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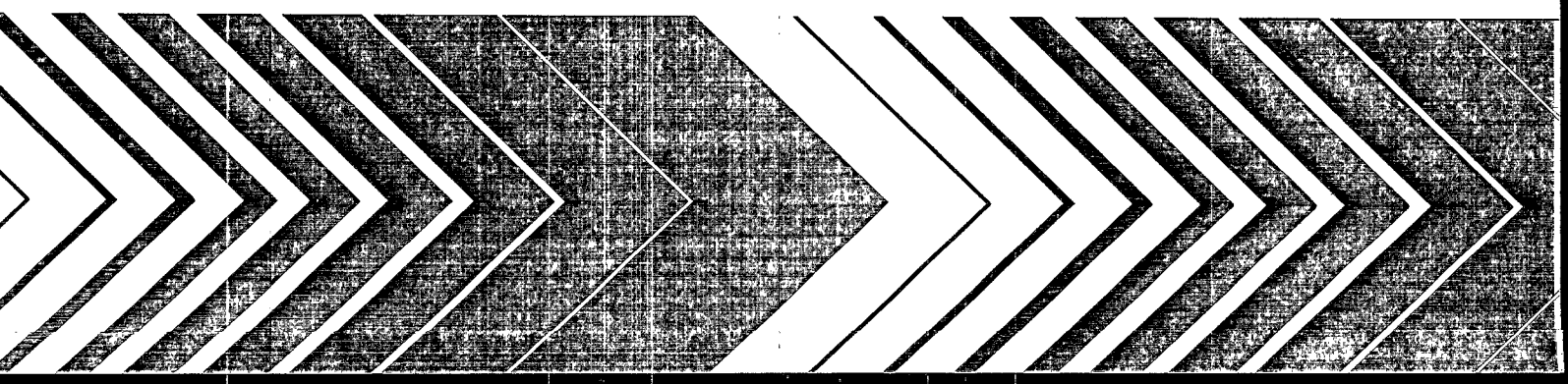
# Revised Evaluation of Health Effects Associated with Carbon Monoxide Exposure:

Final Report

## An Addendum to the 1979 EPA Air Quality Criteria Document for Carbon Monoxide



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## An Addendum to the 1979 EPA Air Quality Criteria Document for Carbon Monoxide

## Final Report

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, North Carolina 27711

NOTICE

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

## ABSTRACT

This addendum reevaluates the scientific data concerning health effects associated with exposure to carbon monoxide (CO) at ambient or near ambient levels by providing: (1) a concise summary of key health effects information pertaining to relatively low-level CO exposure; and (2) an overview of the limited volume of new evidence on the subject. This reevaluation is performed in light of the diminished value of studies by Dr. Wilbert Aronow on human health effects of exposure to low levels of CO. These studies figured in to the preparation of the U.S. Environmental Protection Agency's 1979 Air Quality Criteria Document for Carbon Monoxide and to the Agency's proposed retention of the 8-hour and revision of the 1-hour primary standards for CO (45 FR 55066; August 18, 1980).

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The substance of this document was independently peer-reviewed in public session by the Subcommittee on Air Quality Criteria for Carbon Monoxide, Clean Air Scientific Advisory Committee, and the Environmental Protection Agency Science Advisory Board. The Committee's findings and recommendations on the scientific basis for a revised national ambient air quality standard for carbon monoxide can be found in Appendix C.

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# INTRODUCTION

On April 30, 1971, the Environmental Protection Agency promulgated (36 FR 8186) national ambient air quality standards (NAAQS) for carbon monoxide (CO) under section 109 of the Clean Air Act. Identical primary and secondary standards were set at levels of 9 ppm, 8-hour average, and 35 ppm, 1-hour average, neither to be exceeded more than once per year. The scientific bases for these standards are contained in the Air Quality Criteria Document for Carbon Monoxide (U.S. Department of Health, Education, and Welfare, March, 1970, AP-62). The 1971 standards were primarily based on work by Beard and Wertheim (1967) suggesting that low-level CO exposures resulting in carboxy-hemoglobin (COHb) levels of 2 to 3 percent are associated with impairment of ability to discriminate time intervals, a central nervous system (CNS) effect. The revised Air Quality Criteria Document for Carbon Monoxide (U.S. EPA, 1979) indicated that this study is no longer considered to provide credible evidence for such CNS effects occurring at 2-3% COHB and, therefore, does not represent a sound scientific basis for the standard as discussed in an August 18, 1980 EPA proposal notice (45 FR 55066). However, medical evidence published since 1970 indicated at the time of proposal that aggravation of angina and other cardiovascular diseases may occur at COHb levels as low as 2.7 to 2.9 percent. Assessment of this and other medical evidence led EPA to propose, on August 18, 1980, retention of the 8-hour primary standard level of 9 ppm and revision of the 1-hour standard level from 35 ppm to 25 ppm (45 FR 55066).

The 1980 proposal was based in part on several health studies conducted by Dr. Wilbert Aronow (Aronow et al., 1972; Aronow and Isbell, 1973; Aronow et al., 1974; Aronow et al., 1974; Aronow and Cassidy, 1975; Aronow et al., 1977; Aronow, 1978). Based on evaluation of these studies in 1979 by EPA staff, their expert consultants, and the Agency's Science Advisory Board, it was concluded that these studies demonstrate human health effects of carbon monoxide that should be considered by the Agency in reconfirming existing or proposing new NAAQS for CO. The Aronow studies were an important element in identifying the blood carboxyhemoglobin (COHb) levels that represent a health concern for sensitive individuals. This "critical" range was defined as 2.7-3.0 percent. An additional study by Aronow (1981) later reported findings

suggesting that aggravation of angina symptoms, i.e., small but statistically significant decreases (~10%) in time to onset of exercise-induced angina, may occur in angina patients at COHb levels as low as 2.0 percent.

Since the CO standard was proposed by EPA in 1980, news media reports appearing in early 1983 indicated that the Food and Drug Administration (FDA) raised questions regarding the technical adequacy of several studies conducted by Dr. Aronow on experimental drugs, leading to FDA rejection of use of the drug study data. While there was no specific direct evidence that similar problems might exist for the CO studies conducted by Dr. Aronow, EPA judged that an independent assessment of these studies was advisable prior to a final NAAQS decision on CO. An expert committee was empaneled by EPA and met with Dr. Aronow to discuss his studies and to examine limited available data and records from his CO studies. In their report, the committee (chaired by Dr. Stephen M. Horvath, Director of the Institute of Environmental Stress, University of California-Santa Barbara) concluded that EPA should not rely on Dr. Aronow's data due to concerns regarding problems associated with the studies which substantially limit the validity and usefulness of those study results (Horvath et al., 1983). Dr. Aronow submitted a detailed reply to EPA that disputed, but did not effectively refute, the major points raised by the committee report (Aronow, 1983).

The main purpose of the present addendum is to reevaluate the scientific data base concerning health effects associated with exposure to CO at ambient or near ambient exposure levels, in light of the diminished value of the Aronow studies and taking into account any new findings that have become available beyond those reviewed in the revised Air Quality Criteria Document for CO (U.S. EPA, 1979). This addendum is, accordingly, organized to provide: (1) a concise summary of key health effects information discussed in the 1979 document as pertinent to characterization of health effects associated with relatively low level CO exposures; and (2) an overview of the limited new evidence bearing on the subject which has become available in the past several years.

## MECHANISMS OF ACTION

The 1979 Criteria Document discussed extensive evidence indicating that the binding of CO to hemoglobin, producing COHb and decreased oxygen carrying

capacity, results in decreased oxygen transport and uptake in most body tissues. The resulting hypoxic state (impairing normal biochemical-physiological cellular processes as a function of increasing external CO exposure and consequently increasing blood COHb concentrations), it was concluded, probably represents the main mechanism of action underlying the induction of toxic effects by low level CO exposures.

Several important relationships between COHb levels and other physiological parameters discussed in the 1979 Criteria Document have continued to be the subject of evaluation since then. Of much importance is the relationship between external CO exposure levels and consequent increases in blood COHb levels. Many factors, discussed in the 1979 Criteria Document, can affect the rate at which COHb increases above pre-existing endogenous levels of COHb in response to inhalation of exogenous CO. These include, for example, the pattern of external CO exposure, as in the case of acute short-term exposures to high CO concentrations versus longer term exposure to relatively low levels of CO. CO exposure-COHb concentration relationships have been modeled by Coburn (Coburn et al., 1965), taking into account several pertinent factors (see Chapter 9 of the 1979 EPA CO Criteria Document for discussion of the Coburn model equations). COHb levels predicted by the Coburn equations, as depicted in Figure 1, are widely accepted as the currently best available modeled estimates of COHb levels likely to result from varying CO concentrations, exposure durations and exercise levels. It should be noted that some questions have been raised regarding the specific mathematical approach employed by Coburn in solving his equations to predict COHb concentration as a function of time, considering appropriate physiological parameters (Venkatram and Louch, 1979; Ott and Mage, 1980; Marcus, 1980; Goldsmith, 1981; Joumard et al., 1981). However, the proposed alternative approaches yield very similar estimated COHb levels to those projected by Coburn's approach. In addition, actual blood COHb concentrations observed in response to particular external CO exposure situations have been consistent with those predicted by Coburn (Peterson and Stewart, 1975), although further experimental verification would be useful to demonstrate that the Coburn equation accurately predicts uptake and excretion of CO under widely varying conditions.

