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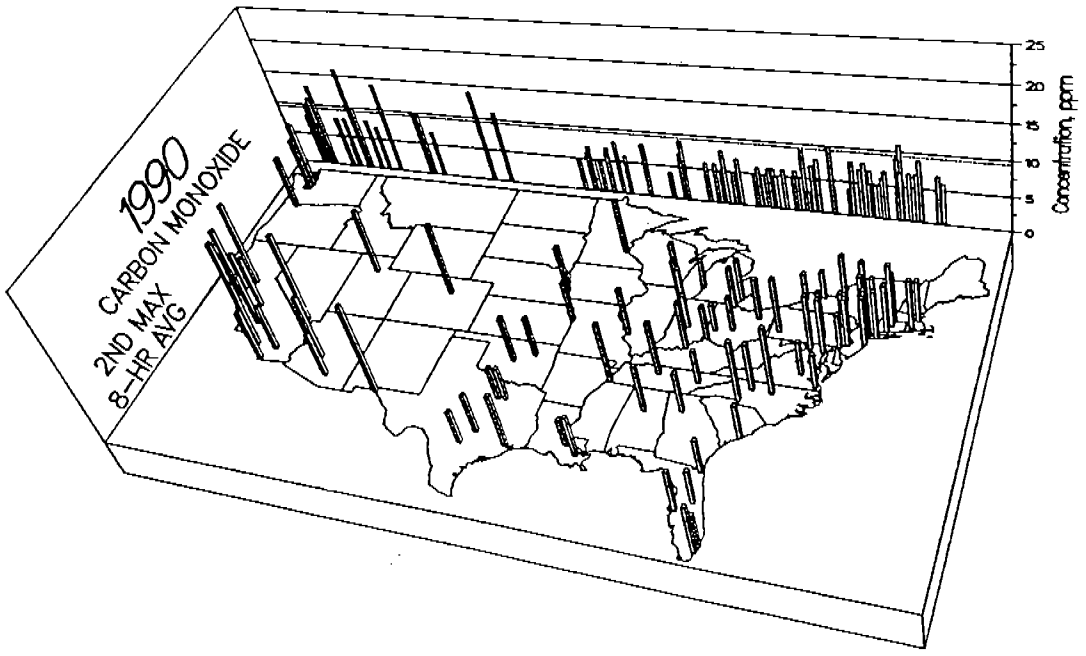
REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR CARBON MONOXIDE ASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

OAQPS STAFF PAPER



The cover illustration is an air quality map of the U.S. which displays the highest second maximum nonoverlapping 8-hour average carbon monoxide concentration by metropolitan statistical area (MSA) for 1990. This illustration can be found on page 4-16 of the National Air Quality and Emission Trends Report, 1990 (EPA-450/4-91-023).

This report has been reviewed by the Office of Air Quality Planning and Standards, USEPA, and approved for publication. Mention of trade names or commercial products is not intended to constitute endorsement or recommendation for use.

Preface

This document was finalized by the Office of Air Quality Planning and Standards (OAQPS) in August 1992 and reviews information from relevant studies of carbon monoxide (CO) health effects and exposure analysis. The assessment contained in this staff paper reflects information in the document "Air Quality Criteria for Carbon Monoxide" (EPA/600/8-90/045F).

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Acknowledgments

This Staff Paper is the product of the OAQPS. The principal authors include Dr. David J. McKee (Carbon Monoxide NAAQS Review Program Manager), Thomas R. McCurdy, and Harvey M. Richmond. This document reflects many helpful comments within the Environmental Protection Agency (EPA) from individuals in OAQPS (Michael H. Jones, John H. Haines, Dr. Thomas C. Curran, Barbara A. Beard), the Environmental Criteria and Assessment Office (ECAO) (James A. Raub), the Atmospheric Research and Exposure Assessment Laboratory (Gerald G. Akland), the Office of General Counsel (Gerald K. Gleason), the Office of Policy, Planning, and Evaluation (John C. Chamberlin), and Region VIII (Dr. Suzanne M. Wuerthele). Comments of the Clean Air Scientific Advisory Committee (CASAC) made at meetings held on April 30, 1991 to review the external review draft of the Air Quality Criteria for Carbon Monoxide and on March 5, 1992 to review the external review draft of this OAQPS Staff Paper also have been carefully considered in revising this draft. A copy of the CASAC closure letter for the criteria document is included as Appendix A of this Staff Paper. Finally, the clerical and support services provided by Patricia R. Crabtree and Barbara Miles are acknowledged and greatly appreciated.

