levels less than 100 ppm to as high as 3000 ppm. Even in a given fire, a range of 200 ppm to over 2000 ppm was recorded, with generally higher CO levels on the second floor of structures. Gordon and Rogers²² found CO levels of 450 to 6850 ppm in six fires, and note that sampling air inside a burning structure is a hit-or-miss venture because the nature of the fire, the times samples are taken, and the place samples are taken are all unquantitated variables.

Human exposures to CO may be quantified by measurements of blood COHb levels taken from fire fighters at the scene of fires. Radford and Levine⁴⁵ performed such a study to determine the importance of exposure times, severity of the fire and the types of smoke, effect of protective equipment, cigarette smoking history and heart rates of the firemen on blood COHb. The results can best be analyzed in terms of the fire itself, use of face masks and personal factors. As one would expect, exposure to smoke at a fire did cause elevations in blood COHb from an average of roughly 2 to 4.5 percent with a shift in the upper level of COHb from 8 percent in non-exposed firemen to 19 percent in exposed firemen. To define the portion of these COHb values attributable to cigarette smoking, the authors separated the data by smoking habits and found that there was a dose-related impact on COHb levels, since nonsmokers averaged 0.48 percent, those who smoked less than 1 pack per day averaged 2.33 percent and those who smoked over 1 pack per day had COHb values of 5.64 percent. Upper levels of COHb for these three groups were also somewhat dose-related, with 2.0, 7.0 and 8.0 percent saturation, respectively. These data indicate that when discussing CO exposures it is necessary to define the population, since post-exposure blood COHb values will reflect both the CO exposure and the COHb level present when the exposure was initiated.

When estimating a smoke "dose", one tends to think in terms of a concentration and time, although evidence from this study shows this is not a feasible practice with an undetectable gas such as CO. Fire fighters describe smoke density as heavy or light based on a subjective

evaluation. When COHb values were grouped according to these descriptions, there were no differences in either mean levels or distribution frequencies. Similarly, when COHb data were arrayed for length of exposure as measured by the time from sounding of the alarm to the time of blood sampling, there were no predictable or significant relationships.

The use of a protective face mask with an air supply was effective when used continuously, but intermittent use was no better than non-use. Average COHb values for continuous mask use were 1.41, while intermittent and non-use resulted in averages of 2.47 and 3.38 percent, respectively.

Higher COHb levels were found in fire fighters who had heart rates above 120 beats per minute than in those below this level (3.21 vs 1.89 percent). No basis for this difference is presented, although it may relate to enhanced CO uptake, which has been found in exercising subjects.¹⁹

A series of studies has been undertaken by Barnard and colleagues⁷⁻⁹ to determine possible mechanisms underlying the high coronary death rate experienced by fire fighters.⁶ The first study examined heart rate and ECG waveform changes over the course of a 24-hour tour of duty.⁷ Heart rates were found to increase within 30 seconds after the alarm sounded, with an average increase of 47 beats per minute by this time. By one minute after the alarm sounded, while on the truck enroute to the fire, firemen's heart rates were still elevated by 30 beats per minute. During fire fighting, heart rates of 175 to 195 beats per minute were observed in the first 3-5 minutes, with sustained heart rates of 160 beats per minute in one man for over 90 minutes and an average rate of 188 beats per minute in another man for 15 minutes. Some of the men showed ECG changes normally associated with myocardial ischemia during the initial time after the alarm sounded, but motion artifacts prevented further analysis of ECG's during fire-fighting periods. The authors note that firemen were exposed to anxiety as well as physical stress, and the occurrence of ischemic ECG indications within 15 to 30 seconds after the alarm suggests a significant anxiety component.

Stress-testing of a group of firemen was the subject of the second paper in this series.⁸ During exercise stress up to near maximal oxygen uptake levels, 9 of the 90 men tested showed signs of electrocardiographic ischemia. This finding of a 10 percent incidence was compared to an 8 percent incidence for insurance executives and was higher than expected, since fire fighters are selected for low coronary risk factors such as blood cholesterol levels, systolic and diastolic blood pressure and smoking habits, when they enter training.

The nine men who had the ischemic ECG changes were evaluated in more detail, and six of them underwent angiography and ventricular function studies.⁹ Only two of these men had significant obstruction of coronary arterial branches, while three others exhibited abnormal ECG

waveforms during tests and two had ventricular wall thickening and decreased wall motion. The picture emerging from these studies is one of ischemic heart disease and/or abnormal left ventricular function that is not due to coronary artery disease such as blockage. The authors concluded that stress(es) of the fire fighting job exert a detrimental effect on the myocardium, possibly due to reduced myocardial oxygen supply. It is not possible to determine the relative importance of hypoxia resulting from CO inhalation, the role of endogenous agents such as catecholamines that are known to be associated with physiological stress, and the effect of other materials that may be inhaled during fire fighting, although any or all of these factors are possible causes of the high coronary disease statistic in fire fighters.

Clinically healthy fire fighters without any overt signs of cardiovascular or pulmonary disease were studied by other investigators for COHb levels and serum enzyme changes that might be associated with myocardial damage.⁴⁷ At 28-day intervals over 5 months, COHb and a group of enzymes were analyzed in venous blood. By comparing data from fire fighters and a control group matched for age, sex, height, weight, smoking habits, race and family history of cardiac or pulmonary disease, the study showed that fire fighters had higher levels of lactic dehydrogenase, heat stable lactic dehydrogenase, hydroxybutyric dehydrogenase and creatine phosphokinase in addition to higher COHb levels than controls (5.0 vs 2.3 percent). The authors conclude that the observed changes indicate myocardial damage, but unfortunately no clinical data were provided to verify these suspicions.

The average age of a fire fighter suffering a heart attack was reported to be 51.3 years,⁶ so that the fire fighter population is considerably older than a military trainee population, and probably even older than the training cadre in the combat arms. It is also probable that the fire fighter has a more chronic exposure to CO and other inhalable toxicants, since in the above noted population, the average length of service was 22 years, and in all likelihood, the exposure to CO was repeated more often than would occur in a military training situation.

Given these caveats, the technology and data base being developed for fire fighters may be applicable to answering the question of whether there are immediate impairments of mental ability or long-term sequelae from intermittent, high-level short-term CO exposures.

G. Analytical Methods - CO and COHb Determinations

The reference standard for blood gas analysis has been and currently is the volumetric or manometric procedure described by Van Slyke and numerous co-workers,^{25,58,59} which is referred to as the Van Slyke method or apparatus. The basic principle of this method involves the introduction of a known volume of blood into a chamber and then acidification of the blood while maintaining a partial vacuum in which gases such as O₂, CO₂ and CO are extracted. The gases are then compressed to a known volume and their pressure measured. The individual

TABLE 5
Summary of Fire Fighter Studies

<u>CO Administered</u>		Peak COHb (%)	Parameters and Results	Reference
Level (ppm)	Time (min)			
3000		19	Measured CO levels at fires	10
6850			Measured CO levels at fires	22
Undetermined			Measured COHb levels in firefighters pre- and post-fire. Average per exposure COHb values of 0.48 for nonsmokers to 5.64 for smokers; post exposure levels were 2.0 and 8.0%. Higher heart rates correlated with higher COHb.	45
Not applicable			Firemen had high heart rates and ECG changes indicative of ischemia.	7
Not applicable			Firemen had 10% incidence of stress-related ischemia compared to 8% incidence in insurance executive.	8
Not applicable			Angiograms showed ventricular wall thickening and loss of motion without signs of coronary artery blockage.	9
Not applicable			Firemen showed some serum enzyme changes suggestive of myocardial damage.	47
Not applicable			Fire fighter mortality from heart disease is higher (45 vs 34%) than for non-fire fighters.	6

gases are absorbed selectively by reagents (sodium hydroxide for CO₂, alkaline pyrogallol for CO₂ and O₂, and cuprous chloride for CO), and the pressure at the same volume is remeasured. From the change in pressure, the volume of gas(es) under study is then calculated. The Van Slyke method of CO analysis⁵⁸ has been used by the U.S. Army as recently as the 1960's.¹⁷

Because this method requires training, time, multiple reagents, glassware including manometers, and considerable effort to obtain precise results, many investigators have developed less rigorous techniques that are more suited to general laboratory and field studies. Among methods used are:

- Photometry (colorimetry) - comparing relative amounts of light transmitted through tubes containing an unknown solution and standard solutions or comparing amounts of light transmitted through a tube containing an unknown solution and a filter
- Spectrometry - involves instruments that pass light from a source through a filter and sample holder and on to a detector. Through the use of filters, gratings or a prism, only desired wavelengths of light are used.
- Spectrophotometry - utilizes a light source that is split into separate beams of different wavelengths. These devices provide a single output reading, which is the ratio of the light transmitted at the two wave lengths.

The method used by Haldane²³ involved colorimetric determinations in dilute blood samples, using carmine solutions as standards. While one author³⁶ reported that the COHb values reported by Haldane may have been too high, Van Slyke and Salvesen⁵⁸ noted that the carmine methods seemed to be very accurate in his hands. This accuracy is reinforced by the fact that Haldane used volumetric techniques to standardize his colorimetric analyses, and his methods were highly accurate.⁵⁸ The carmine solution methods of Haldane was still cited as a method in 1945.¹⁴

Current methods of COHb analysis in addition to the Van Slyke technique, include the CO-Oximeter (Instrumentation Laboratories, Lexington, MA), and breath analyzers such as the Ecolyzer (Energetics Science, Inc., Elmsford, NY). The CO-Oximeter requires blood samples that are collected with an anticoagulant and returned to the laboratory for analysis. The breath analyzers are portable devices used on location. Their use involves having the subject hold his/her breath for 20 seconds and then blowing all expired air into the analyzer. An electrochemical sensor determines the CO concentration in ppm, and through internal electronics, provides a direct readout in terms of COHb percent. These instruments are now in use by investigators monitoring fire fighters⁵¹ and in cigarette smoke cessation clinics.⁵⁷

V. SUGGESTED FOLLOW-ON WORK

While there are obvious gaps in the literature relative to high-level CO exposure, there is little to be gained by laboratory studies of human subjects during high-level, short-term CO exposures. Available evidence indicates that specific populations such as those with a history of coronary heart disease, tendencies toward coronary artery vasospasm and pregnant females should not be exposed to CO at any level.

Information from fire fighters provides data regarding many aspects of concern to the military, such as:

- Exposure level (ambient CO, time of exposure, blood COHb) at which performance becomes impaired.
- Effects of repeated high-level CO exposure on coronary disease (acute and chronic).
- Effects of particular exposure cofactors, such as other gases, cigarette smoking, fatigue, and heat stress on performance (mental and physical).
- Significance of specific audiovisual and motor coordination impairments such as vigilance and auditory discrimination, and their relation to acute and chronic mental impairments.

Animal models are well suited for many acute types of studies, such as coronary and cerebral blood flow, but they have not been particularly useful in discerning more chronic diseases such as possible CO enhancement of atherosclerosis.

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Appendix A

REVIEW OF THE LITERATURE

1. PHYSIOLOGICAL RESPONSE AND ALTERATIONS IN WORK CAPACITY

Human Studies

- Aronow WS and Isbell MW. Carbon monoxide effect on exercise-induced angina pectoris. Ann Internal Med 97:392-395, 1973

Review:

This study with 10 angina patients measured the effect of CO exposure on the mean exercise time until onset of angina. The coronary artery disease in the patients was previously documented by coronary angiography with greater than 50 percent narrowing of the lumen of at least one major vessel. On four successive study mornings, patients in the fasting state were attached to an electrocardiograph, and outputs from leads V₆, V₅, V₄, aVF, II and I recorded with the patients supine. With the test subjects sitting upright on a bicycle ergometer, an electrocardiogram (ECG) was recorded with a modified lead V₅ since this ECG lead usually gives the best indication of ventricular oxygen delivery impairment. The resting heart rate and blood pressure were recorded at this time. Each subject then exercised upright on the constant load bicycle ergometer with a progressive work load until the onset of angina. Blood pressure and heart rate at the onset of angina were recorded. An ECG was recorded at the onset of angina with patients in the upright position. Repeat ECG's were recorded with the patient supine, immediately after angina, and 1, 2, 3, 4, 5 and 6 minutes after exercise-induced angina. Each morning prior to testing, half of the subjects breathed 50 ppm CO for 2 hours and the other half breathed purified air for 2 hours. Carbon monoxide was breathed through a mask days 1 and 4 by one group and on days 2 and 3 by the other. Purified air was breathed through a mask on the other days. Venous blood samples were drawn prior to and after the breathing of either mixture. The exercise protocol outlined above was then followed. Blood COHb levels were determined with an Instrumentation Laboratories Model 182 CO-Oximeter.

The breathing of purified air for 2 hours caused the mean blood COHb levels to decrease significantly ($p < 0.001$) from 1.07 to 0.77 percent, whereas the breathing of 50 ppm CO caused significant increases from 1.07 to 2.68 percent COHb. The exercise performance of subjects breathing purified air showed no significant alteration from performance recorded during control periods. In contrast, the mean exercise time until the onset of angina decreased significantly ($p < 0.001$) from 224.3 seconds while breathing air to 187.6 seconds after the breathing of CO. In addition, CO subjects experienced significant ($p < 0.001$) decreases in systolic blood pressure (2.7 percent), heart rate (7.1 percent), and in

the product of systolic blood pressure times heart rate (9.6 percent). Maximal electrocardiographic S-T segment depression (which is an indication of ventricular ischemia) increased from 1.30 to 1.45 mm after the exercise-induced angina in the CO-breathing experiment but the increase was not statistically significant. The ischemic S-T segment depression after exercise-induced angina occurred earlier and after less myocardial work in patients breathing CO.

Analysis:

This was a well-documented study of a carefully selected population of patients with a confirmed coronary circulatory problem. Data analysis was conducted using analysis of variance. Tabulations of COHb levels before and after breathing air and CO are presented with means and standard deviations. Group means and standard deviations are given for pre- and post-test cardiovascular data. The data show that the subjects were at the same baseline level prior to both test periods. The findings clearly demonstrated the potential problems for a person with a pre-existing coronary problem when exposed to CO and then expected to perform a physical task.

- Ekblom B, Huot R, Stein EM, Thorstensson AT: Effect of changes in arterial oxygen content on circulation and physical performance. J Appl Physiol 39(1):71-75, 1975

Review:

This study investigated the effect of CO exposure on the systemic circulation and physical performance of nine clinically healthy male physical education students (age 23 to 34 years) during submaximal exercise on either a motor-driven treadmill (4 subjects) or a mechanically-braked bicycle ergometer (5 subjects), and during maximal exercise on a motor-driven treadmill (9 subjects). Carbon monoxide exposure of resting subjects was conducted by injecting an unspecified volume of CO into a closed circuit breathing apparatus and achieving blood COHb levels ranging from 12.8 to 15.8 percent saturation after 15 minutes. The subjects did not breathe CO during the different work loads. Blood samples drawn just prior to exercise and during the last minute of each exercise period were analyzed for blood COHb levels and the results were averaged for each exercise period. Heart rates were recorded for 15 seconds of each minute during submaximal exercise and continuously near the end of the maximal run. The average heart rate from the fifth and sixth minute of submaximal exercise and the peak value during maximal exercise were used in characterizing cardiac response during each exercise period. Expired air minute volume ($\dot{V}_E$) was determined during the last 2 minutes of each work load.

Preliminary work tests were conducted to familiarize the subjects with test procedures and to determine maximal oxygen uptake ($\dot{V}O_2$ max) for each subject during normoxic conditions. Measurements of various physiologic parameters were made during supine rest, during two upright

submaximal work loads (at about 30 and 70 percent $\dot{V}O_2$ max), and during maximal exercise. The speed and inclination of the treadmill during the maximal exercise were chosen so that control subjects would be exhausted in about 6 minutes. The time until exhaustion was determined during each maximal run. The subjects did not know the duration of the work time and were not allowed to see a clock during the maximal run.

The authors found that the type of submaximal exercise did not affect the circulatory or respiratory response at a given $\dot{V}O_2$ and, as a result, they pooled the bicycle and treadmill data. They found that CO exposure did not affect the rate of oxygen uptake, pulmonary ventilation, cardiac output, and arterial blood pressure during rest and the two submaximal exercise periods (15.8, 14.1, and 12.8 percent COHb, respectively). Heart rate was significantly higher during both submaximal workloads, and the stroke volume significantly decreased at the higher submaximal load.

During maximal exercise, mild CO hypoxia (13.3 percent COHb) did not affect maximal heart rate, arterial blood pressure, or pulmonary ventilation, but did cause significant reductions ($p < 0.05$) in the duration of maximal exercise (from 5.9 to 3.8 minutes), $\dot{V}O_2$ max (by 14.2 percent), arteriovenous oxygen difference (by 10 percent), stroke volume (by 5.4 percent), maximum cardiac output (by 6.1 percent) and blood lactate levels (increased significantly by 15 percent). The authors demonstrated that the change in $\dot{V}O_2$ max was caused mainly by the different volumes of oxygen transported to the tissues, i.e., cardiac output times the arterial oxygen content. Both of these factors were significantly decreased.

Analysis:

The results of this study show that CO hypoxia (12.8 to 15.8 percent COHb) does not limit oxygen consumption or exercise during submaximal work, and that maximal exercise is impaired by significant reduction in the oxygen transported. These overall conclusions are based on data derived using appropriate methodology. The 14.2 percent decrease in $\dot{V}O_2$ max for subjects with levels of 13.3 percent COHb is also in agreement with the finding that the percent change in $\dot{V}O_2$ max is roughly equivalent to the percent saturation of hemoglobin with CO.

- Vogel JA, Gleser MA: Effect of carbon monoxide on oxygen transport during exercise. J Appl Physiol 32(2):234-239, 1972

Review:

This study with eight males (age 20 to 23 years) investigated the effect of CO hypoxia on oxygen transport during activity that ranged in intensity from rest to maximal levels. Exposures to CO were first to a booster dose of 10,000 to 12,000 ppm CO in 40 liters of air from a large gas bag over several minutes, and then to a maintenance mixture of 225

ppm CO for the remainder of the experiment. Blood COHb levels of approximately 20 percent saturation were achieved. During control experiments, subjects breathed from large gas bags filled with room air in order to replicate respiratory resistances. Half of the subjects were tested first with CO while the other half were tested first with air. After 15-minute equilibration periods, resting measurements were taken. These involved measurement of cardiac output, heart rate, blood pressure, blood sampling for COHb and HbO₂ determination by spectrophotometry, lactate measurements, arterial oxygen tension, carbon dioxide tension and pH. The subjects then exercised on a bicycle ergometer at two submaximal levels (light and heavy) and at maximal work load with a 10-minute rest period after each exercise period. The submaximal exercise was 8 minutes long and the maximal load lasted for 4 to 5 minutes. After at least 1 hour of rest or after the subject's COHb level decreased to below 5 percent by breathing 95 percent O₂ and 5 percent CO₂, the subject exercised under the second condition. All statistical comparisons were made using a paired t-test with $p < 0.05$ considered significant.

Rates of oxygen uptake of subjects with blood levels of 19 and 20 percent COHb during exercise at approximately 50 and 75 percent $\dot{V}O_2$ max, respectively, were no different from controls. There was, however, a 23 percent reduction in $\dot{V}O_2$ max ($p < 0.001$) for subjects when 20.5 percent COHb was attained. Other significant changes reported for CO-exposed subjects included: Expired air volumes were increased during heavy exercise but slightly lower during maximal exercise; lactate levels were higher at all but maximal levels (when they were no different from controls); cardiac outputs and heart rates were greater ($p < 0.05$) at all submaximal levels; arteriovenous O₂ differences were less ($p < 0.01$) during heavy and maximal loads; calculated mixed venous O₂ saturations were less at rest and all submaximal levels of work, but were no different at maximal exercise. Other notable observations included the lack of alterations of stroke volume at all levels of exercise and unaltered cardiac output and heart rate during maximal exercise.

Analysis:

This study provides a volume of information about the effect of CO on oxygen transport in subjects aged 20 to 23 years at rest and during exercise up to maximal levels. Methods used for measuring cardiopulmonary parameters were proper, and data analysis was correct. By collecting data at a total of three exercise levels, the authors were able to follow physiological changes more precisely than some other investigators had.