The exact mechanisms responsible for the hypoxia induced by CO are not known. The most widely accepted mechanism of CO toxicity has been attributed

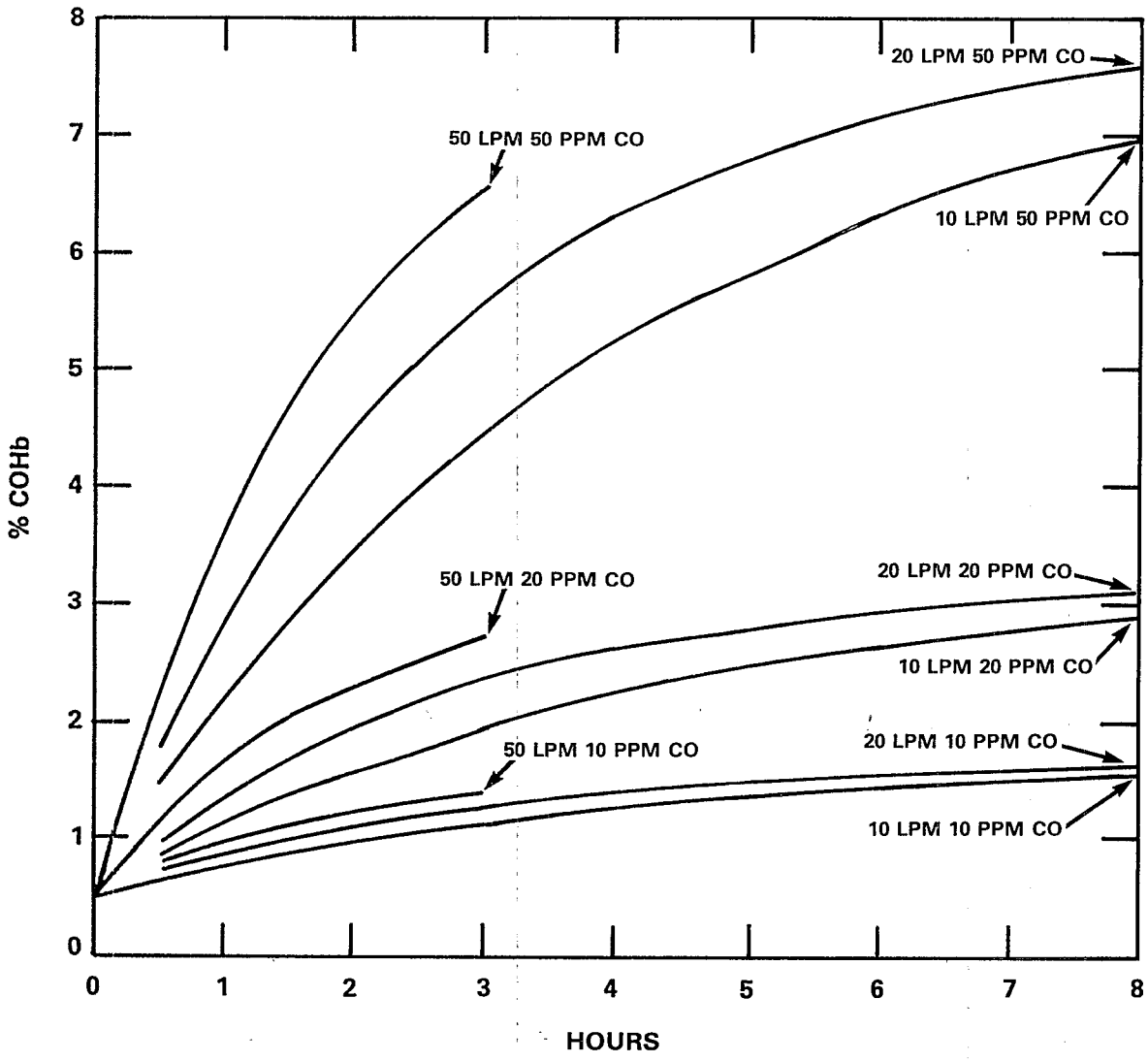


**Figure 1. Blood COHb concentrations predicted by Coburn equations to occur as a function of exposure duration and ambient carbon monoxide concentrations under resting (10 LPM), light exercise (20 LPM), or heavy exercise (50 LPM) conditions. LPM = liters per minute ventilation rate.**

**Source: U.S. EPA (1979).**

to the preferential binding of CO to hemoglobin which produces hypoxia by reducing $O_2$ transport by red blood cells to the tissues and impedes the dissociation of $O_2$ from hemoglobin in the capillaries. However, other mechanisms have been postulated for reducing oxygen transport. It is possible for CO to bind to intracellular hemoproteins such as myoglobin and cytochrome oxidase, which depends on the relationship of oxygen tension ($PO_2$) and CO tension (PCO) to CO binding constants (Coburn, 1979). The affinity of cytochrome oxidase for CO is similar to that for oxygen compared to myoglobin (30-50x) and hemoglobin (220x) which would make it less likely to be responsible for impairment of facilitated diffusion of oxygen to the mitochondria. However, if steep oxygen tension gradients exist between the extracellular and intracellular environment, then the $PO_2$ surrounding the mitochondrial terminal oxidase would be low enough to have increased binding with CO. This hypothesis was tested by Coburn (1979) in studies on isolated vascular smooth muscle. He concluded that significant CO binding to cytochrome oxidase was unlikely to be an in vivo mechanism of CO toxicity in that particular tissue. Myoglobin was also unlikely because it is absent or present in only small quantities. It is possible that CO binds to hemoproteins other than hemoglobin, myoglobin, or cytochrome oxidase. Cytochrome P-450, tryptophan deoxygenase, and tryptophan catalase all have high enough binding affinities for CO in specific tissues to be considered as possible candidates (Coburn, 1979).

The binding of CO to myoglobin in heart and skeletal muscle may be high enough to reduce intracellular oxygen transport in those tissues (Coburn, 1979; Agostoni et al., 1980). Using a computer simulation of a three-compartment model (arterial blood, venous capillary blood, and tissue myoglobin), Agostoni et al. (1980) predicted that conditions would be favorable for formation of carboxymyoglobin at COHb levels of 5-10%, particularly in areas where the $PO_2$ was physiologically low (e.g., in subendocardium) and when conditions of hypoxia, ischemia, or increased metabolic demands were present. This could provide theoretical support for experimental evidence of myocardial ischemia, such as electrocardiographic irregularities and decrements in work capacity discussed later. However, it is not known whether binding of CO to myoglobin could cause health effects (e.g., decreases in maximal oxygen consumption during exercise) occurring at COHb levels as low as 4-5%. Additional research is needed before this possibility can be more definitively evaluated.

Whatever the specific biochemical-molecular mechanisms involved in the induction of CO toxicity in specific tissues or organ systems, it is thought that COHb concentrations in the blood represent a meaningful and useful physiological marker by which to gauge the internal CO dose present at a given time due to the combined cumulative contributions of: (1) baseline endogenous production of CO by internal body processes; and (2) added CO body burden(s) resulting from inhalation exposure to exogenous sources of CO.

## HEALTH EFFECTS OF LOW-LEVEL CO EXPOSURES

In evaluating CO-induced health effects in humans, a crucial question that must be addressed concerns blood COHb levels demonstrated to be associated with effects on specific organ systems. The COHb levels of concern vary with the patterns and concentrations of external CO exposure pertinent to the objectives of any particular health risk evaluation. For example, as discussed in the 1979 CO Criteria Document (U.S. EPA, 1979), some occupations inherently involve exposure to high levels of CO, at times including frequent exposures to CO levels well in excess of 100-200 ppm under certain workplace conditions. On the other hand, it is relatively unusual for members of the general public to encounter such high CO exposure levels.

As examples of possible extreme CO exposure situations encountered by the general public, the 1979 Criteria Document noted that the following scenarios may result in exposure to unusually high ambient levels of CO: (1) On a large city freeway where traffic has come to a halt, the ambient CO level may exceed 44 ppm; (2) Inside a closed automobile where cigarettes are being smoked, CO concentrations may exceed 87 ppm; (3) In enclosed, unventilated garages, CO levels in excess of 100 ppm have been found; and (4) In a heavily traveled vehicular tunnel, a 1-hour maximum of 218 ppm CO was recorded. Under relatively mild exercise conditions likely to occur in such exposure situations for any sustained period of time, the Coburn equations predict COHb blood concentrations of <10 percent, assuming exposure durations of less than 8 hrs. More often, the general (non-smoking) population is exposed to substantially lower CO levels (<20-50 ppm) sustained over 1 to 8 hr. periods, potentially resulting in maximum COHb levels of 6-7 percent but much more often in COHb levels below 2-3 percent. The present evaluation is, therefore, focused mainly on health effects observed at blood COHb levels below 10 percent. The latter COHb

levels are most pertinent for present objectives, i.e., the development of criteria for ambient air quality standards.

Since the writing of the 1979 Criteria Document, several new studies have been published that contribute to the CO health effects data base. These new studies, including both human and animal toxicology data, are concisely reviewed below within a context of integrating the new information with evidence previously reviewed in the 1979 Criteria Document.

## 1. Cardiovascular Effects

The most extensive studies on the cardiovascular effects of CO have been those involving maximum aerobic capacity ($\dot{V}O_{2max}$). Previous data reviewed in the revised CO Criteria Document (U. S. EPA, 1979) demonstrated statistically significant decreases in $\dot{V}O_{2max}$ when COHb levels ranged from 7-20% under conditions of short-term maximal exercise (Ekblom and Huot, 1972; Pirnay et al., 1971; Vogel and Gleser, 1972). In another study (Horvath et al., 1975), the critical level at which COHb marginally influenced ($P < 0.10$) $\dot{V}O_{2max}$ was approximately 4.3%. In this study, work time to exhaustion was also reduced by 4.9 and 7% when COHb levels had attained 3.3 and 4.3%, respectively. Reductions in $\dot{V}O_{2max}$ following exhaustive treadmill exercise have since been confirmed at 5% COHb. In a double blind experiment (Stewart et al., 1978; Klein et al., 1980), 6 physically fit male fire fighters were randomly exposed to either CO or filtered air twice a week for 3 weeks and exercised to exhaustion. On exposure days, the subjects breathed a bolus of 20,000 ppm CO for 47 seconds followed by 30 ppm CO for 4 hours. This resulted in a sustained elevation of COHb at 5.0-5.5% saturation for 4 hours. Similar decrements in maximal exhaustion times were noted following the acute exposure and at the end of 4 hours. No adaptation to this hypoxic stress was observed after 4 hours of exposure or over the 3 weeks of testing. Significant decreases in total exercise time (3.8%) and $\dot{V}O_{2max}$ (3%) were also previously reported by Weiser et al. (1978) in a project designed to determine the effect of 5% COHb exposure on healthy young men residing in Denver at an altitude of 1610m. Blood COHb concentrations were quickly increased to 5.1% from a resting level of 1.0% by adding a bolus of 100% CO to a closed-circuit system from which the subjects rebreathed. The decrement in $\dot{V}O_{2max}$ was consistent with those reported above and the authors concluded that changes in

exercise performance following CO exposure at this altitude were similar to, but not greater than, changes occurring at sea level.

The effects of lower CO exposure levels have also been investigated under conditions of short-term maximum exercise duration (Drinkwater et al., 1974; Raven et al., 1974a,b). In this series of studies, a walking test with progressively increasing grade was used on subjects continuously breathing 50 ppm CO at either of two ambient temperatures, 25°C or 35°C, with a relative humidity of 20%. The two populations consisted of young (23+ years) and middle-aged (48+ years) subjects, both smokers and nonsmokers. During the duration of the test, COHB levels in nonsmokers increased from 0.6-0.9% to 2.3-2.7%, while levels in smokers rose from 2.6-3.2% to 4.1-4.5%. Control studies conducted on these subjects while they breathed filtered air indicated that COHb decreased in both smokers and nonsmokers in the absence of experimental CO exposures. These studies did not find any reduction in maximum aerobic capacity. In fact, the only statistically significant effect related to CO was a small decrease (<5%) in absolute exercise time consistently observed in the nonsmoking subjects but not in the smokers (Drinkwater et al., 1974; Raven et al., 1974a). These observations extend those found earlier by Ekblom and Huot (1972), who reported a large decrease (38%) in work time at 7% COHb.