REVIEW OF THE NATIONAL AMBIENT AIR QUALITY STANDARDS FOR CARBON MONOXIDE
1992 ASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

I. PURPOSE

The purpose of this Office of Air Quality Planning and Standards (OAQPS) Staff Paper is to evaluate the key studies and scientific information contained in the revised EPA document, Air Quality Criteria for Carbon Monoxide (USEPA, 1991; henceforth referred to as CD) and to identify the critical elements that the EPA staff believes should be considered in the review of the national ambient air quality standards (NAAQS) for carbon monoxide (CO). Factors relevant to the evaluation of the current primary NAAQS, as well as staff conclusions and recommendations, are provided in this Staff Paper.

II. BACKGROUND

A. Legislative Requirements

Since 1970 the Clean Air Act (Act) has provided authority and guidance for the listing of certain ambient air pollutants which may endanger public health and/or welfare and for revising, as necessary, the NAAQS for those pollutants. Primary standards must be based on health effects criteria and must provide an adequate margin of safety to ensure protection of public health. Judicial decisions have provided clear guidance that economic and technological feasibility are not to be considered in setting the primary NAAQS, although these factors may be considered in the development of State implementation plans to implement NAAQS (Lead Industries Association v. EPA, 1980; American Petroleum Institute v. EPA, 1981). Guidance was also provided in the legislative history of the Act that the standards should be set

at "the maximum permissible ambient air level . . . which will protect the health of any (sensitive) group of the population," and further that margins of safety are to be included such that NAAQS provide "a reasonable degree of protection . . . against hazards which research has not yet identified" (U.S. Senate, 1974). In weighing risks for margin of safety purposes, EPA takes into account factors such as size of sensitive population(s), nature and severity of all health effects involved, and kind and degree of other uncertainties. It is, however, a policy choice left specifically to the EPA Administrator to select a particular approach for setting a primary NAAQS which provides an adequate margin of safety (Lead Industries Association v. EPA, 1980).

The Act, as amended in 1977 and 1991, requires periodic review of criteria and, as appropriate, revision of existing NAAQS. Thus, if the Administrator determines that review of criteria makes proposal of new or revised NAAQS necessary, such standards are to be revised and promulgated in accordance with section 109(b) of the Act. However, the Administrator may find that revision of NAAQS is not necessary and may conclude review by reaffirmation.

B. Establishment of Carbon Monoxide Standards

On April 30, 1971, the EPA promulgated NAAQS for CO under section 109 of the Act (36 FR 8186). Identical primary and secondary NAAQS were set at 9 ppm as an 8-hr average and 35 ppm as a 1-hr average, neither to be exceeded more than once per year. Scientific and technical bases for these NAAQS are provided in the document, Air Quality Criteria Document for Carbon Monoxide (U.S. Dept. of Health, Education and Welfare, 1970). The NAAQS promulgated in 1971 were based largely upon research by Beard and Wertheim (1967) who reported that CO exposures which produced carboxyhemoglobin (COHb) levels of 2 to 3% were associated with central nervous system (CNS) effects such as impaired ability to discriminate time intervals.