- Ekblom B, Huot R: Response to submaximal and maximal exercise at different levels of carboxyhemoglobin. Acta Physiol Scand 86(1):474-482, 1972

Review:

This study investigated the effect of CO exposure on low, high, and maximal exercise with 10 well-trained, healthy, physical education students or teachers, age 22 to 34 years. Five subjects performed both submaximal bicycle exercise and maximal exercise on a mechanically braked bicycle ergometer and on a motor-driven treadmill while maintaining approximately 7 and 20 percent COHb. In a second part of this study, all ten subjects performed maximal treadmill exercise after breathing air and at three different levels of COHb that ranged from 4.8 to 21.2 percent saturation. In each CO experiment, the subjects breathed air containing CO at unspecified concentrations sufficient to produce the desired blood COHb levels (analyzed by a CO-Oximeter) within 15 minutes. In the first part of the study, baseline values for unexposed subjects were obtained for maximum aerobic capacity ($\dot{V}O_2$ max) and at workloads representing 30 and 70 percent $\dot{V}O_2$ max. The submaximal tests were 6 minutes long and the maximal tests were of constant intensity as indicated by achievement of a steady-state oxygen consumption ($\dot{V}O_2$ max), and the same load was used in control as well as in CO experiments. The workload in the maximal experiments was selected to exhaust subjects in control tests within 5 to 6 minutes. A leveling off of the oxygen uptake with increasing workload was the criterion chosen for maximal oxygen uptake. Heart rate (HR) was obtained from an electrocardiogram during each subject's performance and was recorded for 15 seconds each minute during submaximal workloads and continuously near the end of maximal exercise. The average value for HR during the fifth and sixth minute of submaximal exercise and the peak value during maximal exercise were used in characterizing physical performance. The oxygen uptake was determined from the expired air during the last 2 minutes of each workload.

At the rate of one experiment every fourth or fifth day, the following schedule of tests was followed: at a level of approximately 7 percent COHb on one day, a 30 percent ($\dot{V}O_2$ max) workload (WL), a 70 percent WL and a bicycle maximal WL test were performed, while on a later day a treadmill maximal WL test was performed. The same routine was followed at approximately 20 percent COHb. On bicycle test days the procedure was as follows: supine subjects were administered CO; 5 minutes of rest were allowed to equilibrate alveolar and room air; low submaximal exercise; 5-minute rest period while sitting on bicycle; high submaximal WL; 15-minute rest period during which compensatory dose of CO was breathed to achieve blood COHb levels similar to pre-exercise values; and finally the maximal WL was performed. Treadmill exercise days consisted of a 15-minute warmup period during which subjects ran at half the speed of the maximal run, followed by a 15-minute period during which CO was administered, and finally the maximal WL test was performed. Blood samples for lactate determination were drawn one to three times after the end of each submaximal and maximal workload. The results of this series of tests are summarized in Table A-1, which is abstracted from this paper.

TABLE A-1

The Mean Value of Cardiorespiratory and Metabolic Measurement of five Subjects During Submaximal and Maximal Exercise on a Bicycle Ergometer and Maximal Work on the Treadmill in Normalcy and at Two Levels of COHb.

Type of Exercise	COHb (%Sat)	O ₂ D (l)	V̇O ₂ (l/min)	HR (beats/min)	V̇E (l/min)	HL _a (mM)	WT (min)
Bicycle low submaximal	NM ⁺	0.37	1.16	94	25.9	2.1	-
	7.1	0.30	1.15	99	23.5	1.9	-
	2.0	0.46	1.16	108*	31.7	2.3	-
Bicycle high submaximal	NM	1.71	2.61	150	62.2	5.0	-
	6.2	1.63	2.61	154*	66.3*	5.1	-
	17.2	2.00	2.59	166*	75.1*	7.1*	-
Bicycle maximal	NM	2.90	3.64	184	127.5	12.4	4.13
	7.5	2.98	3.30*	182	135.2	12.4	3.23*
	20.7	3.25*	2.85*	180*	134.4	13.8	2.45*
Treadmill maximal	NM	-	4.32	191	156.1	14.5	5.53
	7.1	-	3.92*	189	160.6	13.4	4.06*
	19.2	-	3.34*	183*	161.9	14.2	2.90*

Abbreviation:

O₂D : calculated oxygen debt

V̇O₂ : oxygen consumption

HR : heart rate

V̇E : minute ventilation

HL_a : blood lactate concentration

WT : worktime until exhaustion during maximum exercise

+NM : not measured

* Statistically significant (p < 0.05) compared to air breathing control.

The authors found that CO exposure at two levels of CO hypoxia did not affect cardiopulmonary adaptation to the increased oxygen needs of low and high submaximal exercise, and that the rate of oxygen uptake of CO-exposed subjects during the last 2 minutes of exercise was no different from controls. In response to the combined stress of high submaximal exercise and CO exposure, HR and the volume of expired air ($\dot{V}_E$) increased significantly at both COHb levels.

Maximal bicycle and treadmill exercise worktime were significantly affected by CO exposure, since the rate of oxygen uptake and the maximum worktime until exhaustion were significantly reduced at both levels of COHb.

When the results of the second set of maximal treadmill experiments were examined, the authors found by regression analysis for COHb concentrations ranging from 4.8 to 21.2 percent saturation that the decreases in maximum oxygen uptake and maximum worktime could be related to the blood concentration of COHb by the equations:

$$\text{Percent decrease in } \dot{V}O_2 \text{ max} = -0.19 + 1.17 \text{ COHb}$$

$$\text{Percent decrease in maximal worktime} = 15.8 + 1.82 \text{ COHb}$$

The correlation coefficients for these two equations ($r = 0.85$ and $r = 0.79$, respectively) indicate that these variables are both significantly correlated with COHb levels.

Analysis:

This paper presents a large amount of data relating cardiopulmonary and metabolic adaptations to varied exercise levels in healthy subjects. Methods used and experimental design are proper. Both raw data tabulations and statistically derived data (means and standard deviations) are provided, so it is possible to analyze findings for each individual and the group in detail.

- Horvath SM, Raven PB, Dahms TE, Gray GJ: Maximal aerobic capacity at different levels of carboxyhemoglobin. J Appl Physiol 38(2):300-303, 1975

Review:

This study examined the effect of CO exposure on the maximum aerobic capacity of four healthy male subjects, aged 22 to 33 years, who were familiar with the experimental procedure and who were free of cardiovascular and pulmonary problems. Carbon monoxide exposures were designed to produce a gradual increase in blood COHb by inhaling 75 ppm CO in air until desired COHb levels were attained (buildup method) or a sudden increase in blood COHb was achieved by injecting a bolus of air containing 100 ppm CO into the inspiratory gas stream, followed by additional boluses at 1-minute intervals until desired COHb levels were

attained (bolus method). On the buildup days, blood samples were taken for analysis of hemoglobin, lactate, hematocrit, plasma protein, and CO content, and then either filtered air, 75 ppm CO in filtered air, or 100 ppm CO in filtered air was breathed for 13 minutes by seated subjects. Repeat blood analysis was performed at this time.

Subjects continued breathing the same air mixture and then began walking on a treadmill at 3.4 mph on the 15th minute, with the grade automatically being increased 1 percent each minute until the subjects were exhausted. Oxygen debt was determined at this time, followed on the fourth minute of recovery by a third blood sample. On bolus days, subjects breathed during 15 minutes a preliminary bolus of CO sufficient to elevate pre-exposure COHb levels to those observed at the end of the previous buildup tests (as determined by blood sampling). Lower concentrations of CO were breathed during exercise to maintain blood COHb levels within 0.1 percent of the desired levels. During rest, exercise and recovery, the ventilatory volumes, respiratory rates, and oxygen and carbon dioxide contents of expired air were continuously monitored and recorded. The electrocardiogram was monitored on an oscilloscope with heart rates recorded during the first 10 seconds of each minute.

The buildup method of CO administration elevated COHb levels from pre-exposure levels of 0.4 to 3.35 and 4.30 percent saturation by the end of exercise for subjects breathing 75 and 100 ppm CO, respectively. Blood COHb levels at the end of exercise by the bolus method were not significantly different from those obtained by the buildup method. Lower levels of COHb did not affect $\dot{V}O_2$ max although the relationship between $\dot{V}O_2$ max and COHb values above 4 percent saturation is expressed by the equation:

$$\dot{V}O_2 \text{ max} = 2.2 + 0.91 (\text{COHb}).$$

The maximum worktime until exhaustion decreased 4.9 and 7.0 percent for subjects with 3.3 and 4.3 percent COHb saturation, respectively, with both changes being significant ($p < 0.05$). The expired air volumes were also significantly decreased with all CO-exposed subjects. Resting blood lactates were not significantly different in any of the test groups, but post-exercise levels were significantly higher ($p < 0.01$) following the filtered air studies than with any of the CO-exposed groups, regardless of the mode of exposure.

Analysis:

While this study was supposedly to examine rates of change of blood COHb, time factors are not given, so that it was not possible to determine if the rates of increase were in fact, different. The authors present data for two levels of COHb that were studied, in what is actually a steady-state trial.

Standard cardiopulmonary methods were used, and probably the most useful data from the study is the equation relating $\dot{V}O_2$ max with COHb levels.

- Ayres SM, Giannelli S, Mueller H: Myocardial and systemic responses to carboxyhemoglobin. Ann NY Acad Sci 174:268-293, 1970

Review:

This study investigated the systemic and myocardial response of 41 coronary and cardiopulmonary patients during diagnostic cardiac catheterization to the breathing of air containing 1000 and 50,000 ppm CO. Catheters were placed in the ascending aorta, the pulmonary artery and in the proximal coronary sinus. Coronary blood flow was measured using ^{131}I . Prior to CO administration, control measurements were made of expired air, coronary sinus, pulmonary arterial, and peripheral arterial blood gas tensions and contents. Blood COHb concentrations were measured using gas chromatography methods. Oxygen and CO₂ tensions and pH were determined with blood gas electrodes. Oxygen and CO₂ contents of blood or expired air were determined manometrically on a Van Slyke apparatus.

Rapid changes in COHb levels were produced in 26 subjects by breathing air containing 50,000 ppm CO for 30 to 120 seconds. More gradual changes were observed in 15 subjects breathing 1000 ppm CO for 8 to 15 minutes. For 26 subjects breathing 50,000 ppm CO, blood COHb levels increased from 1.0 to 9.0 percent, accompanied by significant changes in cardiac output (5.01 to 5.56 l/min), minute ventilation (6.86 to 8.64 l/min), mixed venous O₂ tension (39 to 31 mm Hg), arterial CO₂ tension (40 to 38 mm Hg), and a slight increase in the arteriovenous O₂ difference (4.30 to 4.56 ml/100 ml) which was not significant. The 15 patients breathing 1000 ppm CO experienced an increase in blood COHb of 7.86 percent saturation, unaltered cardiac output, a decrease in arterial CO₂ tension that suggested an increase in alveolar ventilation, and a significant decrease in mixed venous oxygen tension reflecting the increase in COHb concentrations.

Myocardial metabolic studies were conducted following the breathing of 1000 and 50,000 ppm CO, and the results were segregated as to whether the subjects tested were suffering either coronary artery disease or other cardiopulmonary disorder. The authors observed that the arterial oxygen content fell in response to CO but that the coronary sinus oxygen content did not undergo a corresponding decrease since coronary blood flow increased proportionately to maintain coronary oxygen supply.

Analysis:

This study provides considerable information about the systemic and myocardial response of cardiopulmonary patients to mild CO hypoxia brought about by the breathing of two different concentrations of CO.

The reported increases in cardiac output and minute ventilation for the patients in this study are interesting, but are at variance with other published reports. One possible reason for the cardiac output and ventilation changes in the group inhaling 50,000 ppm CO could be a rapid rate of rise for COHb in arterial blood supplying the brain. While venous blood COHb is the usual parameter for determining body CO levels, local CO concentrations in particular sites within the brain may be much higher.⁴⁴ This present study is flawed in that the 41 patients who participated were never clinically described other than referring to them as patients in a cardiac catheterization laboratory and as patients with either coronary artery disease or as having other cardiopulmonary disorders. The experimental design was for each test to be performed on each subject, pre- and post-exposure, although no time for achievement of a steady state was indicated. Statistics were valid but not very detailed, since only group means and F test ratios are presented for systemic tests.

- Paulson OB, Parving HH, Olesen J, Skinhoj E: Influence of carbon monoxide and of hemodilution on cerebral blood flow and blood gases in man. J Appl Physiol 35:111-116, 1973

Review:

This study reports on the effect of CO exposure on cerebral blood flow of five resting patients being given diagnostic angiograms. None of the patients suffered with major intracranial diseases, which would interfere with the regulation of the cerebral circulation. Small polyethylene catheters were introduced in the internal jugular vein and the carotid artery of each subject, the positions being verified by two methods. Both catheters were used for the collection of blood samples during each flow measurement. In addition, the arterial catheter was used for cerebral blood flow (CBF) measurements with intra-arterial injections of xenon 133 dissolved in saline as well as for diagnostic angiograms.

CBF and blood gases were measured twice during control conditions with a 15-minute interval between measurements. A volume of CO in liters equivalent to one-fifth to one-fourth of the body weight in kilograms was then inhaled as a 5000 ppm in air mixture over several minutes. Twelve minutes after inhalation of this mixture, CBF and blood gases were again determined. A subsequent volume of CO was inhaled over several minutes so that the total volume of CO breathed was equivalent to the body weight in kilograms. Twelve minutes later, CBF and blood gases were again measured. Oxygen saturation (HbO₂), COHb, and lactate were each determined spectrophotometrically, while pH, carbon dioxide tension, and oxygen tension were determined using conventional electrodes. The clearance of the xenon isotope was followed by 35 small scintillation detectors placed over the ipsilateral hemisphere, and the clearance curve followed for 10 minutes was used to calculate the CBF. The arteriovenous oxygen difference was calculated according to the following equation:

$$(A-V) O_2 = \frac{\text{Percent } O_2 \text{ sat (art)} - \text{Percent } O_2 \text{ sat (ven)}}{100} \\ \times \text{HB} \times 1.34 \times \frac{100 - \text{Percent COHb}}{100} \frac{\text{ml}}{100 \text{ ml}}$$

The cerebral metabolic rate of oxygen (CMRO₂) was calculated both before and after CO exposure using the following equation:

$$\text{CMRO}_2 = (A-V) O_2 \times \text{CBF ml/100 g/min}$$

The authors reported that subjects administered the higher dose of CO had an average blood COHb concentration of 20 percent saturation (range 14 to 23 percent) and experienced significantly ($p < 0.02$) increased CBF_{initial} in all cases averaging 26 percent, and increased CBF₁₀ (calculated over the first 10 minutes) averaging 21 percent. All 35 regions studied reacted similarly. The jugular venous oxygen tension decreased in all cases an average of 3.4 mm Hg ($p < 0.01$). The CMRO₂ values calculated from the CBF_{initial} showed no significant variation during the studies, while CMRO₂ values calculated from CBF₁₀ measurements showed significant decreases (mean decrease of 11 percent ($p < 0.005$)). The authors suggested that the decrease in CMRO₂ values did not necessarily mean the cerebral metabolic rate was decreased, but that the decrease could have been due to more rapid clearance of the xenon 133 at the high flow level. Systemic acidosis was not evident as reflected by unchanged blood pH, PCO₂, and lactate concentrations.

Subjects administered the lower dose of CO had an average COHb concentration of 8 percent saturation (range 4 to 13 percent) and showed the same pattern of changes as observed with the higher dose, but the magnitude of the changes was much less marked.

These authors reported that moderate CO hypoxia (20 percent HbCO) caused significant increases in cerebral blood flow without apparent alteration in the cerebral metabolic rate of oxygen or evidence of systemic acidosis.

Analysis:

This study of mechanisms controlling blood flow to the brain was conducted with proper experimental design. Blood COHb levels are given along with supporting blood gas data. Statistical analysis was performed on paired data, using a t-test.

Animal Studies

- Adams JD, Erickson HH, Stone HL: Myocardial metabolism during exposure to carbon monoxide in the conscious dog. J Appl Physiol 34:238-242, 1973

Review:

This study with ten mongrel dogs investigated the effect of CO hypoxia on coronary blood flow, myocardial oxygen consumption and cardiac function. During surgical procedures prior to testing, an ultrasonic flow transducer was affixed around the circumflex branch of the left coronary artery to measure the velocity of blood flow through this vessel; a solid-state resistance strain gauge was implanted within the apex of the left ventricle to determine left ventricular pressure as well as the first derivative of left ventricular pressure (dp/dt); a catheter was placed in the left atrium in order to determine left atrial pressure and take arterial blood samples; a second catheter was placed in the coronary sinus to collect samples of venous blood draining the myocardium and to calculate an arteriovenous (A-V) oxygen saturation difference across the myocardium. Pin electrodes were placed subcutaneously in the sternal region to monitor and record the electrocardiogram and heart rate. The partial pressures of O₂ and CO₂ and pH were determined on each arterial and coronary sinus blood sample using blood gas electrodes. Oxygen saturation and hemoglobin saturation with CO (COHb) were determined spectrophotometrically in these same blood samples using an Instrumentation Laboratories Co-Oximeter.

Following a 2-week recovery period, control measurements were recorded on the conscious dogs while they were lying quietly. The animals then breathed air containing 1500 ppm CO for 30 minutes with blood COHb levels rising at the rate of slightly less than 1 percent per minute. Cardiac function data were continuously monitored and recorded at 5-minute intervals and corresponding arterial and coronary sinus blood samples were drawn. Other blood chemical and hemodynamic measurements were made at this time. Myocardial oxygen consumption, which is calculated as the product of coronary flow and A-V O₂ difference, was calculated for each 5-minute interval of exposure. Data analysis was by a Student t-test, with comparison between the control data collected just prior to CO exposure and the data from each 5 percent increment in COHb.

The average pre-exposure COHb concentration was 1.0 percent and the average after the 30-minute exposure was 23.1 percent. Arterial oxygen saturation decreased linearly from an average control value of 97.2 to 73.2 percent. Mean coronary sinus oxygen saturation increased during the period from 22.7 to 32.3 percent. The resulting A-V O₂ difference decreased from 74.5 to 40.9 as a result of the CO exposure. Coronary blood flow increased significantly ($p < 0.01$) at approximately 5 percent COHb and higher, to accommodate the reduced arterial O₂ content. The mean increase in flow was 13 percent at 5 percent COHb and 54 percent at 23 percent COHb. The increased coronary blood flow occurred as a result

of significant ($p < 0.01$) increases in heart rate (4 and 20 percent increases at 5 and 23 percent COHb, respectively) and coronary flow per beat (6 and 34 percent increases, respectively). Myocardial oxygen consumption showed significant decreases beginning at 10 percent COHb (5.4 percent decrease), which at 23 percent COHb amounted to a decrease of approximately 20 percent. Maintenance of left ventricular function in spite of the reduction in myocardial oxygen consumption led the authors to conclude that unidentified metabolic and neural components may have been affected by CO.

Analysis:

This study is a detailed examination of left ventricular function and myocardial oxygen supply and utilization with dogs during exposure to CO. The animals were surgically prepared with appropriate catheters and transducers prior to the study so that measurements could be made in the conscious state. Calibrations of transducers and blood gas monitoring equipment appear to have been carefully performed and well documented. Analysis was facilitated by continuous monitoring of cardiovascular parameters during the entire trial, with blood sampling and detailed measurements at prescribed times. Statistical methods were appropriate and data are presented in a clear manner.

- Becker LC, Haak ED: Augmentation of myocardial ischemia by low level carbon monoxide exposure in dogs. Arch Environ Health 34:274-279, 1979

Review:

This study with 11 anesthetized mongrel dogs investigated the effect of CO on myocardial ischemia associated with acute myocardial infarction produced by coronary artery ligation. Cardiac output was measured by a dye dilution technique, and the aortic pressure was determined by inserting a plastic catheter in the left brachial artery and advancing it to the level of the aortic arch. Baseline measurements of aortic pressure, cardiac output, left atrial pressure, heart rate, and left ventricular ejection time were made prior to ligation of a few free wall branches of the left anterior descending coronary artery. Sixty minutes after ligating the coronary arteries, hemodynamic measurements were repeated and venous blood was sampled for spectroscopic determination of COHb. CO exposure was accomplished by switching the inlet line of the respirator to a reservoir containing 5000 ppm of CO in pure air. A volume of 10 liters of this mixture was administered as an exposure over an estimated 4-minute period. Each dog was given a total of 5 exposures, each separated by 8 to 10 minutes. Three minutes after each exposure to CO, blood samples were drawn and hemodynamic measurements repeated. Epicardial electrograms were recorded for each dog from the surface of the anterior left ventricular wall at 10 to 15 selected sites prior to coronary occlusion, 60 minutes after occlusion, and 3 to 4 minutes after each CO exposure. An index of myocardial ischemia was formed by summing

the significant electrocardiographic S-T elevations present in all leads for each set of measurements. The S-T segment deviations were always adjusted for deviation present prior to occlusion, so that each dog served as its own control. The summation had been previously shown to be stable over the time course of the experiment in the absence of interventions.