The revised CO Criteria Document (U. S. EPA, 1979) also noted that oxygen uptake during short exposures and submaximal work was apparently not affected even at COHb concentrations of 15-20%. Recently, DeLucia et al. (1983) reported that COHb levels of 7.3% in nonsmokers and 9.3% in smokers did not induce any effects involving subjective symptoms, pulmonary function, exercise metabolism, or blood parameters in healthy subjects. In a controlled experimental study designed to test for potential synergism between $O_3$ and CO, 24 male and female volunteers were evaluated while performing moderate aerobic exercise at 50% of $\dot{V}O_{2max}$. After 100 ppm CO exposure for approximately 1 hr., COHb levels in nonsmokers rose from 1.0-2.1% to 6.0-9.6% and COHb levels in smokers rose from 1.9-5.1% to 6.6-11.8%. DeLucia et al. (1983) attributed the lack of CO effects as possibly being due to large cardiovascular reserves found in healthy subjects.

It should be noted that healthy young subjects were used in most of the above studies evaluating the effects of CO on work capacity. A recent study by Calverley et al. (1981) demonstrated a decrease in walking distance in 15

patients with severe chronic bronchitis and emphysema at a mean COHb concentration of 12.3%. They evaluated 11 men and 4 women with severe reversible airway obstruction [$FEV_{1.0}$ = 0.56 ± 0.2 (SD) liters; FVC = 1.54 ± 0.4 (SD) liters] who were hypoxic [$PaO_2$ = 5.2 ± 4.9 (SD) mm Hg]. All patients were medically stable at the time of the study and smokers were asked to stop smoking for 12 hours before each session. Each subject walked while breathing air and oxygen before and after exposure to 200 ppm CO in air, which raised their COHb concentrations from 1.1-5.4% to 9.6-14.9%. There was a significant reduction in walking distance when the patients breathed either air or oxygen after exposure to CO. A significant increase in walking distance when the patients breathed oxygen after exercise was abolished by CO exposure. There was no relationship to normal smoking habits of the patients. It is therefore quite possible that individuals with hypoxia due to bronchitis or emphysema are more susceptible to CO during submaximal work loads typical of everyday exercise.

Other cardiovascular effects of CO are thought to be of greater concern, i.e., those affecting individuals suffering from chronic angina. However, the precise COHb levels at which such cardiovascular effects occur in angina patients are much less well defined than COHb concentrations associated with various health effects discussed above. Angina pectoris is a symptom of pressure and pain in the chest produced during mild exercise or excitement because of insufficient oxygen supply to the heart muscle. Angina patients exposed to low levels of CO while resting have been reported to exhibit statistically significantly reduced time to onset of exercise-induced angina at mean COHb levels of 2.9 (range, 1.3-3.8 percent) and 4.5 percent (range, 2.8-5.4 percent) and to experience significantly increased duration of angina attacks during exercise at a mean COHb level of 4.5 percent (Anderson et al., 1973). Certain questions have been raised regarding the design and conduct of the study, the small number (N=10) of subjects studied, and the absence of credible independent confirmation of its findings. A reevaluation of the Anderson et al. (1973) study, addressing major points of concern, has been conducted recently (see Appendix A), and found that the study, in fact, provides reasonably good evidence for the hastening of angina occurring in angina patients at COHb levels of 2.9 to 4.5 percent. The Aronow et al. (1973) and Aronow (1981) studies were previously accepted as demonstrating decreased time to onset of angina in exercising patients at COHb

levels of 2.0-3.0 percent. However, these Aronow findings are now most appropriately interpreted as providing, at most, suggestive evidence for such effects occurring at COHb levels below 3 percent. More conclusive statements regarding this issue will not be possible until the results of independent studies attempting to replicate such findings become available.

Another cardiovascular effect of possible concern is that of increased blood flow that occurs as a compensatory response to CO exposures (Ayres et al., 1969; Ayres et al., 1970; 1979). This response might result in coronary damage or other vascular effects due to added stress on the cardiovascular system. However, inconclusive results have been obtained in community epidemiology studies examining the relationship between CO exposure, mortality from myocardial infarction (heart attack), sudden death due to arteriosclerotic heart disease, and cardiorespiratory complaints (Goldsmith and Landau, 1968; Kurt, et al., 1978; Kurt, et al., 1979). Hence, the possibility of such an association remains in question, and further research is also needed in order to clarify this issue.

The results of one controlled human exposure study reported by Davies and Smith (1980) are suggestive of possible effects on cardiac function at low to moderate CO exposure in healthy individuals. In a series of replicated experiments, six matched groups of young human subjects lived in a closed-environment exposure chamber for 18 days. They were exposed continuously to 0, 15, or 50 ppm of CO in air during the middle 8 days. Standard 12-lead electrocardiograms were recorded from each subject during the control, exposure, and recovery periods. Although statistical evaluation of the data was not reported, unequivocal P-wave changes were observed during the CO exposure period in 3 of 15 subjects at 15 ppm CO (2.4% COHb) and 6 of 15 at 50 ppm (7.1% COHb) compared to none of 14 at 0 ppm (0.5% COHb). The changes were evenly distributed among nonsmoking subjects and subjects who had stopped smoking 3 days before the start of CO exposure. In addition, one subject, later identified as having evidence of myocardial ischemia, showed marked S-T changes at 15 ppm. In a separate pilot study by these investigators with both smokers and nonsmokers at 75 ppm CO (10.9% COHb in nonsmokers; 14.9% COHb in smokers) significant EKG changes were demonstrated in 7 of 10 subjects. In most cases, the CO-induced changes remained 4 days after exposure ceased. The authors concluded that P-wave abnormalities demonstrated in this study were due to interference of normal atrial pacemaking or conducting tissue activity by CO. In addition, they speculate that CO has a specific toxic effect

on the myocardium rather than (or in addition to) a generalized decrease in $O_2$ transport to the tissue.

Most animal studies on the cardiovascular effects of CO have been conducted at exposure concentrations resulting in rather high (>15-20 percent) COHb levels. Only two studies are relevant for present discussion. Becker and Haak (1979) exposed 11 adult mongrel dogs to increasing concentrations of CO 1 hr. after coronary artery ligation. These sequential exposures produced step-wise increases in the COHb level from 4.9% to 17.0%. Myocardial ischemia, as indicated by the amount of S-T segment elevation in epicardial electrocardiograms, increased significantly at the lowest COHb level and increased further with increasing CO exposure. These changes occurred in the absence of altered heart rate, blood pressure, left atrial pressure, cardiac output, or blood flow to ischemic myocardium. Flow to non-ischemic myocardium increased with CO exposure at a rate approximately double the increase in COHb. They concluded that low level exposure to CO can significantly augment ischemia in acute myocardial infarction, apparently through a reduction in oxygen supplied to the ischemic tissue. They suggested, however, that the hypoxia induced by CO was more severe than could be accounted for by a reduction in tissue $O_2$ delivery alone.

Foster (1981) investigated the arrhythmogenic effects of CO during the initial minutes of acute myocardial ischemia in 8 mongrel dogs. Since each dog served as its own control, brief occlusions of the coronary artery were performed sequentially both before and after the administration of 100 ppm CO which raised COHb levels to 10.4%. Bipolar epicardial electrograms were recorded in each experiment from the ischemic and non-ischemic myocardial zones. An additional 6 dogs were used to confirm the reproducibility of ischemic conduction slowing during successive occlusions in the absence of CO. There was no significant increase in ischemic myocardial conduction slowing after CO. This lack of arrhythmogenic effect of CO was supported by the absence of increased incidence of spontaneous ventricular tachycardia during ischemia after CO administration. The author concludes that clinically encountered COHb levels may not have sufficient arrhythmogenic effect to be of significant health importance during the initial minutes of myocardial ischemia.

## 2. Neurobehavioral Effects

The 1979 CO Criteria Document noted that statistically significant effects on central nervous system (CNS) functions have been most clearly shown to occur at COHb levels of 5-17 percent. This is indicated by studies which demonstrated decrements in vigilance, visual perception, manual dexterity, learning ability, and performance of complex sensorimotor tasks such as driving (Bender et al., 1971; Schutte, 1973; O'Donnell et al., 1971; McFarland et al., 1944; McFarland, 1973; Putz et al., 1976; Salvatore, 1974; Wright et al., 1973; Rockwell and Weir, 1975; Rummo and Sarlanis, 1974). An evaluative review by Laties and Merigan (1979) substantially agreed with these conclusions. Also, as reviewed in the 1979 Criteria Document, some studies (Horvath et al., 1971; Fodor and Winneke, 1972; Groll-Knapp et al., 1972; Putz et al., 1976) have reported significant decrements in vigilance performance (defined as the ability to detect small changes in one's external environment occurring at unpredictable times) to be associated with COHb levels in the 3.0-7.6% range; and one study by Beard and Grandstaff (1975) reported that vigilance effects may occur at levels as low as 1.8 percent COHb. The lowest COHb levels at which vigilance decrements occur, however, are a matter of considerable dispute in view of numerous other studies not finding such effects at COHb levels below 5.0 percent (Haider et al., 1975; Winneke, 1974; Winneke et al., 1976; Christensen et al., 1977; Benignus and Otto, 1977).

Since the writing of the 1979 Criteria Document, several new studies have been published which contribute to the data base of CO-related neurobehavioral effects. In the following, each of the several neurobehavioral endpoints are re-evaluated by integrating new findings.

Vigilance--Since the 1979 document was written, several new pieces of research on CO and vigilance have appeared. In an evaluative review of the CO-vigilance literature, Benignus et al. (1983) concluded that all of the studies (except one) cited in the 1979 document had serious credibility flaws due to (a) non-replication of the work, (b) gross statistical abuse, (c) non-concentration-related effects or (d) combinations of the above.

The single study from the 1979 document which had no serious flaws was that of Putz et al. (1976), which demonstrated vigilance decrements at 5%

COHb. Since that time the same group of researchers have replicated these results on independent subjects (Putz et al., 1979) and have reported their earlier results in peer-reviewed literature (Putz, 1979). The fact that the experimental design and details of the tasks were not the same in the two experiments implies that the effects were robust and thus lends further credibility to these results. The credibility of these findings would be appreciably increased if an independent group of researchers also were to successfully replicate the study.