C. First Review of Carbon Monoxide Standards

A revised Air Quality Criteria Document for Carbon Monoxide (USEPA, 1979a), prepared by the ECAO, and a Staff Paper (USEPA, 1979b), prepared by OAQPS, identified several major factors pertinent to subsequent action taken on the NAAQS for CO. The CASAC met on June 14-15, 1979, to review drafts of these documents and provide advice on the CO standards. As discussed in a notice of proposed rulemaking (45 FR 55066) published on August 18, 1980, although the Beard and Wertheim (1967) study no longer could serve as a basis for the CO NAAQS, other studies available in 1980 provided alternative evidence of decreased time to onset of angina attack at COHb levels as low as 2.7 to 3.0%. This and other scientific evidence served as a basis for EPA to propose: (1) retaining the 8-hour primary standard level of 9 ppm, (2) revising the 1-hr primary standard level from 35 ppm to 25 ppm, (3) revoking the existing secondary CO NAAQS due to a lack of evidence of adverse welfare effects at or near ambient CO levels, (4) changing the form of the standard from deterministic to statistical by stating allowable exceedances as expected values rather than as explicit values, (5) adopting a daily interpretation for exceedances of the CO NAAQS so exceedances would be determined on the basis of days on which the 8- or 1-hr average concentrations were above the standard levels.

On June 18, 1982, EPA announced (47 FR 26407) that a second public comment period was necessary to open discussion on several important issues and additional analyses. These issues included: (1) the role of the Aronow (1981) study in assessing CO effects, (2) consideration of a multiple exceedance 8-hr standard for CO, (3) technical adequacy of the revised draft sensitivity analysis (Biller and Richmond, 1982) on the Coburn, Forster, and Kane model predictions of COHb levels, and (4) technical adequacy of the revised exposure analysis (Johnson and Paul, 1982). The CASAC met on July 6, 1982 to discuss these issues and provide advice, a summary of which was sent to the Administrator on August 31, 1982 (Friedlander, 1982).

The 1980 proposal (45 FR 55066) was based in large part on studies by Dr. Wilbert Aronow (Aronow, et al., 1972, 1973, 1974, 1975, 1977, 1978), which provided CASAC and EPA staff with a basis for concluding that COHb levels of 2.7-3.0% posed a health risk of concern in individuals with angina and other types of cardiovascular disease. A subsequent disclosure in March 1983 by the Food and Drug Administration (FDA) concerning work conducted for FDA by Dr. Aronow caused the EPA to question the scientific credibility of Dr. Aronow's research on CO. As a result, EPA decided it would be prudent to conduct an independent review of his CO research prior to making a decision on the CO standards. A committee of experts was convened and chaired by Dr. Steven Horvath (University of California, Santa Barbara). Following meetings with Dr. Aronow and examination of limited data and records available from his CO studies, the committee concluded in its report (Horvath et al., 1983) that the EPA should not rely on Dr. Aronow's studies for a decision on the level of the CO standards due to problems regarding data collection and analysis.

As a result of this finding, the ECAO prepared a draft Addendum to the 1979 Air Quality Criteria for Carbon Monoxide (U.S. EPA, 1984a), hereafter referred to as Addendum. OAQPS prepared a draft Review of the NAAQS for Carbon Monoxide: Reassessment of Scientific and Technical Information (U.S. EPA, 1984b), hereafter referred to as Staff Reassessment. These documents were prepared to reevaluate the scientific and technical evidence on health effects of CO at or near ambient levels in consideration of the reduced usefulness of the Aronow studies. Both documents were reviewed by the CASAC at a public meeting on September 25, 1983. CASAC sent a closure letter to the Administrator on May 17, 1984, which concluded that the Addendum and the Staff Reassessment represented a scientifically balanced and defensible summary of health effects literature for CO. On August 9, 1984, the EPA announced (49 FR 31923) availability of the final Addendum (1984a) and final Staff Reassessment (1984b), both of which were revised to reflect CASAC

and public comment. In the same notice, the EPA reviewed the basis for proposal to revise the CO standards and solicited additional public comment. In a subsequent notice (50 FR 37484) on September 13, 1985, the EPA announced its final decision not to revise the existing primary (health based) standard and to revoke the secondary (welfare based) standard for CO. In doing so the Administrator determined that the existing 1-hr and 8-hr primary NAAQS provided adequate protection from exposure to ambient CO.