Myocardial blood flow was determined using carbonized radioactive microspheres. Microsphere injections were made just prior to the first CO exposure and again after the second and fifth CO exposures. Following the last CO exposure, the dogs were sacrificed, their hearts removed, and the left ventricular wall removed and cut into 50 to 70 pieces for scintillation counting. The counts were converted to blood flow using standard cardiovascular methods. A reference map for location of the regional blood flow data was superimposed with data from the epicardial electrograms. The non-ischemic region was composed of samples in the uninvolved posterior ventricular walls. The ischemic region was formed from pooled samples in the territory of the ligated arteries with initial flow > 50 percent of the non-ischemic portion. Each dog served as its own control in analyzing regional flow changes.

The five CO exposures caused increases in blood COHb to 4.9, 8.9, 11.3, 14.2, and 17.0 percent saturation. Over the duration of the experiments there were no significant changes in cardiac output, aortic root pressure, mean left atrial pressure, left ventricular ejection time, or heart rate. The electrocardiographic S-T segment elevation showed increases for the ischemic portion of the heart that were significant ($p < 0.025$, paired t-test) at blood COHb levels of 4.9 percent saturation, but no significant changes were observed in the non-ischemic portion. The degree of electrocardiographic S-T elevation showed a significant linear relationship with the level of COHb in the blood. Measurements of myocardial blood flow showed that there was generally good agreement between the area of injury as shown by the electrocardiographic ST segment elevation and the area of low flow. The mean blood flow to the ischemic region did not change significantly as a result of the CO exposures, while the non-ischemic flow showed increases that amounted to 15.8 and 28.7 percent for blood COHb levels of 8.9 and 17.0 percent, respectively. The authors concluded that increased levels of COHb increased the severity of myocardial ischemia.

Analysis:

This study of experimentally produced myocardial damage and the effects of subsequent CO exposure utilizes classic measures of cardiovascular function in addition to validating a relatively new procedure of electrocardiographic myocardial mapping. The science, statistics and experimental design were proper. The results of this study indicate that elevations of COHb may cause harm to patients suffering with acute myocardial infarction. By studying a model system in which ischemic responses are intensified, hypoxic effects that would result from CO exposure can be better understood. Part of the basis for

this is the changes observed on mapping the epicardial S-T segment elevations following CO exposure. Although the use of this technique as a specific measure of ischemic injury has been questioned, the authors felt that there exists sufficient evidence correlating S-T segment elevation with other indicators of myocardial ischemia to justify its use. The non-ischemic portion of the heart responds to the CO hypoxia by increasing blood flow and is thus able to maintain normal tissue oxygenation. In contrast, the infarcted portion of the heart cannot increase blood flow in response to increasing levels of COHb and thus experiences increased tissue hypoxia in response to the diminished quantity of O₂ transported by the blood. These observations support the conclusions drawn from the epicardial mapping experiments that CO exposure increases myocardial ischemia in animals with acute myocardial infarction.

- Traysman RJ: Effect of carbon monoxide hypoxia and hypoxic hypoxia on cerebral circulation. In Otto DA (ed): Multidisciplinary Prospectives in Event-Related Brain Potential Research, pp 453-458 USEPA., 1977

Review:

This report deals with 13 dogs that were exposed to hypoxia resulting from CO and low O₂ in the respired gas. In pentobarbital-anesthetized dogs, cerebral blood flow, arterial blood pressure, cerebral venous pressure and end-expired CO₂ were measured continuously. The animals were paralyzed with succinylcholine and ventilated with a positive pressure respirator adjusted to maintain an alveolar CO₂ level of 4 percent. Oxygen and carbon dioxide partial pressures and pH of arterial blood were measured with blood gas electrodes. Oxygen and COHb saturation and hemoglobin were measured on a CO-Oximeter.

The experimental protocol was for each animal to be maintained at a given level of hypoxic hypoxia (low O₂) for 15-20 minutes and CO hypoxia for 35-40 minutes to allow equilibration of ventilatory and blood gases as well as for hemodynamic responses to stabilize. Hypoxic levels were defined as reductions in O₂ content from control of 17.5 vol percent to 16.0, 14.0, 8.0 and 4.0 percent in steps. For the CO hypoxia, these correspond to 0, 11, 30, 51 and 75 percent COHb.

Cerebral blood flow increased to a peak of 232 percent of control at the highest COHb level, while arterial blood pressure decreased only slightly at the same time. These data indicate cerebral vascular resistance decreased to 30 percent of control, and the brain increased blood flow to maintain oxygen delivery up to the point of severe hypoxia, which in this case was equivalent to a COHb of 51 percent saturation.

A second series of 10 dogs was studied at lower CO levels that produced COHb levels of 2.5, 5.5, 8.0, 12.0, 16.0, 22, 30 and 50 percent saturation, which were maintained for 30 minutes each. In these dogs, a COHb of 2.5 percent resulted in a small but significant increase in

cerebral blood flow to 102 percent of control. Proportional increases in blood flow were found up to a COHb of 22 percent, but at 30 percent COHb cerebral blood flow increased out of proportion to the decreased O₂ capacity, and the brain O₂ consumption began to fail, thus suggesting an upper limit for physiological prevention of brain hypoxia had been reached.

Analysis:

This carefully constructed set of experiments provides data on cerebral blood flow limits in a comprehensive manner. The comparison of two forms of hypoxia (low O₂ hypoxia was noted but not reviewed above) answers many questions such as the role of chemoreceptors and if CO itself has an effect on systemic blood pressure other than via oxygen delivery impairment. Statistical analysis was based on each animal serving as its own control, with paired comparisons analyzed with a t-test. Actual mean values and standard errors are graphed along with percent changes for each parameter.

- Young SH, Stone HL: Effect of a reduction in arterial oxygen content (carbon monoxide) on coronary flow. Aviat Space Environ Med 47:142-146, 1976

Review:

This study with 13 mongrel dogs measured the effect of CO levels resulting in a 30 percent reduction in arterial oxygen saturation on myocardial blood flow. The animals tested were chronically instrumented for ventricular pacing, to measure left circumflex coronary flow (CF), left ventricular and arterial pressure, and to obtain blood samples from the left atrium and coronary sinus. Blood samples were drawn from both the left atrial and coronary sinus catheter of resting animals after initial measurements of left atrial pressure, left ventricular pressure, arterial pressure, electrocardiograms, CF velocity, and heart rate. The animals then breathed air containing CO at 1000 ppm from a demand regulator for 45 to 60 minutes producing an approximate 30 percent reduction in arterial oxygen saturation. The animals ordinarily remained quiet during this period of CO exposure.

The authors reported that the 30 percent reduction in arterial oxygen saturation did not produce significant changes in myocardial oxygen consumption (MVO₂), mean arterial pressure, or lactate extraction, but it did cause significant increases in heart rate (20 percent) and coronary blood flow (100 percent), and a significant decrease in diastolic coronary resistance (52 percent). During preliminary experiments with unexposed animals, it was found that the increased heart rates were associated with increased myocardial oxygen consumption and coronary blood flow. Based on these experiments, the increase in heart rate of 19 beats per minute observed during the CO experiment was expected to be associated with an increase in MVO₂ of 0.5 ml O₂/min and a coronary flow increase of 4 ml per minute with no change in contractility and arterial pressure. The actual changes were zero for

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MVO₂ and 37 ml/min for coronary flow. Although a 14 percent increase in myocardial oxygen consumption was expected (due to the increased work of the heart) and none was seen, the lack of alteration in lactate extraction or any electrocardiographic changes suggests that coronary flow increases were adequate to maintain myocardial oxygen consumption.

Analysis:

This study is flawed only in that blood COHb levels were not determined. While oxygen saturation of blood is a reflection of carboxyhemoglobin levels in blood in animals exposed to CO, the actual COHb values would have been useful. Methods used in the study were otherwise proper and statistical analyses were correct.

2. AUDIOVISUAL AND MOTOR COORDINATION

Review Article:

- Laties VG, Merigan WH: Behavioral effects of carbon monoxide on animals and man. Ann Rev Pharmacol Toxicol 19:357-392, 1979

Review:

The authors reviewed the literature dealing with experimental studies of CO and behavioral and psychometric parameters. The section on animal studies discussed unconditioned behavior, such as running, swimming and digging, and conditioned behavior, such as responding to light flashes or running a maze over a timed interval. The unconditioned behaviors generally declined after CO exposure. It was not possible to directly compare results from trials with 700 ppm of CO for 30 minutes and 200 ppm of CO for 24 hours, even in the same species, because the higher CO level resulted in a COHb value of 19.6 percent, whereas 22.8 percent saturation was achieved after the lower level and longer exposure; however, the greater impairment occurred at the lower COHb level.

The human performance section was organized into vision and audition, motor behavior (tracking, coordination, and driving time discrimination), and vigilance. The authors note that these divisions reflect the types of studies performed and are not the way one would plan to study behavior.

Laties and Merigan concluded their paper with three generalizations that are worth noting:

- There are undoubtedly interactions between CO and the various characteristics that have been studied, but the role of motivational, social and other environmental stressors (sleep deprivation, drugs, vibration, noise, etc.) have not been systematically studied.
- Most CO effects appear to be marginal based on results from low-level and short-term studies, yet high CO levels that may provide unambiguous answers are rarely used in humans.
- Dose-effect and time-effect relationships for CO may not be monotonic, since some effects appeared only transiently and then disappeared or diminished in magnitude.

Analysis:

This review article brings together the findings of over 100 original reports and discusses possible relationships and shortcomings. An overview of this area is useful, because many of the original studies cited provide data that each investigator feels important and relevant, but the conflicting results indicate that the criteria are not totally objective.

The animal work reviewed demonstrated that behavior such as swimming or running was reduced after CO exposures, but it is not clear how the original authors interpret these results as "behavior" modifications as opposed to physical exercise limitations, which have been repeatedly described in man. The literature related to psychological testing in animals and suspected CO impairment is not definitive. Most of the studies reviewed found either no change or the data presented were inadequate to reach a conclusion.

The human performance section reveals that the published reports are, at best, conflicting. Each study reviewed presumes that the parameter measured is a valid indicator of the expected CO impairment. Laties and Merigan have, in effect, written what should have been a discussion in each of the papers reviewed. After reading many of the original papers reviewed in this article, it was our opinion that Laties and Merigan have done a good job in this review.

Original Research Publications

- Stewart RD, Newton PE, Hosko MJ, Peterson JE: Effect of carbon monoxide on time perception. Arch Environ Health 27:155-160, 1973

Review:

This study examined the effect of CO exposure on time estimation, time discrimination, and hand reflex action. A total of 27 (23 male, 4 female) nonsmokers ranging in age from 22 to 43 years were exposed in a double blind manner in random order to CO at concentrations of 2, 50, 100, 200, and 500 ppm for up to 5 hours. During the exposure period, venous blood was drawn hourly and analyzed for COHb by two methods. Upon entering the exposure chamber and every hour thereafter, subjects were tested first for their ability to estimate 10 and 30 seconds, the estimate being repeated twice. Subjects then performed the Marquette time estimation test, a measure of ability to identify correctly the duration of 9 light and 9 tone stimuli and the hand response time to the stimuli, and finally the Beard-Wertheim test, an audiometric time discrimination test requiring subjects to compare sequences of paired tones; the first, 1 second and the second 1.5 seconds later, which was either longer, shorter, or of the same duration. Testing took place primarily in a large room in a group situation, but testing was also conducted with a limited number of subjects who were either isolated in a large room or in an audiometric chamber. Performance measurements in the group situation were conducted over a fairly even distribution of blood COHb levels ranging from 0 to 20 percent; in isolation in a large room at COHb levels from 4 to 12 percent; and in isolation in an audiometric chamber at COHb levels from 4 to 16 percent. During the Beard-Wertheim test, 806 measurements were made in the group situation, 27 in isolation in the large room, and 27 in the audiometric chamber.

The authors found that blood COHb levels up to 20 percent did not alter the ability to estimate time, the ability to correctly identify the

duration of light and tone stimuli or the response time to identify the correct signal, or the ability to discriminate between paired tones when tested in either a group situation or in isolation within a large room. The only alteration in performance was observed when subjects were tested in an audiometric chamber for their ability to discriminate between paired tones. A significant decrease in accuracy of 2.9 percent was observed with 7 of 9 subjects when their mean blood COHb level was 9.74 percent (range 4 to 16 percent).

Analysis:

The study appears to be well done with a large number of measurements performed, the use of double blind protocol, and duplicate determinations of blood COHb levels. Adequate description of blood COHb determinations is provided. Only a limited amount of data is presented for the testing results, so detailed analysis is not possible.

- Stewart RD, Peterson KE, Baretta, JD, Bachand RT, Hosko MJ, Hermann M: Experimental human exposure to carbon monoxide. Arch Environ Health 21:154-164, 1970

Review:

This paper presents the results of a wide variety of behavioral studies with CO-exposed subjects and reports on the toxic symptoms that they experienced during and after testing. Prior to testing, each of 18 healthy nonsmoking male graduate students and medical school faculty (age 24 to 42 years) were given a comprehensive medical exam, including medical history, laboratory studies and physical exam. Pre-exposure venous blood was obtained for clinical testing, Complete blood counts, sedimentation rate, and levels of sodium, chloride, carbon dioxide, calcium, potassium, total serum protein, alkaline phosphatase, bilirubin, blood urea, nitrogen, glucose, serum glutamic oxaloacetic transaminase, and carboxyhemoglobin. This blood analysis was repeated 16 hours after each exposure to CO of 100 ppm or greater. To evaluate the effect of CO on behavioral performance, baseline or pre-exposure values were obtained for the following tests: hand and foot reaction time in a AAA driving simulator, Crawford collar and pin test, Crawford screw test, AAA hand steadiness test, orthorator visual test (which included an evaluation of depth perception, color vision, near and far visual acuity, and near and far vertical and lateral phoria), complete audiogram, resting ECG, standard EEG, visual evoked response (VER), and time estimation test. Subjects exposed to CO concentrations greater than 100 ppm had to demonstrate a normal exercise ECG prior to CO exposure to determine the effect of vigorous running in place for a 3-minute interval. Subjects were given a repeat physical exam 1 hour before entering the exposure chamber and were queried as to whether they were experiencing abnormal or subjective feelings. Blood and alveolar breaths were sampled at this time to measure initial HbCO levels.

Subjects were exposed in a 20 by 20 by 9 foot chamber to CO concentrations of <1, 25, 50, 100, 200, 500 and 1000 ppm for periods of

0.5 to 24 hours. Carbon monoxide concentrations were monitored continuously by infrared spectroscopy and periodically by gas chromatography. The chamber was air conditioned, featuring pleasant lighting, comfortable chairs and study desks. Activity was strictly sedentary. Meals were served to the subjects during the exposures, and coffee and soft drinks were available ad lib. Blood COHb levels were determined periodically after the subjects passed their arm through a small sampling port into an uncontaminated atmosphere.

The authors found that 8-hour exposures to air containing 25, 50, and 100 ppm CO produced increases in mean blood COHb levels for the higher two concentrations breathed, from 0.7 to 5.0 percent (range 5.4 to 6.2 percent) and to 12 percent (range 11 to 13 percent), respectively. These COHb levels had no effect on the performance of any of the aforementioned tests. No untoward subjective symptoms or objective signs of illness were noted during or in the 24-hour period following these exposures. All clinical chemistries, including the repeat battery 16 hours later, remained within normal limits.

Three subjects exposed to 200 ppm CO for 4 hours developed mild headaches in the final hour when COHb levels rose to 15 to 17 percent. The headache remained mild in intensity for one subject and subsided completely within 2 hours; for the other two subjects, headaches vanished during the first 30 minutes following exposure. Clinical chemistries showed no alteration following CO exposure.

In a series of three experiments, two subjects breathed 500 ppm CO for 2 hours resulting in COHb levels ranging from 22 to 25 percent. During one experiment, one subject developed a mild frontal headache after 90 minutes (18 percent COHb). During the other two experiments, both subjects developed mild frontal headaches after 1 hour when COHb levels ranged from 13.1 to 13.7 percent. Minimal exertion caused a transient intensification of pain. Two hours after the exposures produced COHb concentrations of 25.4 percent, the mild frontal headaches intensified into excruciatingly severe occipitofrontal headaches, reaching a peak pain 3.5 hours after exposure, accompanied by mild nausea that persisted for 7 hours and was not ameliorated by aspirin.

A final exposure of two subjects was to a constantly rising concentration of CO, which reached 1000 ppm after 2 hours and was maintained there for an additional 30 minutes. Both subjects reported the presence of mild frontal headaches after 2 hours (23 percent COHb); 2 hours after the CO exposure had produced 31.8 percent COHb, the headaches became moderately severe. Six hours post-exposure, the headaches were incapacitatingly severe and were not ameliorated by aspirin. Twelve hours later, after a night's sleep, the headaches were still noticeable. Electrocardiograms and clinical chemistries remained normal. The performance of the Crawford collar and pin test 5 minutes before the completion of the above exposure (28 percent COHb), the subjects noted marked fatigue of the hand and fingers and their performance scores were reduced approximately 15 percent. Ninety minutes post-exposure, hand fatigue was not noted and performance was near normal. The performance of

the hand reaction time-time estimation test 15 minutes before the completion of the exposure (28 percent COHb) and 2 hours post-exposure revealed a slight increase in reaction time post-exposure but no impairment of time estimation ability.

Analysis:

This study was well done and is a valuable contribution to the literature. Blood COHb determinations were done by two methods and are considered to be accurate. This study is important because the length of time required to reach steady state values of COHb is not known, and this work provides some data. The question of subjective awareness of CO toxicity has also not been well documented, but the headaches reported by some subjects are an indication of this response.

- Halperin MH, McFarland RA, Niven JI, Roughton FJW: The time course of the effects of carbon monoxide on visual thresholds. J Physiol 146:583-593, 1959

Review:

In a study designed to measure the effect of CO on the ability to detect brightness differences under low illumination, four young men (16 to 25 years) thoroughly trained in the test procedures sat in a darkened room, breathed various gas mixtures through a close-fitting oro-nasal mask over 3 to 4 hours, and viewed through a microscope a large circular area uniformly illuminated at an intensity of 0.002 foot-candles, equivalent to moderate moonlight. Flashes of 0.1 sec duration were presented and the least intensity that was distinguishable from background illumination determined as the mean of 10 measurements. Visual determinations were made at 10-minute intervals. During the test period, measured amounts of pure CO ranging from 100 to 300 ml were admitted into the breathing mask, and about half of each volume was absorbed. Blood analysis was used to determine COHb levels.

In the course of one experiment, subjects first breathed room air and then a low O₂ atmosphere (11.09 percent O₂). Baseline visual threshold (or sensitivity) values rose quickly to a plateau level. The breathing of 100 percent O₂ caused a swift return of threshold values to baseline figures. The breathing of 4 doses of 115 ml of pure CO injected into the breathing gas line at 30- to 40-minute intervals resulted in an increase of COHb levels to 4.5, 9.4, 15.8 and 19.7 percent. Each incremental increase in CO saturation was associated with a stepwise increase in the visual threshold, i.e., the visual sensitivity decreased. The changes in threshold values occurred about 50 percent more slowly with the breathing of CO than the breathing of a low O₂ atmosphere. The breathing of pure O₂ for 25 minutes caused the COHb level to decrease to 14.2 percent, and the subsequent breathing of carbogen, 93 percent O₂ and 7 percent CO₂, caused a drop of COHb levels to around 3 percent. While the breathing of each of these atmospheres caused a rapid decrease in visual thresholds towards baseline figures, the subsequent breathing of room air was accompanied by a return of the threshold values to levels

equivalent to approximately 16 percent COHb. The authors suggested that CO became bound to blood and to tissues and that the breathing of O₂ caused a reversible displacement of CO from the tissues; however, during the breathing of air, the low gradient for removal of CO from the tissues resulted from the tightness of bonding to some hemoprotein in the Central Nervous System or peripheral visual system, which causes the visual threshold to remain elevated. During another experiment, subjects breathed 300 ml of pure CO injected into the breathing gas line, which elevated COHb concentrations from 1.1 to 15.0 percent. Threshold values were significantly elevated and remained elevated and nearly unaltered over the next 2 hours when room air was breathed and blood COHb levels dropped to 10.8 percent. In another experiment during which COHb levels were elevated to 10.7 percent, threshold values were significantly increased and the alternate breathing of O₂ and air over the next 2 hours showed that the visual threshold values remained sensitive to the effects of CO at COHb levels as low as 3 to 5 percent. The overall changes that were observed were quite small, apparently less than normal day-to-day variations.