Three other studies on CO and vigilance have appeared since 1979 (Benignus et al., 1983, Davies et al., 1981, Roche et al., 1981), all of which used COHb levels of 5-7%. None of the studies found significant effects on vigilance. It is noteworthy that all of them used vigilance paradigms different from those of Putz et al (1976). Quite possibly the parameters and conditions under which vigilance was studied are so sensitive that unless the proper conditions exist, the effects of such COHb levels will not be detected.

It appears safe to conclude that, at least under some conditions, reliable but small decrements in vigilance occur at about 5% COHb. The fact that 5% and higher levels of COHb were not observed to produce vigilance decrements in many studies is probably a reflection of (a) low experimental test sensitivity in the those cases or (b) the small effects of CO at these levels coupled with what is probably a rather low-slope concentration-effects curve in the region of COHb less than 20%. It must be emphasized that these explanations for the many no-effect studies are conjectural.

Sensory and Time Discrimination--Benignus et al. (1983) concluded that no highly reliable evidence for time discrimination decrements exists. The elegant concentration-related decrements in dark adaption beginning at 5% COHb demonstrated by McFarland et al. (1944) remain to be replicated. The importance of replication should not be overlooked since the decrements were (a) dose-related and (b) showed a decrement at the lowest non-zero COHb level.

Davies et al. (1981) tested visual sensitivity in dark-adapted subjects who had been exposed continuously to 50 ppm CO for a total of 5 days (COHb of 7% by the end of each day). They reported no effects of CO. Luria and McKay (1979) reported that untrained observers showed no decrement in a night vision test, eye movement, or visual evoked potential at COHb levels of 9 percent. The

fact that McFarland et al. (1944) used bolus exposure methods, whereas the above investigators used continuous low level exposure, is perhaps significant. McFarland et al. (1944) also used highly trained observers, which had the effect of reducing variance and thus increasing the sensitivity of their study. Certainly the McFarland et al. (1944) study cannot be said to have been invalidated by newer data.

Some support for visual sensitivity decrements due to CO has been provided by a study measuring the electroretinogram in anesthetized cats (Ingenito and Durlacher, 1979). When cats were exposed to 1000 ppm CO the electroretinogram was decreased in amplitude by 30 minutes after the start of exposure, at which time the mean COHb was 7.5%. Further decreases were concentration-related.

Complex Sensorimotor Performance and Driving--The conclusion of the 1979 document, that driving-like tasks are impaired at COHb levels of 5% or greater, has since been substantially strengthened. Three articles have been published (Putz et al., 1976, 1979; Putz, 1979), using variations of the same task and experimental design but in two independent groups of subjects. In all cases, it was reported that 5% COHb produced decrements in compensatory tracking, a hand-eye-coordination task. In all cases, however, the decrements occurred only during high task difficulty. Other tasks such as reciprocal tapping and digit manipulation were not affected by COHb levels of up to 5% (Mihevic et al., 1982).

Sleep and Activity--Although there has been one new publication in this area (Groll-Knapp et al., 1982), the conclusions remain the same. Marginal increases in deep sleep and concomitant decreases in rapid-eye-movement sleep were reported at 8% COHb due to exposure to 100 ppm CO for 8 hrs. during sleep. As before, the changes did not reach statistical significance when appropriate corrections were made (Benignus and Muller, 1982).

Central Nervous System Electrical Activity--No significant changes have occurred in this area of research since 1979. Marginal, nonsignificant effects have been reported by Benignus et al. (1983) in the electroencephalogram alpha frequency band and by Groll-Knapp et al. (1982) on evoked potentials. Both groups of investigators produced COHb levels of 5-6 percent.

3. Effects of CO Exposure on Fibrinolysis

An area of growing interest, which was not extensively discussed in the 1979 Criteria Document, concerns possible effects of CO on fibrinolysis. The fibrinolytic system is an integral part of homeostatic mechanisms and it has been suggested that derangement of that system may contribute to the pathogenesis of thrombosis. The plasminogen activator may be released from the blood vessel wall by a variety of stimuli, including anoxia, electric shock, and either local or systemic administration of vasoactive substances such as epinephrine, acetylcholine, serotonin, or histamine. The finding that anoxia can release plasminogen activator has suggested to investigators that the presence of COHb with its associated anoxia could also be associated with increased plasminogen activator.

Resting fibrinolytic activity is often low and its measurement may yield conflicting results that do not readily permit intra-individual comparisons. The relationship of tissue activator to vascular activator suggests that they are components of two separate fibrinolytic mechanisms: (1) the vascular activator being part of a humoral system whose main role is maintenance of vascular patency and (2) the basic activator concerned with tissue repair and wound healing.

Animal Studies--Fibrinolytic activity was studied in 12 rabbits (6 control rabbits) continuously exposed for 8 weeks to an ambient concentration of 50 ppm CO (Kalmaz et al., 1977). The COHb levels reached 30.9% by the end of the exposure period. Significant increases in whole blood clotting time, serum fibrin/fibrinogen degradation products, and acceleration of whole blood clot lysis occurred. Euglobulin lysis time was significantly accelerated by the end of the first week of exposure. Although these fibrinolytic activity changes are of interest, their relationship to CO exposure is far from clear.

In another study, Kalmaz et al. (1978) continuously exposed rabbits to 50 ppm for 8 weeks or intermittently to 300 ppm for 4 weeks. Acceleration of the whole blood clot lysis and euglobulin lysis times was observed in all CO-exposed groups. Microscopic examination of large vessels showed endothelial damage -- a possible source for a plasminogen activator release. A more recent study by Kalmaz et al. (1980) involved exposing rabbits to ambient air, 50 ppm CO for

24 hours/day continuously for 8 weeks, and 300 ppm CO for 8 hours/day, 5 days/week for 4 weeks. They found a consistent change in circulating platelet quantity for all CO-exposed rabbits. However, their conclusion that prolonged exposure to low levels of CO may influence changes in circulating platelet counts and/or congenital platelet function disorders in man has not been confirmed.

In a recent in vitro study by Hartiala et al. (1982) a 5-minute exposure to 100% CO was found to have neither an effect on the decrease in prostacyclin ($PGI_2$) production nor a direct effect on ADP-induced aggregability of human platelet-rich plasma. This led the authors to conclude that CO is not responsible for the temporary increase in platelet aggregability after cigarette smoking.

Human Studies--Workers chronically exposed to high levels of carbon monoxide (approximately 100 ppm with occasional levels of 200-400 ppm) were studied by El-Attar and Sairo (1968). They found an accelerated clot lysis time suggestive of an enhancement of blood fibrinolytic activity. Levels of COHb present were only crudely determined and were not related to any specific individual. CO poisoning of 21 workers was suggested by the presence of subjective symptoms, headache, blurred vision, etc. Twenty-eight workers, presumably some of the first group of 21, were restudied after a one day exposure to ambient CO (levels not given). This group also exhibited accelerated lysis times but to a lesser degree. In 15 control subjects no fibrinolytic activity could be detected. This study, although suggestive, was too poorly controlled to be of real value. A similar suggestive study was made by Alexieva et al. (1975) on 100 workers in a coke-chemical plant. Some increase in fibrinogen was observed in these chronically exposed individuals. Panchenko et al. (1977) have also suggested that a relationship between blood coagulation and CO existed. The data presented are far from conclusive.

The possibility that exposure to other substances in addition to CO resulted in alterations of fibrinolytic activity was evaluated by Janzon and Nilsson (1975). Smokers and nonsmokers were studied by techniques superior to those used by the above investigators. Smokers and nonsmokers had the same fibrinolytic activity when smokers were studied after 12 hours abstention from smoking. Smoking 6 cigarettes during 3 hours was associated with an increased

fibrinolytic activity in blood. They believed that this increase was probably due to the combined effects of nicotine and carbon monoxide. Mansouri and Perry (1982) studied the alteration of platelet aggregation by cigarette smoke and carbon monoxide. Inhalation by healthy adults of CO sufficient to raise the COHb level to between 4.5% and 11% was found to be responsible for inhibition of platelet aggregation, which returned to normal after five hours. However, there was no consistent correlation reported between COHb levels and alterations in platelet aggregation.

Brinkhouse (1977) exposed 23 men (15 nonsmokers) for 4 hours to either 0, 50, or 100 ppm CO. COHb levels on the days of carbon monoxide exposure reached 2.17% (50 ppm) and 4.15% (100 ppm). Platelet count, prothrombin time, partial thromboplastin time, thrombin time, fibrin split products, factor VIII, and platelet aggregation were determined before and after the exposure. Coagulation parameters were not significantly affected by the CO exposures. A review by Haft (1979) discusses the role of platelets in the etiology and natural history of coronary artery disease. It is clear that smoking increases the activity of platelets and cigarette smokers have shortened platelet survival time. Endothelial injury may be facilitated by serum CO, by levels of circulating catecholamines, and other factors.

In conclusion, the effects on fibrinolytic activity of exposure to carbon monoxide are far from clear. The studies on acute exposure to CO do not specifically implicate this pollutant in the observed alterations in fibrinolytic activity, and the studies on chronic exposure are too poorly controlled to confirm any definite effects on the blood coagulation system.

4. Suggestive Evidence for Perinatal CO Effects

The Criteria Document (U.S. EPA, 1979) provides discussion of results from certain animal toxicology studies which point toward the possibility that CO exerts perinatal effects on the fetus or newborn. With long-term exposures of pregnant animals to CO, fetal COHb levels have been shown to be higher than maternal COHb levels, and fetal elimination of CO was slower than maternal CO elimination. The ability of CO to decrease the oxygen transport capacity of maternal and fetal hemoglobin may result in interference in fetal tissue oxygenation during important developmental stages. Whereas normal adults have

reserve capacity and compensatory responses which enable them to handle moderately high COHb levels without irreversible consequences, the fetus may under normal situations be operating close to critical levels in terms of tissue oxygen supply. Thus, even moderate CO exposures may have a deleterious effect on fetal development (Longo, 1977) but this, too, remains to be demonstrated along with pertinent dose-response relationships. In several animal studies in which pregnant females were exposed to CO, deleterious effects were generally reported in the offspring (e.g., reduced birthweight, increased newborn mortality, and lower behavioral activity levels) even when no effects on the mothers were detected. In human studies, similar effects have been reported in children of mothers who smoked cigarettes during pregnancy, suggesting that expectant mothers and their unborn children may also represent population groups at special risk for CO effects, but this remains to be more clearly defined along with any pertinent dose-response relationships.