D. Current Review of Carbon Monoxide Standards

In 1987, the ECAO initiated action on a revised CD, which was released for public review in April 1990. The revised CD included discussion of several new studies of effects of CO on angina patients which had been initiated in light of the controversy discussed above. The CASAC reviewed the CD at a meeting on April 30, 1991 and concluded in a letter to the Administrator that the document ". . . provides a scientifically balanced and defensible summary of current knowledge of the effects of this pollutant and provides an adequate basis for the EPA to make a decision as to the appropriate primary NAAQS for CO." (See Appendix A.)

III. APPROACH

The approach taken in this Staff Paper is to evaluate and integrate information provided in the 1991 revised CD and to incorporate consideration of an exposure analysis used to evaluate the adequacy of the current CO primary NAAQS. Due to the EPA decision (50 FR 37484) to revoke the secondary NAAQS and the lack of any substantial new information suggesting the need for a secondary NAAQS for CO to protect public welfare from any known or anticipated adverse welfare effects, only health information and analysis related to evaluation of the primary CO NAAQS are reviewed here.

Critical elements have been identified which the staff believes should be considered in review of the primary CO NAAQS. Particular attention is drawn to those judgments that must be based on careful interpretation of incomplete or uncertain evidence. In such instances, the Staff Paper provides the staff's evaluation of evidence as it relates to a specific judgment, sets forth alternatives that the staff believes should be considered, and recommends a course of action. After a short discussion of air quality information in Section IV, Section V of this Staff Paper provides:

(a) description of probable mechanisms of CO toxicity,
(b) discussion of measurement and estimation of COHb,
(c) evaluation of effects of concern and effect levels,
(d) identification of populations at risk to ambient CO, and,
(e) discussion of COHb levels of concern.

Section VI is a rationale for selection of CO NAAQS averaging times, and Section VII is a discussion of exposure analysis and resulting estimates of exposure occurrences and number of people exposed to the current 1-hr and alternative 8-hr CO levels and various COHb levels upon attainment of the current CO NAAQS. Finally, drawing on information in Sections V, VI, and VII, Section VIII presents staff conclusions and recommendations.

IV. AIR QUALITY INFORMATION

A. Introduction

Carbon monoxide is a colorless, odorless gas which can be emitted into ambient air as a result of both natural processes and human activity. Although CO exists as a trace constituent of the troposphere, much of human CO exposure which results in elevated levels of COHb in the blood is due to incomplete fossil fuel combustion. In 1990, transportation sources of CO accounted for 63% of total ambient CO emissions in the U.S., while other combustion processes (e.g., steam boilers, industrial processes, solid waste disposal) were responsible for most of the rest (CD, p. 1-4). As discussed in Section VII, other significant sources of CO exposure include combustion sources and gas stoves in homes, and passive smoking in many microenvironments. See Chapter 6 of the CD for an extended discussion of CO emission sources, air quality patterns, and CO diffusion models.

B. Nonattainment Status

On November 6, 1991, the EPA published a list of areas that legally do not attain the current 8-hr CO NAAQS (56 FR 56694). There are 42 areas on the list, most of which are metropolitan statistical areas. For the most part, nonattainment designations are based upon 1988-1989 air quality data.

Almost 55 million people live in areas that violate the current 8-hr CO NAAQS (AQMD, 1991). It should not be inferred, however, that everyone in these areas is exposed to the concentration values recorded by ambient monitors used to determine whether or not an area violates a CO NAAQS. Actual exposures experienced by residents of a non-attainment area may be lower or higher than the ambient levels recorded at a fixed-site monitor (CD, Chapter 8). For this reason, EPA undertakes an exposure analysis to better estimate total human exposures to CO as people go about their daily lives. One such analysis for Denver, Colorado is described in Chapter VII.