Analysis:

This study demonstrated a particular visual sensitivity to the effects of CO. Decrements in brightness discrimination were observed at COHb levels as low as 5 percent. This work does suffer several serious deficiencies. First, only a limited number of subjects were used in this study. They were highly trained in the particular task and this could make their performance particularly sensitive to the effects of light intensity changes. However, in certain instances, the authors used only one of the four subjects for a particular experiment. They justified this action by stating that this subject's performance was generally very close to the average performance of the other three subjects. It is not possible to tell whether one subject was tested or all four. In addition, it is not possible to compare the individual responses of the various test subjects.

- Luria SM, McKay CL: Effects of low levels of carbon monoxide on visions of smokers and nonsmokers. Arch Environ Health 34:38-44, 1979

Review:

This study of the effect of CO on vision and reaction time to visual stimuli was conducted with 18 subjects, 12 nonsmokers aged 19 to 39 years, and 6 heavy smokers (at least 30 cigarettes per day) aged 21 to 43 years. Subjects were tested for scotopic sensitivity, simple and choice reaction times, eye movement, and visual evoked cortical responses (VER's). Prior to the experiment, subjects familiarized themselves with the scotopic and reaction time equipment until their performance reached a plateau. Performance of the above sequence of tests was repeated three times during an experimental session (30, 75, and 165 minutes after the start of the session), with 5-minute rest periods between test runs. Measurements of performance were made during 3 hours of breathing either air or 195 ppm CO.

Instrumental analysis of blood samples drawn immediately after testing showed that CO exposure caused the COHb levels to be elevated from 2 percent (assumed) to 9 percent with nonsmokers, and from 3.1 to 7.2 percent (controls) to 10.2 to 13.3 percent with smokers.

Testing for scotopic sensitivity required dark-adapted subjects to respond to 60 pairs of lights of different size and intensity at 12 positions in the visual field that were randomly flashed for 1 second. Results were analyzed for the number of correct stimuli reported, the size and intensity of the test lights seen and the spatial distribution of errors. Simple reaction time was defined as the mean response time over 20 trials for the right hand to turn off a button controlling a blue light. The choice reaction time was the mean response time to 20 random stimuli, 10 red lights and 10 blue lights; the right hand controlled a button for the blue light and the left hand controlled the red. Pressing both buttons did not work. Eye movement during reading was evaluated during two tests. The first involved searching 10 typed lines of p's with 16 to 18 q's interspersed, while the second involved reading paragraphs of uniform length and difficulty. The letter search results were analyzed with a Biometric eye-movement monitor for total reading time, number of fixations and number of reversals. Visual evoked cortical responses were elicited from a 10° blank field of white and a checkerboard of black and white squares of 0.63°, illuminated by a flashing light 2 or 8 times per second. Bipolar electrodes to the scalp with a ground to the ear recorded cortical signals, which were amplified and summed by computation of average transients. One hundred 1-second intervals of cortical activity immediately following the onset of the stimulus were analyzed.

The authors did not find any significant alterations in any of the visual processes tested. There were no significant changes in either simple or choice reaction time as a result of CO exposure. A progressive increase in choice reaction time was noted with CO-exposed subjects, but this increase did not approach significance.

Analysis:

This study provides good evidence that hand reaction times and certain visual functions are unaffected by COHb levels up to 9 percent with nonsmokers and up to 10.2 to 13.3 percent with smokers. Although pre-exposure blood COHb levels were measured for smokers, no pre-exposure measurements were made with nonsmokers.

- Ramsey JM: Effects of single exposures of carbon monoxide on sensory and psychomotor response. Am Ind Hyg Assoc J 34:212-216, 1973

Review:

This study measured the effect of CO on depth perception, visual discrimination for brightness, reaction time, and critical flicker-fusion. Test groups each consisted of 20 healthy young (19 to 21

years) male nonsmokers. A multiple choice reaction timer involving time key response in milliseconds to the stimulus of colored lights was employed for reaction time determinations. In this test 15 trials were averaged, whereas 10 trials were averaged in the other tests. After familiarization and adequate practice with each test, the subjects were scored on their performance of the various tests, and blood samples were drawn and analyzed for CO content. The CO exposure procedure consisted of a double blind administration of either 650 ppm CO, 950 ppm CO, or air for 45 minutes, which resulted in a change of blood HbCO content of 7.6, 11.1 and 0 percent, respectively. Final values of HbCO were 8.5, 12.1, and 0.8 percent, respectively. Following CO exposure, the battery of tests was repeated.

A comparison of the means for the three test groups before exposure showed remarkable uniformity for depth perception, visual discrimination for brightness, and reaction time, while the mean for the three groups for critical flicker-fusion showed significant differences. When a paired t-test was applied to the before-after values for each of the 60 subjects for all four tests, only the reaction time test showed mean decrements which were significant ($p < 0.005$) for both CO-exposed groups. Analysis of variance on the three reaction time means showed significance at 5 percent, while the difference between the two CO-exposed groups was insignificant by Scheffe's test.

Analysis:

This study was well documented and the data for each test are presented along with statistical information so that detailed review is possible. Study design is proper and well described.

- O'Donnell RD, Chjikos P, Theodore J: Effect of carbon monoxide exposure on human sleep and psychomotor performance. J Appl Physiol 31:513-518, 1971

Review:

This study of the effect of CO exposure on mental arithmetic, time estimation (10 and 30 seconds), tracking, monitoring, and visual tasks was conducted upon four subjects after they had been exposed to 75 and 150 ppm CO for 9 hours while asleep. The testing was conducted in the relatively noisy environment of an atmospherically controlled dome. After four nights of adaptation to the dome (which assured a baseline performance), the subjects were alternately exposed on the following four nights to CO or to air. No two CO nights followed each other. Each morning upon waking, the subjects ate breakfast and then performed a 1.5-hour battery of tests followed by sampling of blood for COHb determination by gas liquid chromatography. The mean COHb level prior to testing was 0.6 percent, while COHb levels after exposure were 5.9 percent (75 ppm CO) and 12.7 percent (150 ppm).

The sequence of tests was performed in the following order and, after a 5-minute rest period, was repeated in the reverse order: critical flicker-fusion (CFF), mental arithmetic, auditory time discrimination,

moderate work-load Neptune test, 10-second time estimate, high work-load Neptune test, and 30-second time estimate. A 5-minute rest period was introduced between each run through the battery of tests. The mental arithmetic test required subjects to add four 1-digit numbers, to add the two digits of the answer, to multiply two of the numbers, and to add the two digits of that answer. Scoring was based on the time necessary to correctly solve a problem as well as errors for each problem. A total of 20 problems was given each day. The auditory time discrimination test required subjects to compare the length of two tones presented in rapid sequence. The first tone was of 1-second duration and the second tone varied between 0.675 and 1.325 second in 0.025-second intervals. The interval between tones was 0.5 second. The moderate work-load Neptune test consisted of tracking a needle dial and keeping it centered within small limits for 1 minute. While performing this task, the subject was also required to monitor three other dials located above the tracking dial and periodically to readjust them. Scoring was based on total time off target and in terms of time to see and respond to the offset dials. The high work load required subjects to perform the moderate work load and, addition, monitor three flashing lights and note and remember how many times each light flashed in a 1-minute tracking trial. The authors found that CO exposure did not cause any performance decrements or difference from controls in any of the tests used.

Analysis:

This study of human performance after an extended CO exposure was well designed. The environment of the test and the subjects were carefully monitored. Statistical parameters were appropriate and data are well presented and discussed.

- O'Donnell RD, Mikulka P, Heinig P, Theodore J: Low Level carbon monoxide exposure and human psychomotor performance. Toxicol Appl Pharmacol 18:593-602, 1971

Review:

This study measured the effect of 3-hour double blind exposures of nine male nonsmokers (age 19 to 22 years) to CO at concentrations of 0, 50, 125, 200, and 250 ppm on time estimation, tracking and ataxia. All subjects were exposed to the lowest three concentrations of CO; the test groups at the highest two levels consisted of five and three subjects, respectively. Testing was conducted within an environmentally controlled dome with subjects seated and wearing headphones for the duration of the exposure. Each performance session consisted of five trials on the critical instability tracking task (CITT), 3 minutes of time estimation and then five more tracking trials. This testing sequence of 15 minute duration was alternated with 15 minutes of rest for the duration of exposure. After 90 minutes of exposure, subjects were allowed to walk around and stretch for a few minutes to reduce fatigue and boredom. At the completion of the 3-hour exposure, venous blood samples were drawn within 2 minutes for HbCO determination by GLC. The subjects were then given the Pensacola Ataxia Battery in an adjacent room. In the CITT, t

subject is required to keep a needle from going off the scale of a display dial by manipulating a control stick. Each task begins with relative ease. As the task proceeds, an analog computer makes the task linearly more difficult until the subject is unable to control the position of the needle. The needle goes off-scale, and the trial ends. The test is scored by the degree of difficulty reached just before the needle goes off-scale, the mean of 10 tracking trials determined for each 15-minute test segment, with 6 mean scores determined for each concentration of CO breathed. Time estimation consisted of guessing 10-second intervals, noting the completion of the interval by pressing an electronic switch, and immediately estimating another 10-second interval. The time estimates were recorded automatically. The Pensacola Ataxia Battery was used as a measure of the subject's dynamic equilibrium and included the following tests: Sharpened Romberg, Walk Eyes Open, Stand Eyes Open, Stand Eyes Closed, Stand on One Leg Eyes Closed, and Walk a Line Eyes Closed.

At the end of the 3-hour session, the mean blood COHb levels for the five test groups were, respectively, 0.96, 2.98, 6.64, 10.35, and 12.37 percent. The authors found that CO exposure did not affect the performance of any of the tasks studied. The authors concluded that psychomotor functions ranging from the highly cognitive down to the reflex level should not be affected by CO exposure at the levels and durations employed in this study.

Analysis:

The use of accurate methods for COHb determination contributes to the credibility of the conclusions presented by the authors. The results obtained with subjects breathing the highest concentration of CO do, however, suggest further validation since the test group was quite small (only three subjects).

- Wright GR, Shephard RJ: Carbon monoxide exposure and auditory duration discrimination. Arch Environ Health 33:226-235, 1978

Review:

This study of the effect of CO on auditory time discrimination was evaluated in three separate tests with male nonsmokers ranging in age from 19 to 28 years. The authors used the same tape listened to by subjects in the Beard-Wertheim study. In the first test, two subjects inhaled mixtures of CO in O₂ for a 2-minute period. Levels of CO in the gas mixture were 0, 800, 1400 and 20,000 ppm. The subjects then breathed air for the duration of each 4-hour session, which was performed in a small office. During each hour of each session, subjects were alternately presented three 7-minute sequences of 50 sets of paired tones and three rest periods of approximately 20 minutes each. Unlike the Beard-Wertheim experiment, subjects responded orally when identifying the duration of the second tone as either longer, shorter, or the same as the first tone.

In order to compare the results of this study with those of the Beard-Wertheim study, the performance during the second and third hours of testing, when blood COHb levels (determined by rebreathing methods) were approximately equivalent to those of the Beard-Wertheim study, was analyzed by a paired t-test. During this time, the performance of subjects with 2 percent COHb was not significantly different from controls, but the responses were significantly impaired in the two subjects with 3.2 and 4.7 percent COHb when analyzed with the same techniques used by Beard and Wertheim. The rate of errors during each hour of the 4-hour experiments and the resultant variance analyzed according to a split plot model showed significant components relating to hour and dose by hour. When these results were analyzed on the basis of psychophysical theory by the method of constant stimulus, the author found that the changes observed did not reflect any impairment of auditory duration discrimination due to CO per se, but may have been due to neural fatigue or habituation.

During the second set of experiments, eight subjects were tested in an open office (noise condition) and in an audiometric chamber (isolation condition) after breathing either 100 ml of air or 100 ml of CO diluted with air sufficient to raise initial blood COHb levels from 0.9 percent to a mean of 8.3 percent. Blood COHb levels were maintained by the rebreathing of 25 ml of either air or CO once per hour. To avoid errors associated with a constant order of presentation, the standard 1-second tone was presented first in half of the experiments and second in the remainder. The performance of the controls during the second and third hour was slightly poorer in the noise condition than in isolation. There was no difference between the performance of CO-exposed subjects in the noise condition or in isolation, nor was there a significant difference between CO and control conditions.

In order to evaluate the stability of the psychophysical measures, five subjects carried out a sequence of ten tests, five on control days and five on CO exposure days. Following a brief warm-up period, subjects were given a definite trial of 50 pairs of tones, which was followed by exposure to either air or CO sufficient to raise the mean blood COHb levels to 4.9 percent, and then by another set of 50 pairs of tones. The whole test sequence was 30 minutes long. None of the psychophysical measurements showed any change after CO exposure or in the placebo experiments.

Analysis:

This study appears to have been carefully performed, although the size of the test groups was rather small. The results suggest that auditory time discrimination is not affected by HbCO levels as high as 8.4 percent. It should be noted that blood COHb values were not measured directly, but were estimated from alveolar air samples after a rebreathing period. Since the authors used CO in oxygen rather than CO in air, it is possible that a classical CO hypoxia may not have been produced as they postulated. Experimental design was proper and data analysis and presentation is extensive.

- Benignus VA, Otto DA, Prah JD, Benignus G: Lack of effects of carbon monoxide on human vigilance. Percept Mot Skills 45:1007-1014, 1977

Review:

This study of visual discrimination during vigilance tasks was conducted with 52 male nonsmokers (mean age 22 years) who were exposed in a double blind manner in a small chamber to either 0, 100 or 200 ppm of CO for a combined total of 3.3 hours. Auditory distraction was minimized during testing by maintaining a 60 dB white noise in the test chamber. Subjects were presented a series of single digit numerals displayed on a light-emitting diode at 1.5-second intervals for 0.05 second and were instructed to press a button whenever three consecutive even or odd digits appeared. Ten runs of 16.7 minute duration separated by 3.3 minutes of rest were performed with each run containing 667 stimuli, 27 three-strings (response) and 27 two-strings (no-response) interspersed among random digits of alternating parity. Each sequence of 10 runs consisted of a training run, a baseline run whose error rate was subtracted from the experimental run, a 10-minute break during which subjects left the chamber, and eight experimental runs with CO exposure beginning at the onset of the first experimental run. Blood analysis for COHb was performed at the beginning and the end of the exposure, with blood COHb levels attaining 4.61 and 12.62 percent saturation at the end of exposure to 100 and 200 ppm of CO, respectively. The results of adjacent runs (e.g., runs 2 and 3) were averaged together and the single confidence interval calculated by pooling the variances from each pair of runs and from all CO levels under the assumption of homogeneity of variance. The authors found that there were no consistent differences in performance between CO-exposed and control subjects. A slightly increased error rate was observed at 100 ppm during the first two experimental runs that was not evident in the remaining runs. The authors suggested that increased cerebral blood flow helped compensate for high levels of CO hypoxia, but the increased error rate was not evident initially with the higher concentrations of CO.

Analysis:

This study appears to be well controlled, but data presentation is somewhat meager. Although vigilance impairment was not evident as a result of CO exposure, the authors suggest that it is possible that this task may not be sensitive to CO-induced impairment.

- Wright G, Randell P, Shephard RJ: Carbon monoxide and driving skills. Arch Environ Health 27:349-354, 1973

Review:

This study of the effect of CO on driving skills examined the response of 50 adults (32 male, 18 female) to the double blind administration of CO when tested for brake reaction time, night vision, glare recovery, hand steadiness, depth perception, and operation of a driving simulator. All testing was conducted in the evening shortly after the dinner meal and all smokers were asked to refrain from smoking during this period. After determination of blood COHb by a rebreathing method, each subject

proceeded through the battery of driving tests, followed by a period on the driving simulator. After the initial test, subjects were randomly divided into a experimental group receiving 80 ml of pure CO through a rebreathing apparatus and a control group receiving an equivalent amount of air. Blood COHb levels were remeasured and the driving tasks and simulation task were repeated over the following 30 to 40 minutes. Carbon monoxide breathing caused the COHb level to increase by 4.3 percent for nonsmokers (to 5.6 percent) and 2.6 percent for smokers (to 7.0 percent). The data for smokers and nonsmokers were pooled and showed a deterioration of the mean scores on the six driving skills, but the differences were small and rather inconsistent, so that differences with controls or pre-exposure performance did not reach statistical significance. When the driving skill scores were expressed in a nonparametric form, there were no statistically significant differences when analyzed in a 2 x 3 contingency table, but a single-tailed t-test comparing the number of subjects in each group whose performance deteriorated from the first to the second series of tests was significant ($p < 0.005$) for reaction time, glare recovery, and the total of six tests.

Analysis of driving simulator performance was restricted to two groups of 22 people since the others were inadvertently shown a different film. When the errors of driving performance were summed and analyzed by a single-tailed t-test, both control and experimental groups showed a significant test learning. For the control group, pre- and post-test errors were 12.6 ± 3.9 and 11.6 ± 3.5 , respectively, while for the experimental group, the corresponding values were 12.2 ± 4.7 and 11.4 ± 4.7 . The difference in learning between the two groups was not statistically significant. The actions tested by the simulator were arbitrarily subdivided into two classes associated with brisk automatic responses to emergencies and careful driving habits. When the scores from the first and second viewing were compared, responses to emergency braking tests showed improved scoring in the experimental groups but not in the controls. Situations requiring lifting the foot from the accelerator, or steering right rather than braking deteriorated in both groups at the second viewing, but the overall distribution of the percentages in the experimental and control groups was not statistically significant when analyzed in a 2 x 3 contingency table. Errors in careful driving habits, such as failure to release emergency brake, omission of a left turn signal, and forgetting corrective center steering movements, were diminished during the second run, but the experimental group improved less consistently; the difference in scores for careful driving habits was statistically significant when analyzed by a 2 x 3 contingency table.

The authors concluded that the mean increase in blood COHb level of 3.4 percent was responsible for a loss of care and self-criticism and impaired judgment as indicated by the deterioration in careful driving habits during simulated driving. Such symptoms are recognized as early manifestations of cerebral oxygen lack. The facilitation of automatic emergency movements was thought to be consistent with a release from inhibition from the higher centers of the brain.

Analysis:

Although this study detected a slight deterioration in careful driving habits with subjects exhibiting a mean increase in blood COHb level of 3.4 percent, this analysis has been criticized by Laties and Merigan²⁹ who regard these findings as only a provocative lead for future work. The use of a double blind protocol gives this study more significance, but the grouping of the performance of smokers and nonsmokers together reduces the value and creates doubt about the meaning of these findings. Although the blood COHb level of nonsmoking controls did not change significantly from initial values to post-exposure values, blood COHb levels decreased significantly with smoking controls (as a result of their abstinence from smoking during testing) from 6.2 to 4.8 percent. If slight changes in blood COHb content are responsible for subtle changes in driving performance, the use of controls with decreasing COHb levels would appear to give misleading information regarding the performance of the experimental subjects, i.e., possibly increase slight differences. The combination of test data from all subjects would appear to reduce the value of any findings with nonsmokers.

- Otto DA, Benignus VA, Prah JD: Carbon monoxide and human time discrimination: failure to replicate Beard-Wertheim experiments. Aviat Space Environ Med 50:40-43, 1979

Review:

This study with 13 nonsmoking males (19 to 30 years) was an effort to replicate the Beard-Wertheim experiment, i.e., to determine the effect that CO exposure has on auditory time discrimination. Subjects seated in a dimly lit audiometric booth were randomly exposed twice to air containing CO at a concentration of 0, 75, and 150 ppm for a total of 2.3 hours. Venous blood samples were drawn before and after CO exposure and analyzed spectrophotometrically. The time discrimination task required subjects to decide whether a tone presented 0.5 second after a 1-second tone was of the same duration, longer, or shorter, and to press one of three switches mounted on the arm of the chair. Each test session consisted of nine separate runs during which 50 pairs of tones were presented in the course of 6.25 minutes, and nine rest periods of 13 minutes duration. Each subject received one training session and six experimental sessions at weekly intervals. Each experimental session consisted of a warm-up run to stabilize performance and a baseline reference or pre-exposure run, followed by six runs during which subjects were exposed to CO. The mean COHb levels at the end of the experimental sessions were 0.16, 3.77, and 7.81 percent, respectively.