Sudden infant death syndrome (SIDS) is characterized by the sudden, normally unexplained death of an infant. Research has suggested numerous possible etiological factors (e.g., disease, temperature, maternal smoking, and pollutant levels), but numerous questions remain regarding which are the most significant factors involved. Seasonal incidence of SIDS has been studied in several epidemiological studies (Peterson, 1966; Bergman et al., 1972; Bonser et al., 1978). A pattern which appears to be consistent across countries in the northern hemisphere is increasing incidence in October, peaking in December and January, remaining high until May, and then declining sharply in June and remaining low until October.

CO has been hypothesized to be associated with seasonal variations in SIDS incidence rates, based on certain epidemiologic data. Hoppenbrouwers et al. (1981) have reported that increased seasonal incidence of SIDS in Los Angeles County during winter may be at least partially explained by higher levels of CO, sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$) and hydrocarbons (HC). They suggest that higher ambient levels of these pollutants may be implicated in chronic hypoxia, which often precedes death from SIDS. Related to this hypothesis, they found that SIDS cases in Los Angeles were correlated to daily mean levels of the above pollutants and peaks in these pollutant levels preceded seasonal increases in SIDS by seven weeks. The authors further report that the lifespans of infants dying from SIDS were longer (1) if born in low rather than high pollution areas and (2) if born in months of low versus high pollution.

Finally, a direct proportionality was reported between exposure to pollution for infants from conception to two months of age and bimonthly rate of SIDS.

In an editorial letter assessing the results of the Hoppenbrouwers et al. study, Goldstein (1982) commented on the presence of indoor sources of CO, $NO_2$ and lead. She further pointed out that during colder months infants spend most of their time indoors where concentrations of these pollutants can far exceed ambient levels. Thus, she suggests that the relationship between SIDS and ambient pollution levels may be only coincidental and the evidence for it is at best suggestive and in need of further confirmation before any causal relationships are inferred.

Maternal smoking has been related to SIDS in several studies (Bergman and Wiesner, 1976; Lewak et al., 1979; Peterson, 1981). Because CO is only one of numerous pollutants found in cigarette smoke, however, it is difficult to infer a causal relationship between CO and SIDS. Other factors associated with SIDS include passive smoking, younger maternal age, short intervals between pregnancies, gestational age of less than 40 weeks, birth weight of less than 3000 g., lower socioeconomic status, and male sex. Thus, the number of potentially confounding factors makes finding an association between CO and SIDS extremely difficult.

## POPULATIONS AT RISK

The 1979 Criteria Document directed attention toward identification of sensitive population groups at special risk for CO-induced health effects. One key concept in defining special risk groups for CO effects is the idea that any preexisting or concomitant physiological or pathological condition which interferes or interacts with oxygen absorption into blood or its transport to and perfusion of body tissues can logically be expected to exacerbate CO-induced health effects associated with the hypoxic effects of CO. Thus, certain large segments of the general population can be reasonably hypothesized as likely to be at greater risk for experiencing CO-induced health effects than healthy, non-smoking adults.

These probable risk groups include: (1) fetuses and young infants; (2) the elderly, especially those with reduced cardiopulmonary functions attributable to a variety of factors associated with typical aging processes; (3) other, younger

individuals with overt, severe cardiac damage or acutely severe respiratory diseases, e.g., pneumonia; (4) individuals with chronic bronchitis or emphysema; (5) individuals with symptoms (e.g., angina) indicative of chronic cardiovascular disease; (6) individuals with hematological diseases, (e.g., anemia) that affect oxygen-carrying capacity or transport in the blood; and (7) persons with genetically unusual hemoglobin forms associated with decreased oxygen capacity. In addition to the above, one might reasonably expect that individuals under the influence of certain drugs, used for recreational or medicinal purposes, may be at greater risk for CO-induced effects due to interactive effects between CO and certain pharmacological agents. Lastly, under high altitude conditions (where reduced levels of atmospheric oxygen exist), increased vulnerability to CO health effects of both the above sensitive population groups and otherwise, non-sensitive healthy individuals might be expected.

As noted in the 1979 Criteria Document, relatively little concrete experimental or observational evidence currently exists by which most groups (or conditions) listed above have been clearly demonstrated to be associated with increased risk for CO-induced health effects. Nor have clear-cut quantitative lowest-observed-effect levels or dose-response relationships been delineated for the occurrence of CO effects among the above "at risk" groups or in conjunction with special interacting circumstances (i.e., drug usage or high altitude residence) that might exacerbate CO effects. Only very limited discussion, therefore, can be provided here regarding CO risk factors and sensitive groups likely at special risk for CO effects.

In regard to the first group, fetuses and young infants, certain evidence was alluded to earlier from animal toxicology studies indicating that higher levels of COHb and increased CO excretion time occur among fetuses in comparison to their mothers exposed to CO; and some deficits in postnatal growth and development were noted in the offspring of dams exposed to CO during pregnancy. Also, analogous perinatal effects were noted in human infants born to mothers who smoked during pregnancy, and associations between CO exposure and SIDS have been hypothesized. However, insufficient evidence exists at this time by which to estimate CO exposure levels at which any CO effects on human fetuses or newborn infants may occur or whether the latter types of effects seen in smoking mothers are due specifically to CO versus other components of tobacco smoke either singly or in combination.

Little specific evidence directly demonstrates the increased vulnerability of the elderly for CO health effects in precise quantitative terms. Given the increased vulnerability of the aged to many different kinds of stress, including thermal stress (hot or cold) which taxes decreased reserve capacities to maintain adequate cardiovascular delivery of oxygen to body tissues, it must be expected that CO exposure would render the elderly more vulnerable to the effects of other types of cardiovascular stresses. Also, conversely, it is reasonable to hypothesize that interactive effects involving other stress factors might lead to exacerbation of CO-induced health effects or their occurrence at lower external CO exposure levels than in younger, healthy adults. Similarly, younger individuals with overt, severe cardiac damage or insufficiency or severe acute respiratory diseases, e.g., pneumonia, can be expected to be more vulnerable to CO (i.e., either CO exacerbation of other disease effects or, conversely, increased susceptibility to CO health effects) due to reduced reserve capacities to cope with stress generally or increased sensitivity of already compromised organs or tissues, e.g., heart muscle, to the hypoxia induced by CO.

Turning to individuals with chronic bronchitis and emphysema, again, reduced reserve capacities for dealing with cardiovascular stresses and already reduced oxygenation of blood should exacerbate or hasten the onset of health effects associated with CO-induced hypoxia. Analogously, angina patients or others with obstructed coronary arteries but not manifesting overt symptoms such as angina, should be at greater risk for CO health effects. Both the Anderson et al. (1973) and several Aronow publications on angina patients reported findings previously accepted as demonstrating the increased vulnerability of angina patients to CO in terms of hastening of the onset of exercise-induced angina. These papers, furthermore, appeared to confidently establish 2-3% blood COHb as the range of COHb values associated with the onset of statistically significant effects indicative of CO exacerbation of angina and, probably, associated hypoxic effects on cardiac muscle. It is now clear that the Anderson findings (as of yet not independently confirmed) can be appropriately interpreted as providing reasonably good evidence for exacerbation of angina symptoms occurring at approximately 2.9 to 4.5 percent COHb; and the possibility of such effects occurring at lower COHb levels cannot be ruled out at this time.

In regard to individuals with anemia being at special risk for CO health effects, the 1979 Criteria Document noted that CO poisoning is similar to anemia, wherein the oxygen capacity of the blood is decreased because the affinity of hemoglobin (Hb) for binding oxygen is reduced. The $O_2$ dissociation curve for anemics is similar to that for normals except that it is shifted to the right. However, when curves from individuals with 50% reductions in Hb content are compared with dissociation curves for blood with 50% COHb content, there are striking differences. Consequently, care must be taken to avoid overly simplistic extrapolations regarding the likely impact of particular CO exposures on anemia patients due to additional (CO-induced) reductions of $O_2$ carrying capacity beyond the reductions already evident in their blood. The specific CO exposure levels and associated blood COHb concentrations at which anemia patients may be at increased risk for specific CO health effects remain to be clearly delineated, but little doubt exists regarding the likelihood that the effective CO exposure (and COHb) levels are distinctly lower than for healthy, non-anemic individuals.

Another logically-hypothesized "at risk" group for CO effects are individuals with unusual hemoglobin types that result in chronic elevations of COHb blood levels even in the absence of external CO exposure. Normal adult hemoglobin has a relative affinity or equilibrium constant (M) for CO of about 200 for most animal species, but has been reported to be as high as 240 to 250 in humans (Roughton, 1970). There are approximately 350 human hemoglobin variants, including those found in the fetus, sickle cell anemics, and other individuals with hemoglobinopathy (hemoglobin disorders). Approximately one fourth of the hemoglobin variants now known are considered unstable, i.e., they denature and precipitate when red blood cells or hemolyzates are exposed to heat, red oxdyes, or isopropanol (Bunn et al., 1977). One of these variants, hemoglobin Zurich (HbZ) has been found to have an affinity for CO which is approximately 65 times that of normal hemoglobin (Zinkham et al., 1980; Giacometti et al., 1980; Zinkham et al., 1983). This results in chronic elevation of endogenous COHb levels ranging from 3.9 to 6.7% in nonsmoking HbZ individuals.

As for possible drug-induced enhancement of CO effects, whereas there exists little specific data directly supporting the idea, it is logical to suspect that individuals who use certain drugs would be at increased risk for experiencing health effects associated with CO exposure. For example, drugs

with primary or secondary CNS depressant effects should be expected to exacerbate neurobehavioral effects of CO; and drugs which have primary or secondary cardiac stimulant effects might worsen CO-related cardiac effects. Any vasoconstrictive drugs would be expected to reduce $O_2$ delivery to various organs, thus also exacerbating CO effects on exercise, cardiac or neurobehavioral function. Further speculations about drug-CO interactions are possible, but it should be emphasized that these are predictions based on theoretical grounds that rely heavily on our current understanding of hypoxia as the likely main mechanism underlying the induction of CO-induced health effects. Unfortunately, few data currently exist by which to judge the likely validity of such speculations.

Hypothesized enhancement or exacerbation of CO health effects under high altitude conditions, similarly, rests heavily on hypoxia as the key mechanism of CO toxicity. The interactive effects of high altitude hypoxia and CO exposure, however, appear to be more complex than might be simplistically expected (Collier and Goldsmith, 1983). For example, the 1979 Criteria Document notes that adaptation to high altitudes occurs and alludes to the fact that, analogously, adaptation to CO may alter the position of the $O_2$ dissociation curve as a function of extensive prior CO exposure. Thus, individuals living in high altitude situations with frequently elevated ambient air CO levels may adapt to both the high altitude and CO-induced hypoxia, whereas other individuals newly entering high altitude and elevated ambient CO conditions might experience CO effects at concentrations below those effective at lower altitudes.