There are very few violations of the 1-hr CO NAAQS of 35 ppm, which is determined by evaluating the second-highest 1-hr value in a year. In fact, in the 1988-1989 time period, only two metropolitan statistical areas (MSA's) recorded a violation of the 1-hr NAAQS: Denver, CO and Steubenville, OH. There were fewer than 20 such violations recorded in all site-years of data for all MSA's contained in EPA's Aerometric Information Retrieval Service (AIRS) data base for the 1980 through 1990 time period (AIRS, 1991). In all areas that exceed both the 1-hr and the 8-hr NAAQS, the 8-hr exceedance(s) is(are) proportionally further away from the CO standard than are the 1-hr exceedance(s). Thus, exceedances of the 8-hr CO standard are more significant in terms of control program development than exceedances of the 1-hr CO standard.

C. Air Quality Trends

The EPA analyzes long-term trends of NAAQS pollutants in the Technical Services Division's (TSD) annual Trends Report; the most recent one includes 1990 data (TSD, 1991). During the 1980-1990 time period, the composite national average of the second-highest non-overlapping 8-hr CO average concentration (often known as the "design value") decreased by approximately 30%. The median rate of improvement was about 3% per year. The downward trend in the annual number of exceedances of the 8-hr NAAQS is even more impressive during the same time period. The composite average of the estimated number of annual exceedances (often known as "expected exceedances") decreased about 86% between 1980 and 1990. The Trends Report (TSD, 1991) also provides information regarding trends in CO emissions and probable reasons for the decreasing ambient CO levels monitored around the country; the interested reader should review that report for additional information.

V. HEALTH EFFECTS OF CARBON MONOXIDE

A. Introduction

This section draws on elements which are critical in reviewing primary NAAQS for CO. Identification of the principle mechanism of toxicity is important to establish a linkage between CO exposure and resultant health effects. Methodologies used to measure biomarkers of CO exposure are evaluated based on known limitations discussed in the CD (Chapter 8). Health effects of concern are presented in a manner which discusses the adverse nature of effects and estimates a lowest effects level for purposes of standard setting. Populations at risk to CO exposure also are identified. Finally, staff recommendations are made regarding the range of COHb levels that should be considered in setting CO standards that protect public health with an adequate margin of safety.

B. Mechanisms of Toxicity

The mechanism of toxicity principally associated with health effects of greatest concern from CO exposure is hypoxia induced by elevated COHb levels. The primary exchange route for CO to human tissues is through the lungs. Although CO is a naturally occurring chemical in blood being produced endogenously by normal catabolic processes, blood COHb levels do not often exceed 0.5 to 0.7% in normal individuals unless exogenous CO is breathed. Some individuals with high endogenous CO production can have COHb levels of 1.0 to 1.5% (e.g. anemics). Exogenous CO diffuses through the respiratory zone (alveoli) to the blood where it binds to hemoglobin (Hb) to form COHb. The chemical affinity of CO for Hb is 218 to 250 times greater than that of oxygen (O_2) (Roughton, 1970; Wyman et al., 1982; Rodkey et al., 1969). This preferential binding of CO to Hb limits the availability of Hb for O_2 transport to tissues throughout the body. As COHb levels increase, the dissociation curve for normal human blood is shifted to the left resulting in more reduced delivery of O_2 to

tissues and a greater degree of CO-induced hypoxia. It is this reduced O_2 delivery to heart muscle tissue which is of great concern for individuals with ischemic heart disease because their already compromised condition puts them at increased risk.

Although several other mechanisms of toxicity are discussed in the CD, these are not considered to be as well understood as COHb hypoxia. Intracellular effects of CO (CD, pp. 9-22 to 9-31) have been associated with CO toxicity. Preferential binding of CO to myoglobin, cytochrome P-450, and cytochrome c oxidase has been studied and could lead to impairment of intracellular oxygen transport to mitochondria. However, mechanisms of toxicity associated with CO-induced inhibition of these hemoproteins at relevant CO levels are not well understood at this time and will require additional research.