To reduce the variance in behavior during the rest periods, subjects were required to perform a nonchallenging auditory loudness test, which was performed nearly error-free. The authors thought that behavior would be homogenized by this task, which would increase the reliability of the data. Scalp electrodes were attached to collect electroencephalographic data throughout the experiment.

The authors found that when baseline error rates were subtracted from errors recorded during exposure runs, in no case was there CO-related impairment. The authors attributed this precision to the control of activity during the rest period. The authors concluded that since three laboratories (Stewart et al., O'Donnell et al. and their own) were unable to replicate the Beard-Wertheim results that showed impaired auditory time discrimination, it could be concluded that low-level CO exposure does not reliably impair auditory time discrimination.

Analysis:

The conclusion of this study that low-level CO hypoxia does not affect auditory time discrimination appears to be based on the results of a good solid study.

- Christensen CL, Gliner JA, Horvath SM, Wagner JA: Effects of three kinds of hypoxias on vigilance performance. Aviat Space Environ Med 48:491-496, 1977

Review:

This study of the effect of CO, altitude, and their combination on visual discrimination during vigilance tasks was conducted with ten nonsmoking subjects (5 male, 5 female; age 22 to 34 years). Subject testing in a small soundproof room consisted of judging and responding to a series of 1-second light pulses that were projected on a ground glass diffusing screen at 3-second intervals as either non-signals (dim) or signals (bright). Subjects responded to each light pulse by pressing a button identifying the pulse as either a non-signal or a signal. The experimental signal brightness for each subject was set at least one day prior to testing at a level where subjects identified 80 to 90 percent of the signals with less than 5 percent false detections. The testing consisted of two parts. A 3-minute alertness test consisted of 10 signals interspersed among 50 non-signals. In the 60-minute vigilance test, subjects were shown 9 to 12 signals similarly interspersed among 300 non-signals during each of four consecutive 15-minute periods. A total of 42 signals was presented during this 1-hour test. A 1-minute period separated the alertness and vigilance tasks. Blood samples, drawn prior to entering the chamber (minute 0), before the alertness test (50 to 55 minutes), and after completion of the vigilance test (minute 120 to 125), were analyzed for hemoglobin and COHb.

Each subject was tested under four conditions: filtered air (21 percent O₂), CO (114 ppm), low O₂ (17 percent O₂), and a combination of 113 ppm CO and 17 percent O₂. Breathing of each air mixture was through a demand-type regulator and commenced upon entering the test chamber. The authors found that performance during the alertness test was unaffected by any of the gas mixtures. Signal detection rate in the vigilance test decreased fairly rapidly initially with all test conditions and then leveled off. In neither of the CO conditions was performance significantly different from performance under 21 percent O₂. Blood

COHb of subjects breathing 114 ppm CO was found to rise from 2.5 percent just prior to the alerted task to 4.7 percent after the vigilance task. The percentage of signals identified correctly was significantly decreased (from 71.4 to 59.2 percent) with the subjects breathing 17 percent O₂.

The authors concluded that the hypothesis that CO and hypoxic hypoxia produce the same condition at a given HbO₂ level was not supported by this study. The calculated reduction in O₂ carrying capacity at 114 ppm CO and 17 percent O₂ was approximately 1 percent for each. The results of these experiments prompted the authors to suggest that CO exposure is the least stressful of the three conditions, causing only minor impairment, while inhalation of 17 percent O₂ provides a greater stress to the central nervous system, and the combination of 114 ppm CO and 17 percent O₂ increased the stress to an alarm reaction, evoking compensatory mechanisms that elicited heightened awareness and enhanced performance. The authors suggest that over a long period of such exposure, a stage of exhaustion is reached where performance would be expected to decrease considerably.

Analysis:

Although this study was designed to examine visual parameters associated with CO and low oxygen exposures, the authors collected a variety of other data to correlate with their objectives. Subject monitoring was good, the experimental design and statistical analysis were proper.

- Beard RR, Wertheim GA: Behavioral impairment associated with small doses of carbon monoxide. Am J Public Health 57:2012-2022, 1967

Review:

This study of auditory time discrimination was conducted with 18 nonsmoking university students at rest, exposed in a single blind manner to air containing CO at 0, 50, 100, 175 and 250 ppm for 2.5 hours while isolated in an audiometric test booth. The subjects were presented paired tones well above the auditory threshold, the first of 1-second duration, followed 0.5 second later by a second tone that varied in eighteen steps between 0.675 and 1.325 seconds. Subjects were instructed to judge whether the second tone was of the same duration, longer, or shorter. Comparison stimuli were presented in blocks of 25 pairs, with each trial separated by 7.5 seconds. Each set of 25 trials contained 8 identical, 8 longer, and 9 shorter second tones randomly sequenced. Each test session of 4 hours consisted of 7-minute work periods during which 50 pairs of tones were judged, alternated with 13-minute rest periods during which subjects could either sleep, read, or watch television. A total of 600 trials occurred during each 4-hour session, and each subject's performance was determined three times at each level of CO. Exposure to CO began after 30 minutes in the test chamber and continued for a total of 2.5 hours.

Although the subjects were unable to tell when they were breathing CO and did not experience any motor deficits, their ability to distinguish the duration of paired tones deteriorated with all levels of CO breathed. The time of onset of impaired performance, defined by the reduction in correct responses equal to two standard deviations from the mean performance in uncontaminated air, was found to occur after 90 minutes with 50 ppm, 50 minutes with 100 ppm, 32 minutes with 175 ppm and 23 minutes with 250 ppm. A comparison of the performance during the second and third hour showed that the deterioration was linearly proportional to the concentration of CO in the booth. The accuracy during this period was found to decrease from 80 percent with controls to 70 percent with 50 ppm, 60 percent with 100 ppm, 45 percent with 175 ppm, and 30 percent with 250 ppm. The blood COHb levels attained during CO exposure periods were not determined due to experimental difficulties.

Analysis:

The results of this study appear to be suggestive evidence that auditory time discrimination is affected by low levels of COHb. The failure to determine blood COHb levels is a shortcoming of this study. This study has not been duplicated, although attempts have been made.^{36,56}

- Horvath SM, Dahms TE, O'Hanlon JF: Carbon monoxide and human vigilance. Arch Environ Health 23:343-347, 1971

Review:

This study of the effects of 0, 26, and 111 ppm of CO on the performance of visual vigilance tasks by 20 healthy nonsmoking males (age 21 to 23 years) was conducted in a small chamber. The task consisted of monitoring a ground glass screen through a 1-inch diameter aperture upon which non-signal flashes of light (dim) and signals (bright) were projected. Signal detection was recorded by pressing a button. During preliminary tests, the brightness difference was adjusted for each subject so that signal detection accuracy was maintained at 90 percent. Visual discrimination performance, reflected by the number of correct "signals" detected, was evaluated in a 3-minute alerted test during which 10 signals and 50 non-signals were viewed, and in a vigilance task that followed the alerted test after 1 minute of rest, that consisted of four consecutive periods of 15 minutes duration, with each period containing 10 signals and 290 non-signals. CO exposure was begun 1 hour prior to the alerted test and continued for the duration of the experiment (approximately 2 hours). Blood samples for analysis of COHb levels were drawn prior to CO exposure, prior to the alerted test, and at the completion of the vigilance test.

The authors found that exposure to 26 and 111 ppm CO (blood COHb 1.6 and 4.2 percent, respectively) did not affect performance during the short alerted test and that performance during the vigilance task of subjects breathing 26 ppm CO (mean blood COHb level 2.3 percent after 2-hour

exposure) was no different from controls. The control subjects' performance deteriorated from 90 percent correct signals at the beginning of the vigilance task to 70 percent after 35 minutes. Further deterioration did not occur during the remainder of the test. The performance of subjects breathing 111 ppm CO deteriorated more quickly than controls and after 35 minutes only 55 percent of the correct signals were identified. During this period of testing, blood COHb levels rose from 4.4 to 6.6 percent. The authors concluded that this degree of COHb caused subjects to lose vigilance more rapidly than normal, and statistical evaluation by analysis of variance showed these decreases to be significant ($p < 0.05$ and $p < 0.01$, respectively).

Analysis:

The study appears to have been well designed. Blood COHb values were examined carefully, not just estimated. An example of the attention to detail is the fact that the authors noted that there were large individual differences in the rate of CO uptake and discussed this in the paper. Only limited data are presented for the vigilance testing results.

3. IMMEDIATE HEALTH EFFECTS RELATED TO CO EXPOSURE

- Haldane J: The action of carbonic acid on man. J Physiol (Cambridge) 18:430-462, 1895

Review:

In a heroic set of experiments investigating the toxic symptoms of CO, Haldane exposed himself to CO at concentrations ranging from 210 to 4100 p for durations ranging from 24 to 240 minutes. Blood samples were taken periodically during the exposure period and analyzed colorimetrically using carmine to determine the degree of saturation of Hb with CO. Haldane found that approximately one half of the CO inhaled became bound to the hemoglobin. The observations recorded by Haldane at various stages of CO poisoning are summarized in Table A-2. Estimations of COHb concentrations in this table are denoted by ca. and were arrived at by interpolation. The exposures were generally conducted at rest, but on occasion the effect of increased activity on toxic symptoms was evaluated. This usually involved walking around the laboratory or running up a set of 24 stairs (see Table A-2).

Haldane concluded that the toxic symptoms produced by CO closely resemble those observed with the breathing of a low oxygen atmosphere, i.e. hypoxic hypoxia. Exercise during the early stages of poisoning brought about toxic symptoms much like exercise does with mountain travelers breathing a moderately diminished oxygen supply. The experiments showed that the toxic symptoms occurred only after the blood was considerably saturated with CO and that the severity of symptoms increased and decreased as blood COHb levels rose and fell. Haldane felt that the symptoms were not appreciable until the blood was one-third saturated with CO. The symptoms produced by CO were attributed solely to diminution in the oxygen-carrying power of the blood. Haldane suggested that the aggravation of symptoms by exercise may have been to circulatory changes affecting the oxygen supply to the central nervous system.

Analysis:

This study is a valuable contribution to the literature because it is a step-by-step chronicle of CO toxicity by a man who made careful observations during the exposure. The recorded toxic symptoms range from the trivial to the incapacitating, with levels of exercise ranging from rest to moderate to strenuous. The importance of exercise to the severity of toxic symptoms at a particular level of poisoning is vividly demonstrated. Higher levels of exertion increase the number and character of symptoms at a particular level of COHb.

- Stewart RD, Peterson JE, Fisher TN, Hosko MJ, Baretta ED, Dodd HC, Herrmann AA: Experimental human exposure to high concentrations of carbon monoxide. Arch Environ Health 26:1-7, 1973

Review:

Six healthy males inhaled high CO levels (1000 to 35,600 ppm) for time periods (45 seconds to 10 minutes) to define the rate of CO uptake and blood COHb levels. Pre-exposure venous blood samples were taken for clinical chemistry profiles. Cardiovascular measurements including cardiac output, blood pressure, pre-ejection time, ejection time and stroke volume were performed pre- and post-exposure. Electroencephalograms and visual evoked responses, which monitor spontaneous electrical activity of the brain and functional visual responsiveness, respectively, were analyzed pre- and after each exposure.

During each exposure, the subjects inhaled a measured volume of air through a mouthpiece, and expired gases were collected for CO analysis and volume determinations. Venous blood was collected at timed intervals for COHb determinations. Continuous ECG recordings were taken during exposures.

Increases of 2.72 to 16.5 percent saturation COHb resulted from the tests. Peak COHb in venous blood occurred approximately 2 minutes post-exposure, and was proportional to inhaled CO concentrations. The authors were able to calculate COHb increases and derived the equation:

$$\text{Log}(\text{percent COHb/liter}) = 1.036 \log (\text{ppm CO inhaled}) - 4.4793$$

which relates COHb increases in blood per liter of gas inhaled as a function of CO concentration inhaled. The correlation coefficient for this relationship was 0.995.

There were no significant changes in ECG recordings, blood pressure, heart rate or clinical chemistry values during the tests, nor in EEG data collected pre- and post-testing.

Two subjects reported headaches during or after exposure (15,000 ppm for 2 minutes and 30,000 ppm for 1 minute). Venous blood COHb levels for these trials were reported as 10.2 and 9.1 percent, although the authors note that arterial blood COHb reaching the brain was probably considerably higher. One other subject was aware of his heart pounding in his chest.

Analysis:

The subjects were exposed to high CO levels under carefully controlled and well-documented conditions. Each of the five subjects inhaled CO levels of 10,000 to 35,600 ppm on two different occasions, yet the only subjective complaints were headaches in two subjects and an awareness of "pounding" heart in another. While high venous COHb values were not achieved, the authors were able to derive an equation for the level

inhaled (concentration and volume) and the resulting blood COHb incr
The lack of physiological responses was due to the short term of exp
and the use of 100 percent oxygen for a 20-minute post exposure peri

- Apthorp GH, Bates DV, Marshall R, Mendel D: Effect of acute car
monoxide poisoning on work capacity. Brit Med J 2:476-478, 1958

Review:

This study investigated the effect of moderate to severe CO hypoxia on four subjects performing light exercise. Each subject walked at a speed of 2.5 mph on a motor-driven treadmill. Approximately every 10 to 15 minutes, 100 to 150 ml of pure CO was introduced into the inspiratory side of an open breathing circuit. The mixed expired air was continuously sampled and analyzed by an infrared carbon monoxide meter. Every 15 minutes the pulse and respiratory rates were noted, and when the circuit was shown to be clear of the injected CO, a sample of expired air was collected and analyzed for CO₂, O₂, and CO. Venous blood samples were drawn for CO analysis at the same time expired air was collected. The treadmill was stopped and subjects assisted to a couch when their blood COHb levels were estimated to be between 30 and 50 percent.

The authors found that the only consistent cardiopulmonary change brought about by increasing blood COHb levels to 26.4 to 51.3 percent was an increase in heart rate. The concentration of COHb at which the onset of increased pulse rates occurred was not mentioned. Respiration rates, rate of oxygen uptake, and ventilatory minute volume did not show any consistent changes with increased concentrations of COHb.

The following subjective toxic symptoms were reported by each of the four subjects: headache at 20 percent COHb but no additional symptoms at COHb levels up to 26.4 percent; no symptoms at all at 28.5 percent COHb; unsteadiness when the treadmill was stopped but no additional symptoms at 37.5 percent COHb; felt "muzzy" (confused, dazed, tipsy) at 30 to 40 percent COHb; became ataxic between 40 to 50 percent COHb and unable to stand without support, but did not lose consciousness. None of the subjects reported tiredness or dyspnea during the early stages of poisoning.

Analysis:

This study is very relevant to the issue of high COHb levels and the authors have documented the cardiopulmonary responses well. Exercise was continuous at a moderate rate. The COHb values are the highest exposure values to date for humans. Statistical handling of the data is reasonable and proper.

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- Henderson Y, Haggard HW, Teague MC, Prince AL, Wunderlich RM: Physiological effects of automobile exhaust gas and standards of for brief exposure. J Ind Hyg 3:79-92, 1921

Review:

In experiments designed to simulate the activity level of a car, up to nine subjects were exposed individually in a closed chamber for one hour to air containing CO levels ranging from 200 to 1000 ppm. While subjects sat and read most of the time, they did perform a number of tasks that raised the activity level to "moderate rest." Blood colorimetric determination of COHb were drawn before the subject entered the chamber, at the middle of the period, at the end of exposure, and twice during the next 3 hours. Alveolar air samples were also analyzed for CO several minutes after the exposure period.

The authors found that the typical CO or oxygen deficiency headache proved a most definite and reliable gauge of the effect of CO, and was a more distinct criterion than any artificial test. The characteristic headache consisted of a distinctly localized pain, usually frontal, throbbing, and intensified by lying down or by exertion. Sometimes accompanied by nausea, which readily increased to vomiting. This was not clear, except with effort, and temper was easily upset, much as in alcoholic intoxication. The authors concluded that exposures to concentrations that were too dilute or for durations that were too short to produce the characteristic headache could be considered as harmless. Results of the various exposures are summarized in Table A-3.

In a few cases, the retinal fields were determined and plotted. As to the level of hypoxemia occurring in these experiments, there did not seem to be any significant effect on vision. Subjects exposed to 800 ppm CO (COHb levels ranging from 26 to 34 percent) showed a marked loss of equilibrium when tested for their ability to stand erect with eyes closed without wavering.

Analysis:

This paper presents dose-response information that will probably be useful in high-exposure tests. Methods used were basic and the protocol was descriptive as in many human studies. The toxic symptoms reported by test subjects follow a dose-response relationship. The lumping of individual responses precludes assigning a COHb level at which toxic symptoms are first reported. Subjects exposed to COHb concentrations up to 21 percent did not report any toxic symptoms, while levels of 21 and higher uniformly produced decided headaches that persisted for several hours.

TABLE A-2

Toxic Symptoms Reported by Henderson et al.²³ for
Resting Subjects Exposed to CO in a Closed Chamber

Number of Experiments	Conc. CO in Air (ppm)	COHb After One Hour (%)	Reported Symptoms at End of
2	200	11-12	None
3	300	10, 13, 14	None
11	400	14, 17, 18, 20, 21, 22	None
9	600	16, 17, 18, 21, 25, 26	None in seven cases; slight headache with two subjects.
4	800	26, 27.8, 32, 34	Decided headache lasting 4 subject able to perform eff work in laboratory or at de
1	900	34	Decided frontal headache; for 6 hours, insomnia.
1	1000	38	Throbbing frontal headache at times Cheyne-Stokes' brt averse to work for 5 or 6 h recognizable after 12 hours

4. DELAYED AND ADAPTIVE RESPONSE TO CO

Human Studies:

- Longo LD: Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. Ann NY Acad Sci 174:313-341, 1970

Review:

This paper presents original data in addition to a broad review of other papers dealing with the effects of CO on pregnant females and fetuses.

The relationship between maternal and fetal COHb has been studied in several animals as well as in humans. In man, the ratio of COHb fetus/COHb maternal has been found to be 1.11. This is due to the complex relationship between oxygen and carbon monoxide affinities for maternal and fetal blood, and placental transfer functions for O₂ and CO.

There are few reports of maternal inhalation of high CO levels, but from the 10 pregnancies reviewed in which the mothers showed classical signs of CO poisoning, eight of the delivered infants showed neurological sequelae, and three of the infants, who subsequently died, had indications of brain damage at autopsy. There is of course, no way of knowing if CO per se or cerebral anoxia caused these effects.

The author notes that several possible mechanisms may account for the effects of CO on a fetus tissue. Oxygenation is the primary consideration, since the fetus normally has slightly less oxygen than the mother. The example given for a maternal COHb of 10 percent results in a decrease in the 50 percent hemoglobin saturation (P₅₀) from 26.5 to 21 mm Hg in maternal blood, and a decrease in fetal blood from 20 to 15.5 mm Hg. Changes of this magnitude may affect tissue oxygenation and the maintenance of an adequate intracellular oxygen tension for normal enzyme processes.

Analysis:

This paper highlights a potential problem if pregnant women are exposed to CO. Evidence from smoking pregnant women and their infants suggests that lower birth weights, increased numbers of still births, abortions and deaths during the prenatal and postnatal periods are the result of cigarette smoke inhalation, although there is no method of assigning a risk factor to CO, nicotine or any other specific component of smoke.

A specific role of CO in the maternal-fetal relationship is unknown but should be carefully considered.

Animal Studies:

- Hugod C: The effect of carbon monoxide exposure on morphology of lungs and pulmonary arteries in rabbits. Arch Toxicol 43:273-281, 1980

Review:

Rabbits were exposed to CO at two levels to determine if there were histological changes in arterial and pulmonary tissue after long-term (3 to 6 weeks) or short-term (5 hours) exposure. The low level exposure was at 210 ± 25 ppm ($X \pm SD$) while the high level was 1900 ± 360 ppm when measured by a Beckman infrared CO analyzer. Average COHb levels were between 11.9 and 19.0 percent for the low level group and averaged 34.8 percent (31-39 percent) immediately before sacrifice in the high-level group.