## SUMMARY AND CONCLUSIONS

As was stated at the outset, the main purpose of the present addendum is to reevaluate the scientific data base concerning health effects associated with exposure to CO at ambient or near-ambient exposure levels. The reevaluation includes both (1) summarization of information contained in the revised EPA Air Quality Criteria Document for CO (U.S. EPA, 1979) and (2) new information and studies that have become available beyond that reviewed in the 1979 document. The most important points of information reviewed and key conclusions derived from this evaluation of the CO health effects data base are summarized below.

Mechanisms of Action--The binding of CO to hemoglobin, producing COHb and decreasing the oxygen-carrying capacity of blood, appears to be the main mechanism of action underlying the induction of toxic effects of low-level CO exposures. The precise mechanisms by which toxic effects are induced via COHb formation are not yet fully understood, but likely include the induction of a hypoxic state in many tissues of diverse organ systems. Alternative mechanisms of CO-induced toxicity (besides COHb) have been hypothesized, but none have yet been demonstrated to operate at relatively low (near-ambient) CO exposure levels. Blood COHb levels, then, are currently accepted as representing a useful physiological marker by which to estimate internal CO burdens due to the combined contribution of (1) endogenously derived CO and (2) exogenously derived CO resulting from exposure to external sources of CO. COHb levels likely to result from particular patterns (concentrations, durations, etc.) of external CO exposure can be reasonably well estimated from equations developed by Coburn.

CO Exposure Levels--Evaluation of human CO exposure situations indicates that occupational exposures in some workplace situations can regularly exceed 100 ppm CO, often leading to COHb levels of 10 percent or more. In contrast, such high exposure levels are much less commonly encountered by the non-occupationally exposed general public. More frequently, exposures to less than 25-50 ppm CO for any extended period of time occur among the general population and, at the low exercise levels usually engaged in under such circumstances, resulting COHb levels most typically remain below 2-3 percent among non-smokers. Those levels can be compared to the physiologic norm for non-smokers, which is estimated to be in the range of 0.3 to 0.7 percent COHb. Baseline COHb concentrations in smokers, however, often greatly exceed 3 percent, reflecting absorption of CO from inhaled smoke.

Health Effects of Low Level CO Exposures--Four types of health effects reported or hypothesized to be associated with CO exposures (especially those producing COHb levels below 10 percent) were evaluated: (1) cardiovascular effects; (2) neurobehavioral effects; (3) fibrinolysis effects; and (4) perinatal effects. In regard to cardiovascular effects, decreased oxygen uptake capacity and resultant decreased work capacity under maximal exercise conditions have been clearly shown to occur in healthy young adults starting at 5.0 percent COHb;

and several studies observed small decreases in work capacity at COHb levels as low as 2.3 to 4.3%. These cardiovascular effects may have health implications for the general population in terms of potential curtailment of certain physically demanding occupational or recreational activities under circumstances of sufficiently high CO exposure. However, of greater concern at more typical ambient CO exposure levels are certain cardiovascular effects (i.e., aggravation of angina symptoms during exercise) likely to occur in a smaller, but sizeable, segment of the general population. This group, chronic angina patients, is presently viewed as the most sensitive risk group for CO exposure effects, based on evidence for aggravation of angina occurring in patients at COHb levels of 2.9 to 4.5 percent COHb. Such aggravation of angina is thought to represent an adverse health effect for several reasons articulated in the 1980 proposal preamble (45 FR 55066), and the Clean Air Scientific Advisory Committee (CASAC) concurred with EPA's judgment on this matter (see Appendix B). Dose-response relationships for cardiovascular effects in coronary artery disease patients remain to be more conclusively defined, and the possibility cannot be ruled out at this time that such effects may occur at levels below 2.9 percent COHb (as hinted at by the results of the now-questioned Aronow studies).

No reliable evidence demonstrating decrements in neurobehavioral function in healthy young adults has been reported at COHb levels below 5%. Much of the research at 5% COHb did not show any effect even when behaviors similar to those affected in other studies were involved. However, if any CO effects on neurobehavioral functions in fact occur below 5% COHb, then none of the significant-effects studies would have found such decrements, because none of them used COHb levels below 5%. Other workers who failed to find CO decrements at 5% or higher COHb levels may have employed tests not sufficiently sensitive to reliably detect small effects of CO. From the empirical evidence, then, it can be said that the COHb levels in the 5% range do produce decrements in neurobehavioral function. However, it cannot be said confidently that COHb levels lower than 5% would be without effect. One important point made in the 1979 document should be reiterated here. Only young, healthy adults have been studied using demonstrably sensitive tests and COHb levels of 5% or greater. The question of groups at special risk for CNS effects, therefore, has not been explored. Of special note are those individuals who are taking drugs which have primary or secondary depressant effects which would be expected to exacerbate CO-related neurobehavioral decrements. Other groups at possibly increased risk

for CO-induced neurobehavioral effects are the aged and ill but these groups, also, have not been evaluated for such risk.

In contrast to the data available which demonstrates associations between cardiovascular and neurobehavioral effects and relatively low-level CO exposures, much less clear evidence exists that other types of health effects are associated with low-level CO exposures. For example, only relatively weak evidence points towards possible CO effects on fibrinolytic activity and, then, generally only at rather high CO exposure levels. Similarly, whereas certain data also suggest that perinatal effects (e.g. reduced birth weight, slowed postnatal development, Sudden Infant Death Syndrome) are associated with CO exposure, insufficient evidence presently exists by which to either confirm such associations qualitatively or to establish any pertinent exposure-effect relationships.

Population Groups at Risk for Ambient CO Exposure Effects--Angina patients or others with obstructed coronary arteries, but not yet manifesting overt symptomatology of coronary artery disease, appear to be best established as a sensitive group within the general population that is at increased risk for experiencing health effects (i.e. exacerbation of cardiovascular symptoms) of concern at ambient or near-ambient CO exposure levels. Several other probable risk groups were identified, i.e.: (1) fetuses and young infants; (2) the elderly (especially those with compromised cardiopulmonary functions); (3) younger individuals with severe cardiac or acutely severe respiratory diseases; (4) individuals with chronic bronchitis or emphysema; (5) individuals with hematological diseases (e.g. anemia) that affect oxygen carrying capacity or transport in the blood; (6) individuals with genetically unusual forms of hemoglobin associated with reduced oxygen carrying capacity; and (7) individuals using medicinal or recreational drugs having CNS depressant properties. However, little empirical evidence currently is available by which to specify particular COHb levels at which such individuals are likely to experience specific health effects associated with ambient or near-ambient CO exposures. Nor does unambiguous evidence yet exist which clearly establishes that healthy non-sensitive individuals or those in the above probable risk categories are affected at lower CO exposure levels under high altitude conditions than CO exposure concentrations effective at lower altitudes.

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# APPENDIX A

## EPA HEALTH EFFECTS RESEARCH LABORATORY
## REEVALUATION OF ANDERSON ET AL. (1973) STUDY

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
HEALTH EFFECTS RESEARCH LABORATORY
RESEARCH TRIANGLE PARK
NORTH CAROLINA 27711

DATE: February 1, 1984

SUBJECT: Evaluation of Anderson et al. (1973) Study of Carbon Monoxide (CO) Effects on Angina Patients.

FROM: John J. O'Neil, Ph.D., Chief
Clinical Research Branch, ITD/HERL

TO: Lester D. Grant, Ph.D.
Director, ECAO (MD-52)

THRU: F. Gordon Hueter, Ph.D., Director
Health Effects Research Laboratory, RTP (MD-58)

This memo replaces one dated August 19, 1983. Changes have been made to clarify some points. The discussion of carboxyhemoglobin (COHb) analysis (section 1a) and Table 1 have been notably expanded. An analysis of possible reasons for the differences between the measured values of COHb reported by Anderson et al. and estimates of COHb calculated using the Coburn-Forster Kane Equation are also offered. The conclusions of the memo remain the same.

Thank you for the opportunity to comment on the paper by Einar Anderson and his co-workers which is entitled "Effect of Low-Level Carbon Monoxide Exposure on Onset and Duration of Angina Pectoris." I have re-read it, have discussed it with several colleagues, especially Dr. Vernon Benignus, and would offer the following observations by way of review.

This is a good paper. The work appears to be carefully done, the data seem reasonable, and the paper is well written. Critical review reveals some flaws in the design and conduct of the research, but this is typical of most scientific work and, therefore, significance of these comments may be interpreted differently by different readers.

DESIGN

1) ST segment depression reported in this paper is not useful and does not constitute any physiological support to the observations regarding the onset and duration of angina. The authors recognize this shortcoming. The important data in the paper are the measurement of time to onset of pain and the measurement of the duration of pain.

2) The paper would have been considerably strengthened by more careful selection of the subject population. For example, 5 subjects were smokers and 5 were non-smokers and one subject was taking digitalis. In my opinion, the study would have been strengthened considerably had the subject population been more homogeneous.

3) The number of subjects (n) is very small. Only ten subjects were studied and of these there are three for whom there are missing data points. I have been told anticdotally that this study was intended as a pilot study. It is unfortunate that it was not possible to design and complete the proper follow-up study. Given the situation, this is valuable data to have published and should be used to develop our understanding of the response of angina patients to carbon monoxide (CO).

METHODS AND RESULTS

1) It is disconcerting that the measured COHb levels appear to be lower than we would predict on the basis of our knowledge of CO-COHb kinetics. Why is this measured value lower than we would expect?

a) Measurement of COHb. The measurements were done in triplicate using the Buchwald analysis. As best as I can determine there is no evidence which causes me to doubt this analysis. However, this technique is less precise than other methods that are used today. That is, more scatter occurs in the data for repeated measurements at a given concentration. At low COHb concentrations this scatter might have a disproportionately large effect which, in turn, might lead to an over-estimation of the "zero" COHb sample analysis. If this occurred, estimations of COHb concentration calculated using the Coburn-Forster-Kane equation would be over-estimates because this initial measurement is also used as the initial concentration in the Coburn-Forster-Kane equation.

b) It is also possible that the exposure mask used in this study was loose fitting and leaked. This would reduce the exposure level and the final COHb levels.

c) Though not reported in the paper, the subjects were apparently allowed to rest ad libitum during the study. This amounted to approximately 10-15 minutes out of the hour. This "rest" period would have reduced the exposure time and the final COHb levels.

Using a minute ventilation of 5 l/min, a blood volume of 5500 ml and a hemoglobin concentration of 15 g/100ml, Dr. Benignus calculated a predicted COHb with the Coburn-Forster-Kane Equation. These data are presented in Table 1. He concludes that there is an apparent and unexplained inconsistency between the predicted value for COHb and that actually measured.