Histological evaluation of tissue was conducted by both light and electron microscopy. Presence of edema either in endothelial cells or in subendothelial spaces of blood vessels, presence of parenchymal infiltration with inflammatory cells, and increase in number of type II cells and edema were criteria for CO-related changes in lung tissue studied by light microscopy. Electron microscopy searched for edema, mitochondrial structure changes and/or platelet thrombosis, or accumulation in pulmonary capillaries.

No macroscopic differences related to CO exposure were found in lungs or in pulmonary arteries. No microscopic changes due to CO occurred in lung tissue of rabbits after either low- or high-level exposure.

Analysis:

The author demonstrated that morphologic changes did not occur when evaluations were scored by objective measurements rather than by subjective judgments. The number of animals in both CO and control groups (12 each) should be sufficient to show a CO effect if it were present. It should be noted that many studies of CO and arterial changes involve feeding a high cholesterol diet which may itself cause some changes that have been ascribed to CO.

- Thomsen HK: Carbon monoxide-induced atherosclerosis in primates. Atherosclerosis 20:233-240, 1974

Review:

This study with monkeys (Macaca irus) examined the effect of exposure to 250 ppm CO for 2 weeks on the ultrastructure of the coronary arteries. Six animals were exposed continuously to CO, six other animals were exposed intermittently for 12 hours a day to the same gas mixture, and eight animals served as controls. Blood COHb levels and serum cholesterol were measured using standard spectrophotometric methods. At the end of 2 weeks, the animals were sacrificed, biopsies were taken from the left and right coronary arteries and slices of the myocardial tissue were excised in order to examine the smaller intramural arteries. Tissue sections were examined by light and electron microscopy.

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The mean COHb level of the exposed group was 20.6 percent and the controls 0.6 percent. The mean serum cholesterol value showed no significant difference in any of the groups. One control and two continuously exposed animals were excluded from the study when it was found that they experienced fibro-muscular intimal wall thickening that resembled spontaneous atherosclerosis. All of the continuously exposed animals showed more or less pronounced widening of the subendothelial space in which cells with or without lipid droplets were accumulating. These subendothelial cells often contained myelin bodies, and the endothelial cells in these areas were quite rich in organelles--especially mitochondria. In a few sections a gap was seen between two endothelial cells and monocyte-like cells were always present beneath the gaps. The intermittently exposed group showed no intimal changes but in two animals medial edema with collagen formation was noted. The smaller intramural coronary arteries were quite normal in the exposed groups.

The author concluded that the widening of the subendothelial space of the coronary arteries and accumulation of lipid-laden cells possibly represents an early step in the formation of fatty streaks and may be a consequence of subendothelial edema. The author suggests that the present findings may relate to the well-known risk factor in cardiovascular diseases related to smoking where blood COHb levels up to 20 percent are not uncommon in heavy smokers.

Analysis:

The paper reports the results of an acute high CO exposure in very few animals. This represents a pilot study that could be expanded if there is need for information on this type of exposure. The authors discarded some animals because of atherosclerosis, but this may have proven to be useful information. The data are interesting, but the relevance of data obtained in the rabbit may not extrapolate directly to man and is therefore questionable..

- Astrup P, Kjeldsen K, Wanstrup J: Effects of carbon monoxide exposure on the arterial walls. Ann NY Acad Sci 174:294-300, 1970

Review:

This study with cholesterol-fed rabbits reports on the effect that extended periods of CO hypoxia had on the development of atherosclerotic plaques. Groups of 12 rabbits fed high-cholesterol diets were exposed in airtight cages to air mixtures containing CO either continuously for 10 weeks (15 percent COHb for 8 weeks and 30 percent COHb for the last 2 weeks) or intermittently 8 hours per day for 10 weeks, leading to COHb concentrations of 20 percent. In another experiment, cholesterol-fed rabbits breathed in an apparently continuous manner an atmosphere of 10 percent O₂ in N₂ for 8 weeks. Analysis of the cholesterol content of the aortic tissue of animals continuously exposed to CO found the

concentrations 2.5 times higher than control animals, while intermittent exposure produced levels as high as 5 times greater than controls. The low oxygen atmosphere produced cholesterol contents 3.5 times that of controls. Macroscopic and microscopic examination of the aortic lesions showed that there was no difference in the lesions between animals exposed to CO and to a low O₂ atmosphere. The aortas of the experimental animals were readily distinguished macroscopically from the control animals by the number and size of plaques. The microscopic changes of experimental animals were readily distinguished as well and were characterized by a marked lipid accumulation in intima and subintima.

The exposure of rabbits fed normal diets to CO for 3 months to maintain 11 percent COHb induced arterial lesions that appeared as endothelial hypertrophy and proliferation-splitting of the subintima structure with a tendency to pronounced focal subintimal edema. The authors concluded that rabbits exposed to CO or to low O₂ atmospheres developed vascular lesions that were indistinguishable from spontaneous arteriosclerosis in these animals and that by cholesterol feeding could lead to considerable increase in lipid accumulation.

In about 20 percent of the CO-exposed animals, fluid occurred in the serous cavities: pleura, pericardium, and peritoneum. The protein concentrations in the fluid were high, from 3 to 5 percent. The authors suggested that the formation of transudates in the serous cavities as well as subintimal edema resulted from an increased permeability for macromolecular plasma components. The authors noted that research of their own and others indicate that the increased permeability may explain the enhancing effect that CO and low oxygen atmospheres have on the development of atheromatosis.

Analysis:

Although this study demonstrates that significant development of vascular lesions results from the breathing of CO or low O₂ atmospheres, it can be faulted for presenting very few experimental details. The concentrations of CO breathed and the method of COHb determination were not mentioned. The animals exposed intermittently to CO experienced blood COHb levels of 20 percent, although the number of animals exposed intermittently was not mentioned. Only average values were presented for the cholesterol content of aortic tissues. No mention was made of the percentage of animals who experienced significant increases in vascular lesions.

The increased incidence of vascular lesions in rabbits following CO exposure parallels the increased risk in man of smokers developing obliterating arterial diseases.

- Thomsen HK, Kjeldsen K: Threshold limit for carbon monoxide-induced myocardial damage. Arch Environ Health 29:73-78, 1974

Review:

This study with rabbits investigated the effect that CO exposure had on inducing myocardial damage. Forty-two healthy, castrated, male rabbits, free of any signs of infection or pulmonary inflammation, were divided into 14 groups of three animals and placed in exposure chambers. Six groups were continuously exposed to 180 ppm for 0.5, 2, 4, 8, 24, and 48 hours while another group served as a control. The animals were all killed by stunning. Biopsies taken from the papillary muscles of the left ventricle were examined using light and electron microscopy for ultrastructural changes. Since myocardial damage was evident in animals exposed for 4 hours or more, the remaining animals were divided into six test groups exposed to 50 and 100 ppm CO for 4, 8 and 24 hours and one control group. The concentration of CO breathed was continuously monitored by infrared spectroscopy and the COHb levels determined at the end of each experiment from ear vein blood samples.

The authors reported that the blood COHb levels measured after exposure to 50, 100, and 180 ppm CO were 4 to 5, 8 to 9, and 16 to 18 percent, respectively. However, they did not report the duration of the exposures. No macroscopic changes in the myocardium were evident in any of the exposed animals. Contraction bands were revealed by light microscopy in some of the animals exposed to CO for 8 hours or more, but the concentrations of CO at which these changes were observed were not mentioned. No other changes were observed at this level of magnification. Ultrastructural myocardial degeneration in the form of contraction bands, myofibrillar disintegration, myelin body formation, or dehiscence of the intercalated disks was seen in rabbits of different groups. No qualitative changes were demonstrated in animals exposed to less than 100 ppm CO or for less than 4 hours; however, in some of these animals, the number of lipid droplets increased. Lesions in the myofibril system included an overcontraction that became more pronounced with increasing exposure time up to the formation of regular contraction bands, and irregular disorganization of the myofibrils was occasionally seen in the area without contraction bands. Myelin bodies were found regularly in rabbits exposed to CO for 4 hours or more. The amount of mitochondria seemed to be increased in myocardium in which myelin bodies occurred. The amount of ribosomes seen in the sarcoplasm as polysomes was greatly increased and these were more numerous around mitochondria, especially in animals exposed to 180 ppm CO for 4 hours. Membrane-bound ribosomes were frequently seen along with an increased amount of lipid droplets. The sarcolemma appeared intact; however, in areas with contraction bands, papilliferous arcades were noted. Dehiscence of the intercalated disks was seen in several animals, but was most regular and pronounced in animals exposed to CO for 4 hours. Some areas of edema were present in the interstitial space, but fibroblastic activity was absent, the number of macrophages was not impressive, and the capillaries were normal.

The authors noted that the morphologic changes found in this study do not differ from those reported with other forms of hypoxic myocardial damage. Carbon monoxide concentrations of 50 ppm did not produce any changes within 24 hours, while exposure to 180 ppm CO for 4 hours or more invariably produced myocardial changes. Some animals exposed to 100 ppm CO showed ultrastructural changes. The authors regarded 100 ppm as the threshold limit for CO-induced myocardial damage, but suggested that a more precise determination of the threshold would require studies with a larger number of animals in each group.

Analysis:

This paper presents the most graphic response to CO inhalation in the rabbit. Relevance to man has yet to be shown, since humans have not shown this magnitude of myocardial derangement yet. To our knowledge this study has not been duplicated. The science appears correct, since artifacts are not obvious in control tissue that was supposedly processed the same way as the CO-exposed tissue.

- Kjeldsen K, Astrup P, Wanstrup J: Ultrastructural intimal changes in the rabbit aorta after a moderate carbon monoxide exposure. Atherosclerosis 16:67-82, 1972

Review:

This study with male rabbits examined the effect of 2 weeks of continuous exposure to 180 ppm CO on the arch and thoracic aorta. Four animals breathed the CO atmosphere while another four breathed air. Carboxyhemoglobin levels of the exposed animals was 16 to 18 percent. The animals were killed by a stunning blow to the head. The heart and the thoracic part of the aorta were excised. Specimens were taken from the aortic arch just proximal to the most proximal intercostal arteries and from the most distal part of the descending thoracic part of aorta. Specimens were examined by both transmission and scanning electron microscopy.

Macroscopic examination revealed visible intimal changes in two of the CO-exposed animals where a few tiny elevated plaques were noted in the aortic arch as well as in the thoracic part of the artery. Pathologic changes revealed by light microscopy included edema of the inner aortic coats, fragmentation of the subintimal membrane texture and collagen formation. Examination of the tissues by the electron microscope revealed a very pronounced intimal edema, subendothelial blisters, deformation of the folding structure, and confluence of blisters to plaques. Areas with plaque formation were characterized by considerable widening of the subendothelial space, accumulation of amorphous material, elastic fibers, collagen fibrils, and occasional calcifications.

Analysis:

The results of this study demonstrated that extended periods of moderate CO hypoxemia cause changes of the arterial walls provoking increased endothelial permeability and formation of edema leading to changes indistinguishable from early atherosclerosis. One shortcoming of this study is that data presentation is quite lacking. It is not possible to tell how many animals experienced the various pathologic abnormalities.

5. FIRE FIGHTERS - A RELEVANT OCCUPATIONAL EXPOSURE

- Balanoff T: Fire Fighter Mortality Report. Washington, DC, Int Assoc of Fire Fighters, 1976

Review:

This report concluded a 15 month investigation of 101 deaths of fire fighters in the line of duty. In addition to statistical data, each death is evaluated to define steps which may lead to reducing fire fighter mortality.

Major sections of the report focus on fire fighter deaths while fighting fires, fire fighters killed in non-fire fighting situations and fire fighters killed by heart attacks. Every death is analyzed for the individual's level of training, protective equipment, officer leadership, communication, apparatus and tools. In the section dealing with heart attacks, exposure to smoke/toxic fume inhalation, stress and over-exertion were studied.

Forty-five percent of all fire fighters killed in the line of duty died from heart attacks. The average age of the fire fighter heart attack victim was 51.3 years with 22 mean years of service. Arteriosclerotic heart disease was present and was judged to be the immediate contributing factor in every case at autopsy.

Analysis:

The report is a statistical compilation of fire fighter mortality. Facts surrounding each death were constructed from reports and interviews and are presented in detail.

- Radford EP, Levine MS: Occupational exposures to carbon monoxide in Baltimore firefighters. J Occup Med. 18:628-632, 1976

Review:

Blood COHb determinations were made at the scene of fires and data were collected to allow analysis of exposure time, severity of the fire, smoking history, heart rate and use of protective masks. A total of 519 samples were collected at fires and compared to 57 control samples drawn from fire academy students and administrators.

Effects examined and blood COHb levels were:

- Effect of smoke exposure

COHb levels elevated in exposed firemen. Controls had average COHb of 2.12 percent, exposed COHb level was 4.53 percent. Upper level of COHb rose from 3 percent to 19 percent in exposed men.

- Effect of cigarette smoking Dose-related increases in COHb. Nonsmokers = 0.48 percent, below 1 pack/day = 2.33 percent and above 1 pack/day = 5.64 percent. Cigarette smoking + smoke exposure shifted COHb values upward for both light and heavy smokers.
- Effect of smoke density Subjective evaluation as to "heavy" or "light" smoke had no effect on measured COHb levels.
- Effect of exposure time Length of exposure to fire and CO had no effect on COHb levels. Less than 30 minute exposure = COHb of 2.77 percent; 30-60 minute exposure = 2.3 percent; over 60 minute exposure = 1.95 percent.
- Effect of protective equipment (facemasks) Blood COHb level were lowest in men who wore a mask continuously (2.84 percent), while intermittent face mask use (4.76 percent) was no better than no use at all (4.64 percent).
- Effect of pulse rate Elevated pulse rates were associated with higher COHb levels. Pulse rates of above 120 beats per minute were associated with COHb levels of 3.21 percent compared to 1.89 percent in men with pulse rates of 100-120 beats per minute.

The authors note that exposures to fire may include other gaseous or airborne contaminants that have not been identified and may exert harmful effects that are unknown at this time. The effects reported were all more pronounced in smokers than nonsmokers, and the results were considered routine exposure and not overexposure. Estimated degree of exposure based on smoker density or length of time at the fire were not correlated to blood COHb levels.

Analysis:

This report of a large population of fire fighters surveyed for blood COHb levels and the factors that could influence these levels presents a wealth of data and a comprehensive evaluation. Data presentation is good since mean values, standard deviations and sample numbers are given along with t-test probability levels and graphic displays of cumulative frequency displays of each data set analyzed.

- Barnard RJ, Weber JS: Carbon monoxide: a hazard to fire fighters. Arch Environ Health 34:255-257, 1979

Review:

Carbon monoxide levels were measured in 25 fires in the city of Los Angeles to determine fire fighter CO exposure levels. Levels as high as 3000 ppm were observed. In general, when CO levels were above 100 ppm smoke was heavy and noxious, but in some cases smoke was heavy while CO levels were minimal. Measured CO levels were below 100 ppm in 12 percent of fires; between 100 and 500 ppm in 40 percent of fires; between 500 and 1000 ppm in 28 percent of fires; and above 1000 ppm in the remaining 20 percent of fires. The detector used was an Interscan model 1142 CO-detector (Interscan Corp., Chatsworth, CA).

Analysis:

This paper establishes ranges of CO to which fire fighters are exposed. There are no statistics, since each fire is a unique case. The authors have presented data regarding the type of structure or material burning, along with comments on locations within the structure and characterization of smoke density and measured CO levels.

- Barnard RJ, Duncan HW: Heart rate and ECG responses of fire fighters. J Occup Med. 17:247-250, 1975

Review:

Thirty-five firemen wore a small recorder that monitored their ECG intermittently over 24-hour periods. They also maintained log books in which they noted the exact times recorders were turned on, the times of all alarms and a description of their activities. Recorders were subsequently played back and analyzed for ECG waveform and heart rate changes during a control period before the alarm sounded, every 30 seconds after the alarm sounded and at 1-minute intervals while the men were responding to the fire call. Data were obtained from a total of 189 alarms.

Heart rate increases averaged 47 beats per minute within 30 seconds after the alarm sounded (range of 47-112 beats/min increase). By 1 minute after the alarm sounded, while on the trucks, heart rates were still elevated by 30 beats per minute (range of 1-80 beats per minute). There was considerable variability in responses, with no consistent increase in heart rate in one individual, while another had two instances in which heart rate rose 50 beats per minute and for a third alarm his heart rate increased by 104 beats per minute.

During fire fighting, heart rates of 175-195 beats per minute were observed in the first 3-5 minutes, with sustained rates of 160 beats per minute in 1 man for over 90 minutes, while another has an average heart rate of 188 beats per minute for 15 minutes. Movement artifacts prevented analysis of ECG patterns during fire fighting.

Analysis:

This paper demonstrates that fire fighters have job-related heart increases due to both anxiety and physical work. Some of the men showed ECG changes normally associated with myocardial ischemia (S-T segment depression) during the first 15-30 seconds after the alarm sounded, but unfortunately, further tracings during fire fighting were not obtainable due to motion artifacts. These findings suggest anxiety as a cause of ischemia, but there is no indication in the paper if any work limitations resulted after these ischemic episodes.

- Barnard RJ, Gardner GW, Diaco NV, Kattus AA: Near-maximal ECG stress testing and coronary artery disease risk factor analysis in Los Angeles City fire fighters. J Occup Med 17:693-695, 1975

Review:

Stress tests were conducted on a random group of 90 fire fighters 40 and 59 years old (average of 46 years) who were considered to be in good health and without any overt symptoms of heart disease. The results were compared to data derived in a study of insurance underwriters of similar age distribution (40 to 59 years, average of 47 years).

In the testing protocol, the subjects completed a questionnaire, height and weight measurements taken and were given a resting ECG and blood pressure check. At a second visit, they were examined by a physician and questioned about health history, physical activity and habits and had blood samples drawn for cholesterol determinations. Skinfold body fat was measured and the stress test conducted with continuous ECG monitoring up to near maximal oxygen uptake levels.

Data derived for coronary heart disease risk factor analysis revealed that the fire fighters scored relatively low in commonly accepted factors including blood cholesterol levels, systolic diastolic blood pressure, smoking habits. Only one man had an elevated cholesterol, was a smoker and was hypertensive at the time of the testing. Only five men had two of the three risk factors elevated and 47 had none of the risk factors elevated.

Nine of the fire fighters had ischemic ECG responses indicative of coronary heart disease during the stress test. One of the 90 men had a normal resting ECG and suffered a myocardial infarct at a fire 2 days later and died. One other 47-year-old subject had a normal ECG stress test and suffered a myocardial infarct 20 minutes later. This subject had a normal blood pressure (125/80 mm Hg) and cholesterol (234 mg percent) values at the time of the test.

The incidence of stress-related ECG changes in fire fighters was 9 percent, while insurance executives had an 8 percent rate. The authors note that this difference may not be statistically significant, but was unexpected, since firemen were selected for low risk factors for coronary

heart disease during pre-employment screening. The authors suggest ischemic heart disease may be job associated.

Analysis:

This paper defines the relationship between coronary heart disease risk factors and electrocardiographic evidence of ischemia at rest during exercise. It is worth noting that the population tested was a random one and of adequate size (90 men) to provide data that should probably be an accurate reflection of older fire fighters who have been exposed to occupational factors for an extended time, although they provide no data for length of service. Comparing fire fighters with an age matched set of insurance executives seems to be a valid comparison. Electrocardiographic responses to stress, since these investigators used the same protocol for both populations.

• Barnard RJ, Gardner GW, Diaco NV: "Ischemic" heart disease in fire fighters with normal coronary arteries. J Occup Med 18:818-820, 1976.

Review:

This is a report of follow-up studies done on nine firemen who were found to have ischemic ECG changes during stress testing (previous article). After the initial testing showed S-T segment depression, nine men were tested a second time and blood samples were taken for cholesterol, triglyceride and lipoprotein determinations. Six of the men were then given cardiac catheterization and angiography to enable the physician to observe coronary arteries for signs of obstructions.

Only two of the men had significant (greater than 50 percent) obstruction of coronary arterial branches. Of the other four, three had abnormal ECG waveforms during tests, while two had decreased left ventricular wall motion and increased thickness of the left ventricular wall. All nine subjects had normally functioning cardiac valves and pressures were within normal limits. The authors note that the subjects with ventricular hypertrophy (thickened ventricular wall) were avid handball players, although hypertrophy from athletic training is associated with decreased ventricular wall motion and function.

As a group these subjects had low risk factors for coronary heart disease, since only one had high skinfold fat measurements and hypertension, one had elevated triglycerides, and two were smokers.

The authors conclude that fire fighters have "ischemic" heart disease and/or abnormal left ventricular function that was not due to coronary artery disease or any other known cause. They concluded that stress of the fire fighting job had a detrimental effect on the myocardium, possibly due to reduced myocardial oxygen supply or greatly increased myocardial oxygen demands.

Analysis:

This detailed cardiovascular examination is useful because it provides evidence that factors related to occupational exposure to CO and physical stresses do not necessarily have to result in anatomical or pathological changes to cause functional difficulties. In conjunction with the earlier paper, the authors demonstrated that out of 90 subjects, 10 of obstructive coronary disease were found, along with four who were diagnosed as impaired by electrocardiographic findings such as ST-segment changes.

● Sammons JH, Coleman RL: Firefighters' occupational exposure to carbon monoxide. J Occup Med 16:543-546, 1974

Review:

This is a report of 27 fire fighters and 27 non-fire fighters matched for age, sex, height, weight, smoking habits, race and family history of cardiac or pulmonary disease who were studied for COHb and several serum enzymes associated with myocardial damage. Enzymes studied were total lactic dehydrogenase (LDH), heat stable lactic dehydrogenase (LDH-S), heat labile lactic dehydrogenase (LDH-L), hydroxybutyric dehydrogenase (HBD) and creatine phosphokinase (CPK). Blood samples were collected at 28-day intervals for 5 months. A CO-Oximeter was used for COHb determinations, and enzymes were measured with reagents and procedures of Sigma Chemical Company.

Although the population tested had no signs of specific organ dysfunction or clinical heart disease, members of the fire service had significantly higher ($p < 0.02$ to 0.001 level) LDH, LDH-S, HBD and CPK enzyme levels than their paired counterparts. Nonsmoking fire fighters had COHb levels that averaged 5.0 percent as compared to 2.3 percent for nonsmoking controls. This difference was highly significant ($p < 0.001$).

The authors note that nonsmoking fire fighters have COHb levels that do not reach NIOSH maximum levels, and all fire fighters exceeded the current recommended time-weighted average for an occupational CO exposure. Enzyme levels measured suggested myocardial damage, but regression analysis of length of service, age, etc. did not show a trend over time.

Analysis:

The method of carefully matching subjects may be one approach to studying physiological differences that are not statistically significant when comparing group means. The results presented appear to indicate enzymatic changes, although no clinical data are presented to substantiate the suggested myocardial damage. The enzymes tested are not limited solely to the heart, so there is a possibility of other sources of enzyme release, such as skeletal muscle contributing to the measured values. No data are

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given as to the time of sampling in regard to activity levels in the period preceding blood collection. From the presented COHb levels in nonsmoking firemen, with values of 6.9, 7.3, 5.9 and 6.1 percent saturation, it is possible that smoke exposure and high physical activity levels had occurred not too long before blood was collected.

- Stewart RD, Stewart RS, Stamm W, Seelen RP: Rapid estimation of carboxyhemoglobin level in fire fighters. J Amer Med Assoc 235:390-392, 1976

Review:

This paper is a report of a field study in which fire department medical technicians were trained to use a CO breath analyzer (Ecolyzer model 2100) and then derive data to define the relationship between alveolar CO and blood COHb levels in fire fighters.

Data are presented showing average blood COHb levels in 55 nonsmoking fire fighters of 5.0 percent, with a range of 1.4 to 9.1 percent. For 56 cigarette smoking fire fighters, average blood COHb was 7.0 percent (range 1.9 percent to 13.0 percent). The authors note that these data indicate that nonsmoking firemen had COHb levels comparable to those of heavy cigarette smokers, and that five of the cigarette smoking firemen had COHb levels above 10 percent saturation.

Accuracy of the breath analyzer was confirmed by gas chromatography on random samples. Over the range of 1.4 to 132 ppm, the two methods agreed within 1.2 ppm.

A figure is presented showing a nonlinear relationship between alveolar CO and blood COHb. The authors reported that the relationship between these parameters could be calculated by the equation:

$$CO_b = \frac{COHb (\overline{PCO_2})}{O_2Hb (P_b) (M)}$$

where CO_b = alveolar CO in ppm; COHb = carboxyhemoglobin saturation; O_2Hb = percentage of oxyhemoglobin; P_b = barometric pressure in mm Hg; M = the affinity of hemoglobin for CO; and $\overline{PCO_2}$ = pulmonary capillary blood oxygen tension in mm Hg. They used a value of 210 for M, a value 80 for $\overline{PCO_2}$ and P_b was given as 750 mm Hg for an average value for Milwaukee.

Analysis:

This paper is useful because it documents the field use of this particular breath analyzer for CO and provides data to relate alveolar CO and blood COHb levels up to 33 percent COHb saturation. A curve based on the equation is presented as a figure showing that calculated COHb values do agree with actual data. However, the curve may mislead some readers, because the curve is extrapolated up to an alveolar CO that would correspond to a COHb of 50 percent, whereas the data only goes to 240 ppm for CO in alveolar air and 33 percent COHb saturation in blood.

Appendix B.

CALCULATION OF THE RATE OF CO UPTAKE

The first attempt to describe the rate of COHb formation in man was made by Haldane in 1895. He noted that definite symptoms of CO poisoning occurred in a subject at rest when the saturation of Hb reached around 33 percent, and that lower concentrations in the air breathed took longer to cause effects. Because a blood volume of 5000 ml contains enough Hb to absorb either one liter of O₂ or one liter of CO, he reasoned that at a breathing rate of 7000 ml/minute and a CO concentration of 1 percent, it would take 5 minutes to absorb the 330 ml of CO necessary to obtain 33 percent saturation of hemoglobin. At 0.5 percent CO, it would take 10 minutes, and at 0.1 percent it would take 50 minutes to obtain 33 percent saturation. In contrast to the predictions, however, actual times for saturation were roughly double those predicted (Table B-1). Approximately 50 percent of the CO inhaled was actually absorbed and the percent absorbed appeared to be independent of concentration.

Subsequent studies have confirmed Haldane's finding that, during light activity or rest, 50 percent of the inhaled CO was actually absorbed during the early stages of exposure. As levels of COHb increased, the proportion of absorbed CO decreased due to an increase in the average back pressure of CO in the blood of the lung capillaries. Theoretically, the rate of CO uptake would be proportional to the difference between alveolar CO partial pressure (pCO) and the average back pressure of CO in the blood of the lung capillaries. Both values rise during the course of exposure. The back pressure rises slowly at first and then rapidly as Hb saturation increases. As the saturation increases, alveolar pCO rises because progressively less CO is extracted by the blood from the inspired air; when equilibrium between the pCO in the capillaries and the alveoli is reached, absorption ceases.

The exposure of individuals to CO during exercise resulted in significantly enhanced rates of COHb formation. Ventilation rates rise rapidly with increased work loads, and as a consequence more CO is brought into the alveoli. Ventilation rates may vary from 6000 ml/min at complete rest to 30,000 ml/minute during hard work. The increased rate of CO uptake obtained as the activity level increases may be due not only to increased quantities of CO in the alveoli, but also to increased diffusivity of the lungs. The increased diffusing capacity is attributed to dilation of the capillaries of the alveoli, resulting in a larger available surface area for the diffusion of CO.

TABLE B-1

Observed and Calculated Times for Various Levels
of Hemoglobin Saturation as Reported by Haldane²¹

No. of Exp.	Percentage of CO in air breathed	To produce 50% saturation		To produce 33% saturation		To produce 15% saturation	
		Minutes actually required	Required if all the CO breathed had been absorbed	Minutes actually required	Required if all the CO breathed had been absorbed	Minutes actually required	Required if all the CO breathed had been absorbed
2	.39	--	--	24	12	10	5.5
3	.40	--	--	30	12	--	--
4	.36	--	--	26	13	11	6
5	.41	--	--	27	12	18	5
6	.12	--	--	107	40	38	18
7	.21	72	34	34	23	18	10
Average	.31	72	34	41	19	19	9

The following equation describes the rate of CO uptake, accommodating observations on the effect of physical activity and the pCO in the pulmonary capillaries.

$$\text{Rate of CO uptake} = k p_{\text{CO}} \times \frac{\% \text{COHb equilibrium} - \% \text{HbCO at time } t}{\% \text{COHb equilibrium} - \% \text{HbCO at time zero}}$$

where:

k = a constant which varies with the activity level of the subject but not with pCO.

pCO = partial pressure of CO in the inspired air

% COHb equilibrium = final COHb level if the exposure continued until the CO uptake ceased.

The first term in the equation accounts for the fact that the initial rate of CO uptake is proportional to the CO pressure in the inspired air. The terms in the brackets take account of the back pressure of CO as equilibrium is approached. When the equation was used to plot COHb levels resulting from exposure to CO at concentrations ranging from 0.01 to 0.20 percent for a light activity level, the discrepancy with 41 experimental observations varied by 2 percent, which was the error of the method used in the COHb determination. Two of the individuals consistently deviated from the average by 10 to 15 percent, one above and one below. It was felt that this variation of approximately 25 percent in the absorption rate reflected individual variations in the ratio of tidal air to dead air space of the lungs and the diffusion constant of the lungs. In individuals with higher ratios of tidal air to dead space, a greater proportion of the CO breathed will reach the alveoli, and CO will be absorbed more quickly. Larger diffusion constants also result in enhanced CO absorption.

The level of COHb in the blood is influenced by CO produced from endogenous sources as well as by that from inspired air. Endogenous CO is apparently produced mainly in the liver and spleen as a catabolic by-product of heme. Methods developed for measuring the rate of endogenous production of CO ($\dot{V}_{\text{CO}}$) in man have made it possible to study the relationship of $\dot{V}_{\text{CO}}$ and other variables to COHb levels. The value of $\dot{V}_{\text{CO}}$ is of particular interest because it reflects the rate of destruction of circulating erythrocyte hemoglobin. For normal, healthy young men exposed to air free of CO, an average value of 0.41 ml/hour has been reported, while for patients suffering from hemolytic anemia, values ranging from 0.7 to 3.44 ml/hour are common. On the basis of this work, Coburn, Forster and Kane¹⁵ reported development of an equation describing the rate of change of total body CO from both endogenous and

exogenous sources. The Coburn-Forster-Kane (CFK) equation has proven to be a very satisfactory model for estimating changes in COHb concentration in the blood. The equation follows:

$$\frac{dCO}{dt} = \dot{V}_{CO} - \frac{[COHb]}{[HbO_2]} \frac{\bar{P}_{CO_2}}{M} \times \left[\frac{1}{\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A}} \right] + \frac{P_{ICO}}{\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A}}$$

Where:

$\frac{dCO}{dt}$ = the rate of change of carbon monoxide in the body

$\dot{V}_{CO}$ = the carbon monoxide production rate from endogenous sources

$[HbCO]$ = the level of carbon monoxide in the blood

$[HbO_2]$ = the level of oxyhemoglobin

$\bar{P}_{CO_2}$ = the mean pulmonary capillary oxygen pressure

M = the Haldane constant, which represents the relative affinity of hemoglobin for CO and O₂

D_L = the diffusion capacity of the lungs

P_B = the barometric pressure

P_{H_2O} = the vapor pressure of water in the lungs

$\dot{V}_A$ = the alveolar ventilation rate

P_{ICO} = the inspired carbon monoxide pressure

By assuming that the total body stores of CO are proportional to COHb and equal to COHb x effective blood volume in milliliters (Vb), the equation, once integrated, takes the following form:

$$\frac{\frac{[COHb]}{[HbO_2]} \frac{\bar{P}_{CO_2}}{M} - \dot{V}_{CO} \left[\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A} \right] - P_{ICO}}{\frac{[COHb]_0}{[HbO_2]_0} \frac{\bar{P}_{CO_2}}{M} - \dot{V}_{CO} \left[\frac{1}{D_L} + \frac{P_B - P_{H_2O}}{\dot{V}_A} \right] - P_{ICO}} = e^{-\frac{\bar{P}_{CO_2} t}{M \dot{V}_b [HbO_2] \left(\frac{1}{D_L} + \frac{713}{\dot{V}_A} \right)}}$$

The expression describes the changes in COHb with time from an original value COHb_0 , when any of several parameters are altered to a new level and maintained there. Under steady state conditions, the right hand portion of the equation becomes zero, as does the numerator on the left hand portion, so that the equation becomes:

$$[\text{COHb}] = \frac{P_{\text{I CO}} M [\text{HbO}_2]}{\bar{P}_{\text{CO}_2}} + \frac{\dot{V}_{\text{CO}} M [\text{HbO}_2]}{\bar{P}_{\text{CO}_2}} \times \left[\frac{1}{D_L} + \frac{P_B - P_{\text{H}_2\text{O}}}{\dot{V}_A} \right]$$

Peterson and Stewart³⁸ tested several mathematical models for predicting COHb levels and found that the CFK equation fit their experimental data most satisfactorily. In experiments designed to test the various models, 18 sedentary, healthy male nonsmokers ranging in age from 24 to 42 years were exposed continuously to CO at concentrations of 1, 25, 50, 100, 200, 500 and 1000 ppm for periods of 0.5 to 24 hours; to 50 ppm discontinuously over 7 hours; and to concentrations that rose steadily from 0 to 1000 ppm over 2.5 hours. The continuous exposures to various concentrations of CO resulted in COHb levels ranging from 3.05 to 24.80 percent. Comparison of 339 individual measurements of COHb levels with those calculated by the CFK equation resulted in a standard deviation of 0.97 percent COHb. For twenty-four individual exposures to CO concentrations of 50 ppm for 24 hours resulting in COHb levels of around 8 percent, the standard deviation was 0.41 percent COHb. For discontinuous exposure resulting in COHb levels of roughly 4 percent, the standard deviation for four experiments was 0.30 percent COHb. For steadily rising concentrations, resulting in COHb levels as high as 33.3 percent, the standard deviation for 20 trials was 1.53 percent COHb. The calculated half-life for release of CO from the body was 252 minutes, which compares quite favorably with the average of 320 minutes observed during 39 experimental determinations.

Peterson and Stewart³⁸ reported that the CFK equation could be satisfactorily employed to describe the absorption and excretion of CO for 19 men and 3 women at exercise rates ranging from sedentary to 300 kpm/minute (moderate work) when they were exposed to steady concentrations of 50, 100 and 200 ppm for 0.33 to 5.25 hours. In the course of each experiment, blood samples were taken from several individuals prior to their entering a CO exposure chamber; after a 45-minute period of either rest or exercise on a bicycle ergometer; once again after the routines had been reversed; and after a final rest period. Measurements of blood COHb levels were confirmed by measurements of CO in the expired air. The predicted COHb levels at the end of each exposure segment were then calculated using either a "continuous" technique in which the calculated COHb level at the end of each particular segment became the new $[\text{HbCO}]_0$ for the next segment, or by a "segmental" technique in which the actual COHb level at the end of a particular segment was used as the new $[\text{HbCO}]_0$ for the next segment. A total of 429 exposure segments were analyzed using both the continuous and segmental techniques. The fit of the CFK equation as a function CO concentration was very good. The mean correlation coefficient using the

segmental technique was 0.88, and using the continuous technique, 0.78. When the fit of the exercise data for individual subjects was analyzed, the mean correlation coefficient by the segmental technique was 0.93; by the continuous technique, 0.88. Exercise sufficient to increase the alveolar ventilation rate by a factor of 2.5 from sedentary levels did not materially alter the fit of the equation to the data (correlation coefficients were 0.93 and 0.95, respectively).

To evaluate the impact of the various parameters of the CFK equation on calculated COHb levels, Peterson and Stewart varied each of them, one at a time, for simulated CO exposures. The results of these calculations are presented in Table B-2.

Only the barometric pressure, the affinity ratio, M , and the oxygen concentration appear to have an effect on the COHb levels at equilibrium. The remaining variables exert some effect on the rate at which equilibrium is approached. The primary factors affecting the level of COHb in the blood of a subject exposed to CO are the concentration of CO, the time of exposure and the level of activity during the exposure.

The only variables affected by the level of work are the alveolar ventilation rates ($\dot{V}_A$) and the diffusivity constant of the lungs (D_L). The significance of selecting an appropriate value of $\dot{V}_A$ is illustrated by the fact that increasing the alveolar ventilation rate from 6000 ml/minute (rest) to 15,000 ml/minute (light work), while holding all the other variables constant during a simulated 1-hour exposure at a CO concentration of 1000 ppm, results in an increase of the calculated COHb level from 23.2 percent to 37.6 percent. The impact of D_L is not so significant. For example, increasing the value of D_L from 30 to 50 ml/minute-mm Hg results in an increase of HbCO from 23.2 to 25.0 percent during a 1-hour exposure to 1000 ppm of CO.

TABLE B-2

Effect of Varying Parameters of CFK
Equation on Calculated COHb Levels

Parameter	60-Min Exposure					480-Min Exposure				
	CO (ppm)					CO (ppm)				
	8.7	35	50	100	1000	8.7	35	50	100	1000
Nominal	1.08	1.68	2.02	3.16	23.2	1.40	4.25	5.83	10.9	59.8
$P_B = 400$ mm Hg	1.11	1.62	1.90	2.86	20.0	1.64	4.53	6.15	11.4	65.2
$P_B = 600$ mm Hg	1.09	1.66	1.99	3.07	22.2	1.49	4.37	5.98	11.2	61.7
$P_B = 1500$ mm Hg	1.05	1.70	2.07	3.31	24.8	1.19	3.82	5.27	9.9	55.0
$\dot{V}_A = 15$ l/min	1.12	2.17	2.77	4.75	37.6	1.41	4.93	6.85	12.8	60.7
$\dot{V}_A = 50$ l/min	1.16	2.77	3.68	6.69	49.9	1.39	5.15	7.18	13.4	60.8
$\dot{V}_A = 100$ l/min	1.18	2.99	4.02	7.39	52.8	1.39	5.17	7.21	13.4	60.8
$V_b = 1000$ ml	1.33	3.66	4.96	9.22	57.6	1.55	5.35	7.38	13.6	60.8
$V_b = 2000$ ml	1.20	2.63	3.45	6.13	46.8	1.54	5.25	7.25	13.4	60.8
$V_b = 7000$ ml	1.07	1.55	1.82	2.73	18.9	1.36	3.87	5.28	9.8	58.6
$[\text{HbCO}]_0 = 2\%$	1.93	2.53	2.87	4.00	23.9	1.67	4.50	6.08	11.1	59.8
$[\text{HbCO}]_0 = 7\%$	6.14	6.73	7.06	8.19	27.8	3.00	5.76	7.29	12.2	59.9
$\text{DLCO} = 10$ ml/min-mm Hg	1.07	1.50	1.74	2.55	17.0	1.39	3.73	5.05	9.3	57.7
$\text{DLCO} = 50$ ml/min-mm Hg	1.09	1.74	2.11	3.34	25.0	1.41	4.37	6.01	11.3	60.1
$\% \text{O}_2 = 10$	1.19	1.82	2.18	3.38	24.8	2.25	6.35	8.66	16.1	79.8
$\% \text{O}_2 = 100$	0.50	0.90	1.13	1.88	14.5	0.24	0.85	1.19	2.3	19.0
$\text{Hb} = 10$ g/100 ml	1.12	1.98	2.47	4.11	32.0	1.48	4.79	6.62	12.3	60.6
$\text{Hb} = 20$ g/100 ml	1.06	1.52	1.78	2.65	18.1	1.35	3.80	5.17	9.6	58.3
$M = 150$	1.02	1.59	1.92	3.02	22.1	1.06	3.35	4.63	8.7	51.1
$M = 250$	1.10	1.71	2.05	3.20	23.4	1.53	4.57	6.26	11.7	62.8
$\dot{V}_{\text{CO}} = 0.000$ ml/min	1.05	1.65	1.99	3.13	23.1	1.24	4.09	5.67	10.8	59.8
$\dot{V}_{\text{CO}} = 0.014$ ml/min	1.12	1.72	2.06	3.19	23.2	1.57	4.41	5.99	11.0	59.8
$\dot{V}_{\text{CO}} = 0.070$ ml/min	1.39	1.99	2.33	3.46	23.4	2.87	5.67	7.22	12.2	60.2

Appendix C.

APPLICATION OF THE COBURN-FORSTER-KANE (CFK) EQUATION TO THE COMBAT SITUATION

The CFK equation has proven to be a reliable tool for accurately predicting COHb levels in the blood following exposure to CO under a variety of conditions. Good correlation with experimental values has been found for concentrations ranging from 50 to 1000 ppm, for constant, intermittent and steadily rising concentrations, and for activity levels varying from rest to moderate work.