Table 1. Concentrations of Carboxyhemoglobin Reported by Anderson et al. and Estimated Using the Coburn-Forster-Kane Equation

| Exposure Concentration (ppm) | 50 | 100 |
|---|---|---|
| Initial measurement (% COHb) | 1.4 | 1.6 |
| Final measurement (% COHb) | 2.9 | 4.5 |
| Coburn-Forster-Kane Calculated Value (% COHb) | 3.3 | 5.8 |
| Difference (% COHb) | +0.4 | +1.3 |

d) The Coburn-Forster-Kane equation was derived to deal with endogenously produced CO. Its application to situations involving exogenous CO, though widely done, may be inappropriate.

e) There exist, therefore, at least three possible explanations for the differences in the reported COHb measurements and the estimates derived using the Coburn-Forster-Kane equation.

1) The final measurement of COHb in the study by Anderson et al. underestimates the true COHb concentration.

2) The initial measurement of COHb in the study by Anderson et al. overestimates the true COHb concentration and when this number is used in the Coburn-Forster-Kane equation, it results in an overestimation of the final COHb concentration.

3) The Coburn-Forster-Kane equation over-estimates COHb concentrations in the range of interest for this study.

2) There is considerable variability in the data reported. The following table gives the mean and range of the time to onset of pain for each day of the study.

Table 2. Time to Onset of Pain
Mean (Range)

| | | |
|---|---|---|
| Mon (Air) | 294 | (215-480) |
| Air (Control) | 325 | (220-435) |
| 50 ppm | 264.5 | (65-390) |
| 100 ppm | 263.5 | (85-425) |
| Friday (Air) | 300 | (185-485) |

The exposures on Monday and Friday were included to demonstrate the comparison of two air exposures separatead by the study itself. The air control and the exposures to 50 or 100 ppm CO were randomized on Tuesday Wednesday, and Thursday. The data for Monday and Friday are both considerably closer to the data for 50 and 100 ppm CO exposure than to that for the air control. This is, I believe, associated with the small number of subjects used in the study. Dr. Benignus and his colleagues analyzed the data for the different air days and did not show any significant differences between these days.

STATISTICAL ANALYSIS

Dr. Benignus has developed an analysis of the paper by Anderson et al. and I have excerpted part of his critique here.

Critique of the Study by Anderson et al. (1973)

Vernon A. Benignus

The statistical tests used in the study were anticonservative (Benignus and Muller, 1982) and thus would have tended toward showing a significant effect even if none were present in the population.

The data of Anderson et al. were reanalized using one multivariate analyses of variance for each of the two measures (time to onset of angina and duration of angina). Multivariate tests were used because the data for 0, 50 and 100 ppm exposure were collected from the same subjects. Since two separate significance tests were to be run (one for time to onset and one for duration) Bonferroni corrections were used to keep experimentwise $\alpha = .05$. Each test would then be evaluated at $\alpha/2 = .025$.

Table A. Overall Test Results

| Variable | F | df | p< |
|---|---|---|---|
| Time to Onset | 7.72 | 2,8 | .014 |
| Duration | 3.10 | 2,7 | .11 |

Table A shows the results of the overall tests. This table agrees with Anderson et al. that time to onset of angina would have been significantly affected by CO exposure but does not agree with Anderson et al. that duration of Angina is affected by CO exposure. Stepdown tests of the time to onset data revealed that the 50 ppm exposure showed a CO

effect, $p<.017$ and the 100 ppm exposure showed a CO effect $p<.002$.

Table B. Means of Time to Onset Data

| CO Level | Mean time to onset of Angina |
|---|---|
| 0 ppm | 310 |
| 50 ppm | 265 |
| 100 ppm | 264 |

Table B shows the mean times to onset for the 0, 50, and 100 ppm exposure days. While both the 50 and 100 ppm exposures produced shorter times to onset, they did not differ among themselves. (The fact that the p value for the 100 ppm day was lower than for the 50 ppm day was due to the fact that the data on the 100 ppm day were more closely correlated with the 0 ppm values. Thus Table B shows a puzzling non-dose-related finding.)

Inspection of Table 1 in Anderson et al. (1973), reveals that all COHb values were related to the exposure level so that the non-dose-related findings in time to onset remain unexplained. To be sure, the variability was high on all days and with the small number of subjects, such non dose related findings can occur even if the effects are dose related in the population. This is especially true since the COHb values were both close to the lower limits for CO effects and the general dose-effects curve can be plausibly argued to have a rather low slope.

The tests of signficance employed in this critique are quite conservative. Thus, the fact that significant results would have been reported even if appropriate and conservative tests had been done, lends credibility to the study. On the other hand, the non dose related findings are mildly disturbing. Considering (1) the small number of subjects, (2) the high variability of the data, (3) the fact that both doses were near the no-effects level and (4) the low p values on the significance tests, the data are strongly suggestive of an effect but are sorely in need of replication and extension. More subjects should be run and a wider dose range should be studied to be able adequately to quantify a dose-effects curve.

## Conclusions

Several aspects of the study were of above average quality. The study was conducted in a double-blind fashion; very commendable, especially by comparison to the extant literature. Only a small number of variables

were studied, thus minimizing the chances of finding some spurious variable which accidentally covaried with CO exposure; another positive quality.

When compared to an ideal study the study by Anderson et al. has several flaws in its design and execution and the results have inconsistencies. However, when compared to the extant literature, the design and execution of this study is commendable. None of the inconsistencies are of a major nature and several plausible explanations exist for them. The results of this study suggest that angina is exacerbated by small increases in COHb.

This study is sorely in need of replication and extension. More subjects should be run and a wider dose range should be studied to be able to adequately quantify the dose response relationships. Even if no inconsistencies were present in this study, it would be rash to rely entirely upon one study with 10 subjects. It would be equally irresponsible to disregard these findings. The greatest imprudence would be to fail to do the follow-up studies suggested by these results.

# APPENDIX B

## CASAC LETTER (AUGUST 31, 1982) TO EPA ADMINISTRATOR CONCERNING ISSUES INVOLVED IN SETTING OF NAAQS FOR CO

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

August 31, 1982

OFFICE OF
THE ADMINISTRATOR

Mrs. Anne M. Gorsuch
Administrator
U.S. Environmental Protection Agency
Washington, D.C. 20460

Dear Mrs. Gorsuch:

The Clean Air Scientific Advisory Committee (CASAC) met on July 6 to provide its advice on several issues related to the ambient air quality standard for carbon monoxide. The Committee had previously advised the Administrator of the scientific adequacy of the criteria document and staff paper in a closure memorandum dated October 9, 1979.

At its most recent meeting the Committee provided advice to the Agency on four issues. These included: 1) setting a revised eight-hour carbon monoxide standard that includes five allowable exceedances; 2) the role and significance of the 1981 study published by Dr. Wilbert Aronow; 3) sensitivity analysis and exposure analysis predictions of carboxyhemoglobin (COHb) levels and ambient CO concentrations under alternative air quality standards; 4) range of scientifically acceptable alternative standards for CO.

I would like to briefly summarize for you the Committee's views on each of these issues.

1. Development of a Multiple Exceedance 8-Hour Standard.

The CASAC reached a consensus that a multiple exceedance standard has both scientific as well as administrative merit. From a scientific point of view this approach recognizes the stochastic or random-like character of meteorological events; administratively, it reduces the element of chance in determining compliance with the standard. In recommending that you adopt a multiple exceedance standard, the Committee notes that an increase in the number of allowable exceedances will, in effect relax the existing standard if the standard level remains unchanged. In order to provide protection to the public health with an adequate margin of safety you should consider the impact of a multiple exceedance standard upon ambient CO concentrations and levels of blood COHb.

2. Role of the 1981 Aronow Study.

CASAC reached no overall consensus on the significance which the Agency ought to attribute to the Aronow study. The study reported a 10 percent reduction in the time to onset of angina during treadmill exercise at blood carboxyhemoglobin levels of 2 percent. CASAC discussed the fact that the response observed at 2.0% COHb was more subtle than that observed at higher levels (2.7 - 2.9% COHb) and speculated that even more subtle responses might be found at COHb levels below 2.0%. The Committee concluded that there may be no physiological response threshold for carbon monoxide. One CASAC consultant, while noting that the study data are solid and irrefutable, concluded that activity and exposure patterns of angina patients are far different from the general population. He also observed that there is no reason to believe that changes in the time of onset of angina during treadmill exercise are a valid biologic endpoint for the determination of an adverse health effect. Another Committee consultant, however, concluded that shortening of exercise time prior to the onset of an angina attack clearly is an adverse health effect.

While reaching no consensus on the role of this study, the Committee's earlier position as stated in the October 9, 1979 closure memorandum -- that the critical effects level for COHb occurs between 2.7% - 3.0% and that the onset of angina represents an adverse effect -- remains as the CASAC consensus on this issue.

3. Scientific and Technical Adequacy of Sensitivity and Exposure Analyses.

The sensitivity and exposure analyses were prepared by the Agency to compare the relationship between ambient CO concentrations and various levels of blood COHb. In addition, the analyses estimated the number and distribution of individuals who were projected to experience various COHb levels under alternative CO standards.

CASAC has reviewed the exposure and sensitivity analyses and has concluded that both are scientifically acceptable given the current state-of-the-art of the scientific community's ability to model physiological and other parameters related to this pollutant. Specifically, the Committee would draw to your attention two of its conclusions on these analyses: 1) the Agency's use of the Haldane constant with a value set at 218 is a reasonable selection among a variety of physiological parameters

discussed in the sensitivity analysis; and 2) the draft preamble states that an Agency objective is to keep 99% of the population below a COHb level of 2.5%. Since there may be no threshold concentration level for carbon monoxide below which no adverse effects will be experienced by anyone, and since one hundred percent protection is not feasible, a social policy choice must be made to limit societal risk from this pollutant. From a scientific standpoint the 99% objective is within the realm of reason, but there may be other than scientific factors you wish to consider in reaching a decision on this particular issue.

4. Scientifically Acceptable Range for the 8-Hour CO Standard.

In commenting upon the staff's proposals for a revised 8-hour CO standard set at 9 parts per million (p.p.m.) with five exceedances, or 12 p.p.m. with one exceedance, the Committee made the following consensus observations:

- o a standard set at 12 p.p.m. with 5 exceedances is not scientifically acceptable

- o a standard established at 12 p.p.m. with 1 exceedance would provide a very small margin of safety

- o the scientific evidence alone cannot identify an exact level at which to set a standard for carbon monoxide. Given the need to protect sensitive members of the population from this pollutant, the Committee advises you to choose a standard level and a corresponding number of exceedances that will limit COHb below the critical effects level of 2.7 - 3.0%, with an adequate margin of safety.