The application of this equation to the problem of estimating COHb levels of soldiers exposed to CO during combat seems appropriate, since the levels and patterns of exposure tested generally fall within the scope of possible troop exposures. The selection of appropriate numbers for certain variables in the CFK equation depends on the assumptions made concerning probable conditions during combat missions. These are:

1. Exposure times (TE) to elevated levels of CO during combat will be brief (2 to 60 minutes) and accompanied by increased levels of physical activity.
2. During intervals between engagements (TI), CO levels in inspired air will approach zero and the level of physical activity will be light.
3. COHb levels will build up during combat and be released from the body in the intervals between engagements. This pattern may occur as often as six times per day, for as many as 14 consecutive days.

The calculation of $[HbCO]_t$ during such a pattern of intermittent exposures requires use of the "continuous" technique employed by Peterson and Stewart. The $[HbCO]_t$ calculated from the first combat exposure becomes the value of $[HbCO]_0$ used to initiate the calculation of $\frac{1}{2}[HbCO]_t$ for the end of the first rest period, etc. The process can be repeated for a series of combat exposures and intervals between engagements to calculate a final value of $[HbCO]_t$.

The assumption that activity levels are either light or moderately hard requires the use of two sets of variables. The parameters that vary with level of activity are alveolar ventilation rates ($\dot{V}_A$) and lung diffusivity (D_L). Table C-1 presents actual values for $\dot{V}_A$ and D_L associated with varying levels of activity from rest to heavy work. Based on the assumptions and these data, values of $\dot{V}_A$ and D_L selected as representative of the activity levels of armored crewmen during combat and during the interval between engagements were 24,000 and 10,000 ml/minute ($\dot{V}_A$) and 50 and 30 ml/minute-mm Hg (D_L), respectively. The physical demands of certain situations may suggest that other assumptions should be made; in fact, to obtain more precise values for $\dot{V}_A$ and D_L for use in the equation, actual measurements under simulated combat conditions might be appropriate.

TABLE C-1

Variation of Alveolar Ventilation Rates ($\dot{V}_A$) and Lung Diffusivities (D_L) with Level of Activity

Level of Activity	D_L (ml/min-mm Hg)	$\dot{V}_A$ (ml/min)	Reference
Rest	30	6000	NIOSH
Rest	31	5400	Coburn <i>et al.</i> ¹⁵
Rest	30	6000	Coburn <i>et al.</i> ¹⁵
Rest	-	10,000	Peterson and Stewart ³⁸
Light Work	40	18,000	NIOSH
Moderate Work	-	24,000	Peterson and Stewart ³⁸
Heavy Work	60	30,000	NIOSH

The values assigned to the remaining parameters of the CFK equation are listed below:

- $\dot{V}_{CO} = 0.42$ ml/min. This value was reported by Coburn *et al.*¹⁵ for normal humans and was discussed earlier.
- $V_b = 5500$ ml. The blood volume of men averages 74 ml/kg; a total blood volume of 5500 ml would correspond to that for a soldier weighing 165 pounds. An average value of 5440 ml was reported for 19 male students and medical school faculty by Peterson and Stewart.³⁸
- $M = 218$. The exact value of M does not seem especially critical to the calculated value of $[HbCO]$. For example, Peterson and Stewart³⁸ found that changing the value of M from 150 to 250 for a one-hour exposure to CO at 1000 ppm resulted in an increase of calculated $[HbCO]$ from 22.1 percent to only 23.4 percent.
- $[HbCO]_0 = 1.2$ percent or 0.0024 ml CO/ml blood. This value represents an average figure for nonsmokers. The 19 subjects used in the study by Peterson and Stewart³⁸ had an average COHb level prior to CO exposure of 1.18 percent.

The value of $[HbCO]_0$ for smokers is higher than that for non-smokers, but the degree of elevation depends on the quantity of cigarettes smoked, the depth of inspiration of the smoke, and the time of the day that the level is measured. An individual who smokes 29 cigarettes over 7 hours has been reported to have COHb levels in excess of 13 percent. The average level of COHb in smokers is about 5%. While it is recognized that the higher levels of $HbCO_0$ in smokers will certainly affect $[HbCO]_t$ resulting from any given exposure, the large variability of

$[\text{HbCO}]_0$ among individual smokers and the lack of any data on the smoking habits of armored crewman have discouraged any attempt to take the effects of smoking into account in the calculations. One should recognize, however, that since calculations of $[\text{HbCO}]_t$ are based on $[\text{HbCO}]_0$ values found in nonsmokers, calculated $[\text{HbCO}]_t$ values will be on the low side for smokers.

- $(\text{HbO}_2)_{\text{max}} = 0.2$ ml of O_2 /ml of blood. A normal male has about 15 g of Hb/100 ml of blood, and each gram of hemoglobin is capable of carrying 1.34 ml of oxygen. This results in the transport of 20 ml of O_2 /100 ml of blood. Peterson and Stewart³⁸ used a value of 0.2 for $[\text{HbO}_2]$ when solving the CFK equation. Since CO and O_2 compete for the same binding sites on hemoglobin, the oxyhemoglobin concentration is always less than $[\text{HbO}_2]_{\text{max}}$ by a value of $[\text{HbCO}]_t$. The value of $[\text{HbCO}]_t$ must be solved for in a trial and error method in which $[\text{HbO}_2] = [\text{HbO}_2]_{\text{max}} - [\text{HbCO}]_t$.
- $\text{PCO}_2 = 100$ mm Hg. Coburn et al.¹⁵ and Peterson and Stewart³⁸ used a value of 100 mm Hg for the average partial pressure of oxygen in the lung capillaries.

A simulated battlefield scenario involving actual firing of the infantry fighting vehicle, XM2, was conducted at Aberdeen Proving Grounds, Maryland in October 1979 by the US Army Test and Evaluation Command. The scenario, designed to provide what was considered to be a worst-case exposure to CO, consisted of two identical periods of firing of 3 hours each separated by a 3-hour break. Each period of firing consisted of four phases during which various combinations of weaponry were fired in a series of brief bursts. The hatches were closed during the 4 phases of firing and open during all but the second and sixth time intervals between phases of firing. A brief summary of the types of weapons, the approximate total number of rounds fired from each, the time interval between bursts, the approximate duration of each phase of firing and the time interval between each phase of firing are presented in Table C-2.

Instrumental measurements of CO concentrations were made at four positions within the vehicle. The instruments automatically recorded any CO concentrations above 50 ppm, the time that concentrations exceeded 50 ppm (TE), peak concentrations, and equivalent exposure times (EET), i.e., the area under the curves of concentration versus time. By dividing the EET's by the times that exposures exceeded 50 ppm, average concentrations over the exposure periods could be calculated (PICO) for each position. Various time intervals (TI) between each phase of the firing period were arbitrarily selected before the firing sequence began. Rather than repeating two identical periods of firing, the measurements of the first period were used as values for the second period to complete the battlefield scenario. The various measurements recorded during the battle scenario are presented in Table C-3.

TABLE C-2

Simulated Battlefield Scenario with Infantry
Fighting Vehicle, XM2

Phase	Rounds Fired					
	25-mm Auto- matic gun	7.62-mm Coaxial machine gun	Firing port weapon	Time between bursts (min)	Duration of firing phase (min)	Time between each firing phase (min)
1	77	-	-	0.5	5	45
2	98	80	-	1.0	13	5
3	196	120	60	1.0	14	60
4	245	520	240	0.5	20	180

TABLE C-3

Test Data from Battle Scenario in
Infantry Fighting Vehicle, XM2⁵¹

		Position			
Phase		Rear	Turret	Left Side Firing Port Weapon	Driver
1	CO max (ppm)	-	-	-	-
	EET (ppm·min)	8.35	8.16	6.16	8.35
	TE (min)	6.5	6.5	6.5	6.1
	PICO (ppm)	128	126	102	137
	TI (min)	45	45	45	45
2	CO max (ppm)	380	370	180	440
	EET (ppm·min)	14.27	13.84	7.63	15.06
	TE (min)	14.1	13.8	13.7	13.7
	PICO (ppm)	101	100	55.6	100
	TI (min)	5	5	5	5
3	CO max (ppm)	345	290	655	515
	EET (ppm·min)	25.13	23.89	24.01	18.65
	TE (min)	17.7	17.8	17.5	17.3
	PICO (ppm)	142	134	137	108
	TI (min)	60	60	60	60
4	CO max (ppm)	750	580	930	690
	EET (ppm·min)	81.63	77.01	72.51	65.71
	TE (min)	27.1	26.7	26.3	26.0
	PICO (ppm)	301	288	276	253
	TI (min)	180	180	180	180

To complete the battle scenario, repeat the above sequence a second time using different combinations of variables (CO max, EET, TE, PICO, TI).

It was assumed that soldiers at the four positions within the vehicle exercise at moderate levels during the periods of firing when CO concentrations exceeding 50 ppm are generated (TE) and at light levels during periods between firing when CO concentrations are less than 50 ppm (TI). Lacking actual CO concentrations during the times between firing, it was assumed that background CO levels were equivalent to the amount necessary to generate COHb levels of 1.2 percent, i.e., 6.3 ppm. This assumption may result in an underestimate of the COHb levels, but since exercise is expected to be light during these periods the error is assumed to be slight. Application of the CFK equation with the parameters appropriate for the various exercise states during the battlefield scenario resulted in a series of COHb levels calculated for nonsmoking soldiers at the four positions at the end of each exposure or nonexposure time segment. These values are presented in Table C-4.

The results of these calculations demonstrate that nonsmoking soldiers exposed during this battlefield scenario might likely experience blood COHb levels as high as 15.8 percent and that the greatest impact on blood COHb levels occurs during the combined firing of all of the weapon systems. Although there was a 3 hour period of "nonexposure" following the fourth phase of firing, this period of time was not sufficient for blood COHb levels to return to initial pre-exposure values. As a consequence, the blood COHb levels at the end of the last exposure segment during the second period of firing were slightly higher (approximately 2 percent COHb) than the values witnessed at the end of the fourth exposure segment during the first period of firing. Although blood COHb levels were not calculated for subjects for the time 24 hours after the initiation of the scenario, it may be safely assumed that the COHb values return to values that are comparable to those observed prior to the first battle scenario.

The simulated battle scenario conducted with the Infantry Fighting Vehicle, XM2, gives some insight to the potential for significant buildup of blood COHb levels during combat. Carbon monoxide levels have been measured during test firings with other armored vehicles, and in a few cases blood COHb levels have been determined. The Human Engineering Laboratory reports published in 1954 on "The Relation of Toxic Gases to Equipment Design" told of average CO concentrations of 1730 ppm being experienced over a 12-minute period by the loader in a M7 tank following the firing of 300 rounds in 8 minutes by the turret machine gun. Blood COHb levels of 18.1 percent were reported for the loader, and the gunner experienced levels of 23.3 percent. During test firing of a 105-mm howitzer with the M4A4 tank, CO concentrations of 1100 ppm were reported following the firing of 15 rounds; the loader experienced an increase of 14.6 percent COHb. Blood COHb levels of approximately 15 percent were found in the loader following an 8-minute exposure during the test firing of a turret machine gun in the M4A4E1 tank. More recent tests conducted with the Main Battle Tank, XM1, report CO concentrations under a variety of firing conditions. A review of the various average CO concentrations and times above 50 ppm finds that values less than 100 ppm to as high as

TABLE C-4

Calculated Blood COHb Levels for Nonsmoking Soldiers at Four Positions in the Infantry Fighting Vehicle at End of Each Exposure or Nonexposure Segment During Simulated Battlefield Scenario

	Position			
Time Segment	Rear	Turret	Left Side Firing Port Weapon	Driver
TE ₁	2.26	2.24	1.98	2.27
TI ₁	2.08	2.07	1.85	2.09
TE ₂	3.72	3.65	2.65	3.85
TI ₂	3.67	3.60	2.62	3.79
TE ₃	6.37	6.15	5.33	5.67
TI ₃	5.20	5.04	4.41	4.67
TE ₄	13.94	13.29	12.37	11.75
TI ₄	7.05	6.76	6.36	6.08
TE ₅	7.77	7.49	6.87	6.89
TI ₅	6.61	6.38	5.87	5.89
TE ₆	7.69	7.44	6.19	7.19
TI ₆	7.55	7.31	6.09	7.07
TE ₇	9.64	9.27	8.27	8.44
TI ₇	7.70	7.47	6.66	6.78
TE ₈	15.79	15.07	14.07	13.36
TI ₈	7.86	7.54	7.11	6.80

900 ppm span worst-case concentrations while the duration of exposures range from less than 1 minute to slightly more than 30 minutes with most values falling in the range of 10 to 25 minutes.

Since most of the values reported here are from isolated tests rather than a simulated battlefield scenario, estimations of likely COHb levels from a battle sequence are not so readily made. In an effort to calculate the likely blood COHb levels from repeated exposures to fixed concentrations of CO, a range of worst-case CO concentrations (PICO) and times of exposure (TE) were selected. Time intervals (TI) between exposures were selected so that exposures could occur as often as 1 to 6 times daily. The values selected for PICO, TE and TI are presented in Table C-5. As with the calculations performed on the simulated battle scenario with the XM2, moderate and light exercise were assumed for the periods of exposure and intervals between exposure, respectively. In addition, the background concentration of CO during the intervals between exposure was assumed as 6.3 ppm.

The calculation of possible blood COHb levels from repeated exposures to CO under the previously mentioned conditions generates 45 sets of data. Rather than present all of the data, those sets of conditions that produce blood COHb levels less than 5, 10, 15 and 20 percent after 6 exposures are shown. The time intervals (TI) between exposures are the minimum durations that allow the COHb level to fall below the selected value (see Table C-6).

A slightly different presentation of the data involves determination of the maximum number of exposures to each CO concentration that produces blood COHb levels below the selected values. For example, blood COHb levels of 15 and 20 percent allow an infinite number of 30-minute exposures to 100 ppm, as long as there is a 10-minute time interval (TI) between exposures. For 10 percent COHb and exposure to 100 ppm, a matrix can be used to describe the maximum number of exposures for each combination of TE and TI. Similar derivations are presented for all four COHb levels and for the three CO concentrations (see Tables C-7, C-8, C-9 and C-10).

A number of conclusions regarding possible troop exposure can be drawn from these tables of permissible number of exposures, but only one important aspect will be addressed. The military criteria for exposure to carbon monoxide (MIL-STD-800; TOP 2-2-614) states that for multiple exposures in a single mission, the summation of concentrations (in ppm) multiplied by exposure times (in minutes) shall not exceed 6000.

- 6000 ppm for 1 minute
- 1200 ppm for 5 minute
- 400 ppm for 15 minutes
- 200 ppm for 30 minutes
- 100 ppm for 60 minutes.

TABLE C-5

Selected Worst-Case Concentrations of CO (PICO) and
Times of Exposure (TE) and Arbitrary Time Intervals
Between Exposures (TI)

PICO (ppm)	TE (min)	TI (min)
1000	1	10
500	10	60
100	30	180
		360
		1440

TABLE C-6

CO Exposure Conditions Producing Calculated Blood
COHb Levels Below Selected Values After Six Exposures

			Percent Blood COHb			
PIC0 (ppm)	TE (min)	TI (min)	5	10	15	20
100	1	10	x	x	x	x
100	10	10		x	x	x
100	10	60	x	x	x	x
100	30	10			x	x
100	30	60		x	x	x
500	1	10	x	x	x	x
500	10	60				x
500	10	180			x	x
500	10	360		x	x	x
500	30	1440				x
1000	1	10		x	x	x
1000	10	360				x
1000	10	1440			x	x

x = Exposure conditions which would maintain COHb
levels below established threshold.

TABLE C-7

Permissible Numbers of Exposures to CO that
Maintain COHb Levels Below 5 Percent as a
Function of Duration of Exposures (TE) and
Intervals Between Exposures (TI)

[CO]

TE (min)	30	0	0	0	0	1000 ppm
	10	0	0	0	0	
	1	2	3	∞	∞	
		10	60	180	360	1440
		TI (min)				

TE (min)	30	0	0	0	0	500 ppm
	10	0	0	0	0	
	1	6	∞	∞	∞	
		10	60	180	360	1440
		TI (min)				

TE (min)	30	1	1	1	1	∞	100 ppm
	10	3	6	∞	∞	∞	
	1	∞	∞	∞	∞	∞	
		10	60	180	360	1440	
		TI (min)					

TABLE C-8

Possible Numbers of Exposures to CO that Maintain
COHb Levels Below 10 Percent as a Function of Duration
of Exposures (TE) and Intervals Between Exposures (TI)

[CO]

TE (min)	30	0	0	0	0	1000 ppm
	10	0	0	0	0	
	1	7	∞	∞	∞	
		10	60	180	360	1440
		TI (min)				

TE (min)	30	0	0	0	0	500 ppm
	10	1	1	1	∞	
	1	∞	∞	∞	∞	
		10	60	180	360	1440
		TI (min)				

TE (min)	30	3	∞	∞	∞	100 ppm
	10	∞	∞	∞	∞	
	1	∞	∞	∞	∞	
		10	60	180	360	1440
		TI (min)				

TABLE C-9

Permissible Number of Exposures to CO that
Maintain COHb Levels Below 15 Percent as a
Function of Duration of Exposures (TE) and
Interval Between Exposures (TI)

[CO]

TE (min)	30	0	0	0	0	1000 ppm
	10	1	1	1	∞	
	1	14	∞	∞	∞	
		10	60	180	360	1440
		TI (min)				

TE (min)	30	0	0	0	0	500 ppm
	10	2	2	∞	∞	
	1	∞	∞	∞	∞	
		10	60	180	360	1440
		TI (min)				

TE (min)	30	∞	∞	∞	∞	100 ppm
	10	∞	∞	∞	∞	
	1	∞	∞	∞	∞	
		10	60	180	360	1440
		TI (min)				

TABLE C-10

Permissible Number of Exposures to CO that
Maintain COHb Levels Below 20 Percent as a
Function of Duration of Exposures (TE) and
Interval Between Exposures (TI)

[CO]

TE (min)	30	0	0	0	0	1000 ppm
	10	1	1	2	5	
	1	∞	∞	∞	∞	
		10	60	180	360	1440
		TI (min)				

TE (min)	30	1	1	1	1	∞	500 ppm
	10	3	6	∞	∞	∞	
	1	∞	∞	∞	∞	∞	
		10	60	180	360	1440	
		TI (min)					

TE (min)	30	∞	∞	∞	∞	100 ppm	
	10	∞	∞	∞	∞		
	1	∞	∞	∞	∞		
		10	60	180	360	1440	
		TI (min)					

It is important to recognize the deficiencies of such a criterion. The most important shortcoming is that exercise and its influence on the amount of CO breathed and the degree of CO hypoxia is completely ignored. As shown earlier, ignoring this factor can lead to vastly different conclusions regarding likely blood COHb levels. Since health hazards and impairment of performance are related to blood COHb levels, the setting of standards for CO exposure requires the selection of upper limits for possible COHb concentrations. Such a process leads to vastly different conclusions regarding the total permissible exposure to CO, i.e., the number of ppm min may exceed 6000 ppm min without likely harm. If 5 percent COHb was selected as the highest level of COHb to which soldiers could be exposed, the table of permissible number of exposures indicates that for nonsmokers exposed to 100 ppm CO, a total of six 10-minute exposures (6000 ppm min) with a 60-minute interval between exposures could be experienced without exceeding 5 percent COHb. Seven 10-minute exposures (7000 ppm min) could be experienced if the interval between exposures was extended to 180 minutes. If 10 percent COHb was selected as the limiting concentration, a soldier could experience roughly four 10-minute exposures to 500 ppm (20,000 ppm min) without exceeding this limit as long as 6 hours intervened between exposures. If the CO concentration was only 100 ppm, a soldier could experience an unlimited number of 10-minute exposures without exceeding the limit as long as a 10 minute interval existed between exposures (for a 24 hour period, a total of 72,000 ppm min could be experienced). If the limiting COHb level was 20 percent, a soldier could experience as many as 108,000 ppm min in a day through repeated 30-min exposures to 100 ppm or 35,000 ppm min if the exposures were of 10-minute duration to 500 ppm CO. It seems obvious from these illustrations that the use of the arbitrary standard of 6000 ppm min for repeated exposures needs to be reviewed with respect to desired limiting COHb levels and with respect to expected activity levels during exposure.

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