The Committee appreciates the opportunity to advise you on the carbon monoxide standard and hopes that its comments will be useful as you finalize the standard. We urge you to proceed expeditiously in this matter because the criteria document and staff paper, reviewed by CASAC more than three years ago, will be increasingly subject to challenge because of any newly published literature on this pollutant. In addition, both the private sector and individual citizens need to know the standard level for the next five years for planning purposes and for reassurance that public health is being adequately protected.

Sincerely yours,

Sheldon K Friedlander

Sheldon K. Friedlander
Chairman, Clean Air Scientific
Advisory Committee

cc: Dr. John W. Hernandez
Kathleen Bennett
Dr. Terry F. Yosie

# APPENDIX C

## CASAC LETTER (MAY 7, 1984) TO EPA ADMINISTRATOR CONCERNING FINDINGS AND RECOMMENDATIONS ON THE SCIENTIFIC BASIS FOR A REVISED NAAQS FOR CARBON MONOXIDE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460
May 17, 1984

OFFICE OF
THE ADMINISTRATOR

Honorable William D. Ruckelshaus
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Mr. Ruckelshaus:

The Clean Air Scientific Advisory Committee (CASAC) has completed its review of two documents related to the development of revised primary National Ambient Air Quality Standards (NAAQS) for Carbon Monoxide (CO). The documents were the Revised Evaluation of Health Effects Associated with Carbon Monoxide Exposure: An Addendum to the 1979 Air Quality Criteria Document for Carbon Monoxide written by the staff of the Office of Research and Development (ORD), and a staff paper entitled Review of the NAAQS for Carbon Monoxide: 1983 Reassessment of Scientific and Technical Information prepared by the Office of Air Quality Planning and Standards (OAQPS). The Committee unanimously concluded that both documents represent a scientifically balanced and defensible summary of the current basis of our knowledge of the health effects literature for this pollutant.

As you know, the latest CASAC review of the CO documents took place in an atmosphere of great scientific uncertainty and controversy due to the fact that a group of scientists conducting a review of the protocols for a major series of peer reviewed studies, carried out by Dr. Wilbert Aronow, had shortly before concluded that adequate standardized procedures for scientific research were not utilized in those studies. Confronted with this situation, Agency staff in both ORD and OAQPS moved quickly and resolutely to analyze the remaining scientific basis for the Clean Air Act requirement to finalize a revised CO standard. The CASAC concludes that, even without the use of the Aronow studies to determine a critical effects level from CO exposures, there remains a sufficient and scientifically adequate basis on which to finalize the CO standard.

As a result of its review of the information contained in these documents, the CASAC recommends that you consider choosing the 8-hour and 1-hour carbon monoxide standards to maintain approximately current levels of protection. A more extended analysis of the factors that led to this recommendation is contained in the enclosed report.

Thank you for the opportunity to present the Committee's views on this important public health issue.

Sincerely,

Morton Lippmann

Morton Lippmann, Chairman
Clean Air Scientific
Advisory Committee

Enclosure

cc: Mr. Alvin Alm
Mr. Joseph Cannon
Dr. Bernard Goldstein
Dr. Terry Yosie

CASAC Findings and Recommendations on the Scientific Basis for a Revised NAAQS for Carbon Monoxide

Addendum to the CO Air Quality Criteria Document

1. A key issue in the evaluation of public health risks from carbon monoxide (CO) exposures concerns the relation between CO in air and its displacement of oxygen in blood hemoglobin. The index for this displacement, known as carboxyhemoglobin (COHb), is expressed as a percentage of the blood hemoglobin. There is a scientific consensus that relatively low levels of COHb are associated with critical (i.e., health impairing) health effects. The discussion of the scientific evidence thus centers on what percentage of COHb causes a critical effect.

On October 9, 1979, CASAC submitted a report to the Administrator concluding that the critical COHb level occurred within a range of 2.7--3.0%. The Committee reached this finding following an extensive review of the scientific literature, including a series of studies performed by Dr. Wilbert Aronow. CASAC expressed some reservations about one of these studies (Aronow, 1978 which reported effects at levels [1.8%] well below the 2.7-3.0% range) in view of the fact that some confounding factors in the study protocols were not appropriately accounted for. The Committee further recommended that "given the uncertainties stemming from the methodological approach, [the Agency]...should utilize the [1978 Aronow] study for margin of safety considerations rather than using it for the determination of a threshold value" (CASAC report, October 9, 1979, p.5). On August 31, 1982 CASAC sent a follow-up report on several issues related to the NAAQS for carbon monoxide. In that report the Committee reaffirmed its prior findings on the critical COHb effects level. It should be noted that CASAC's 1982 recommendations were reached after the Committee members

had an opportunity to review an additional (1981) study by Dr. Aronow which concluded that a 10% reduction in the time to onset of an angina attack occurred during treadmill exercise with 2% COHb.

A review of the most recent update of this scientific literature in the August 1983 draft EPA Addendum to the CO Air Quality Criteria Document persuades CASAC that there is no significant reason to substantively alter its previous findings. An elaboration of CASAC's current reasoning on several issues will clarify the Committee's position. These include:

A. The role of the Aronow studies

A key question raised about Aronow's work was whether or not the procedures used insured that the studies were double blind. A double blind protocol is one in which neither the subjects nor the laboratory technicians conducting the experiments and collecting the data are aware of key parameters of the study (exposure conditions, timing, etc.) and the results of the responses by the experimental group and the control group. It is apparent that such double blind procedures were not applied in Aronow's work because technicians who were directly involved with the subjects knew some of the important parameters of the study. The lack of quality assurance checks represents another issue of concern. In these respects, the results of Aronow's work do not meet a reasonable standard of scientific quality for a study of the kinds of responses of interest, and therefore, they should not be used by the Agency in defining the critical COHb level.

B. The role of the Anderson study

The 1973 study by Anderson et al. reported that angina patients exposed to low CO levels while at rest experienced a statistically significant reduction in time to onset of exercise induced angina at average COHb levels of 2.9% and 4.5%. The study further concluded that there was a significantly lengthened

angina attack during exercise at an average COHb level of 4.5%. The 1983 CO criteria document addendum noted concerns expressed by some parties about the study due to the small number of subjects studied, apparent inconsistencies between predicted and observed COHb levels, the possibility that the protocols were not truly double blind, and the lack of subsequent confirmatory findings.

CASAC reached several conclusions concerning this study. It was troubled that so few patients were included in the study design and that there was uncertainty about the exposures to which the patients were subjected. The Committee agreed that it is important to replicate such a study, but the notion that a study has no validity until it's been replicated is flawed. Based upon its current knowledge of how the study was conducted, CASAC presumes that double blind protocols were, in fact, observed and that discrepancies between observed and predicted COHb levels are not as great or as serious as originally suggested. In summary, while CASAC treats the Anderson et al. study with caution, it can find no substantive reason at this time to dispute the reported values, and it recommends that the Agency not disregard its findings.

C. Additional studies

CASAC wishes to point out two sets of additional studies which lend support to concerns about low level CO exposures. In 1974, both Raven et al. and Drinkwater et al. reported statistically significant decreases (less than 5%) in exercise time for work capacity in healthy, nonsmoking young and middle aged men at approximately 2.3 - 2.8% COHb. Also, a 1980 controlled human exposure study by Davies & Smith observed changes in electrocardiogram (EKG) measurements in a small number of healthy nonsmoking young men at 2.4% COHb. Such CO induced changes are a cause for public health concern and should be factored into the Agency's thinking for setting a standard with an adequate margin of safety.

D. Use of the Coburn-Foster-Kane (CFK) equation

The CFK model is the most important available tool for analyzing a number of physiologically important variables (blood volume and endogenous CO production rate, for example) in order to project a relationship between ambient CO exposures and resulting COHb levels. While this model, like any model, is subject to the need for additional evaluation of COHb in different population groups, it is reasonable to conclude that the CFK equation accurately predicts CO uptake under differing exposure conditions.

E. Summary of cardiovascular effects

The Committee unanimously agrees that: 1) the key mechanism of CO toxicity is the decreased oxygen carrying capacity resulting from the greater affinity of blood hemoglobin for carbon monoxide than for oxygen; 2) reduction in time to the onset of an angina attack is a medically significant event and should be considered an adverse health effect; and 3) following a review of the peer reviewed scientific literature (not including the Aronow studies), the critical effects level for NAAQS setting purposes is approximately 3% COHb (not including a margin of safety).

2. A second important public health issue in setting a NAAQS for carbon monoxide concerns CO-induced central nervous system effects. Decreased vigilance or sensory-motor function is a health effect which the standard ought to protect against. CASAC's position is that such behavioral effects are observed between 5-8% COHb.

3. The Committee was asked to address the issue of the role of CO in Sudden Infant Death Syndrome (SIDS). A review of the current scientific

literature leads to the conclusion that there is not a sufficient scientific basis to establish a connection between a CO exposure level and SIDS.

OAOPS Staff Paper Review of the NAAQS For Carbon Monoxide

Based upon the addendum to the revised Air Quality Criteria Document for Carbon Monoxide, OAQPS developed a staff paper analyzing alternative ranges of concentration levels for a final promulgated standard. The current suite of primary standards is set at 9 parts per million (ppm) for the 8-hour averaging time and 35 ppm for the 1-hour average.

CASAC was asked to advise the Agency on several issues associated with the proposed ranges. The following discussion responds to the Agency request.

1. CASAC reaffirms the judgment it reached in its October 1979 report that reduction in the time to onset of angina aggravation represents an adverse health effect.
2. The Committee concurs with the Agency that 8-hour and 1-hour standards are the appropriate averaging times, but it recommends that there be additional discussion and more explicit comparison in the regulatory package concerning the relationship between the two averaging times, particularly in terms of what attainment of the 8-hour standard portends for the health protection provided by the 1-hour standard.
3. The factors identified by OAQPS for margin of safety consideration are appropriate. Underlying CASAC's view of the margin of safety, however, is its traditional belief that

where the scientific data, as in this case, are subject to large uncertainties, it is desirable for the Administrator to consider a greater margin of safety than the numerical values of COHb generated by the Coburn equation might otherwise suggest.

4. The OAQPS staff recommends that the Administrator retain or select an 8-hour primary standard in the range of 9 to 12 ppm. With regard to the 1-hour primary standard, the staff recommends that a selection be made within the range of 25 to 35 ppm. CASAC concurs that the proposed ranges for both the 8-hour and 1-hour primary standards are scientifically defensible. Given the uncertainties within the scientific data base and discussion of margin of safety issues, the Committee recommends that you consider choosing standard limits that maintain approximately current levels of protection.



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