Based on the review and conclusions drawn in the CD, COHb levels provide the most useful estimate of exogenous CO exposures and serve as the best biomarker of CO toxicity for ambient-level exposures to CO. Thus, COHb levels are used in this Staff Paper as the measure of health effects and to identify the lowest effects level for CO.

C. Measurement and Estimation of Carboxyhemoglobin Levels

1. Measurement of Carboxyhemoglobin Levels

As noted in the section above, the best indicator of CO exposure to relate to health effects of concern is blood COHb levels. Since the last CO NAAQS review, significant concerns have been raised about the accuracy of CO-Oximeters (CO-Ox), which are the instruments most commonly used to measure COHb in health effects studies, at levels in the range of 0 to 5% COHb.

While CO-Ox measurements have been shown to be very precise (i.e. replicable), research has shown that the accuracy (i.e., ability to detect the true level) of these optical instruments is not always sufficient to use alone at levels below 5% COHb (Allred et al., 1989a,b, 1991). As indicated in the CD (pp. 8-72 to 8-73), the results from linear regression analyses of

comparisons between IL 282 CO-Ox instruments and various reference instruments (involving gas chromatography, GC) show a fairly linear slope (range 0.895 to 1.122) and a wide range of intercept values (range -1.279 to +1.17). In the only health effect study that used both CO-Ox and GC methods to measure COHb levels in subjects with cardiovascular disease, researchers also found the spread of COHb values to be much greater for the CO-Ox values than for the GC values (Allred et al., 1989a,b, 1991).

In order for optical instruments such as CO-Ox to be used to measure COHb levels accurately at low levels they must be calibrated routinely with an alternative method (CD, p. 8-64). When properly calibrated, CO-Ox instruments can provide useful information on mean values. However, variation in individuals' oxyhemoglobin (O_2Hb) levels appears to influence COHb readings (Allred et al., 1989a,b) and, as noted above, CO-Ox instruments also give too broad a range of COHb values when compared to GC measurements on the same samples (Allred et al., 1989a,b, 1991). In the section assessing health effects and effect levels associated with CO exposure, the measurement method used to obtain COHb values will be indicated in parentheses (GC or CO-Ox). The fact that most of the health effects literature for CO has relied on CO-Ox measurements of COHb levels introduces additional uncertainty as one attempts to assess lowest effects levels and dose-response relationships.

2. Estimation of Carboxyhemoglobin Levels Using the Coburn, Forster, Kane Equation

In order to set ambient CO standards based on an assessment of health effects at various COHb levels, it is necessary to estimate the ambient CO concentrations that are likely to result in COHb levels of concern. The CD (p. 9-21) concludes that the best all around model for predicting COHb levels is the Coburn, Forster, Kane (CFK) differential equation (Coburn et al., 1965). The CFK model estimates COHb levels resulting from exposure to CO concentrations as a function of time and various physiological

and environmental factors (e.g., blood volume, endogenous CO production rate, ventilation rate, altitude).

Over the last 20 years, modelers have developed and evaluated both linear and nonlinear solutions to the CFK model. The linear CFK model assumes that O_2Hb is constant and does not vary with COHb level. The nonlinear CFK model incorporates the interdependence between O_2Hb and COHb. At COHb levels below 6% both approaches give estimates that are within 0.5% COHb (Smith, 1990). While the linear CFK model is easier to solve and gives approximately the same COHb estimate in the range of interest (i.e., 1 to 5% COHb), we have chosen to use the nonlinear solution in the remainder of this Staff Paper because it is more accurate physiologically. With the assumption of a linear relationship between O_2Hb and COHb, there is an analytical solution to the nonlinear CFK equation (Muller and Barton, 1987).

Table V-1 presents baseline estimates (i.e., typical physiological parameters are used) of COHb levels expected to be reached by nonsmokers exposed to various constant concentrations of CO for either 1 or 8 hrs based on the CFK model. (Smokers are not included because they have voluntarily exposed themselves to high CO levels.)* There are, however, two major uncertainties involved in estimating COHb levels resulting from exposure to CO concentrations. First, among the population with cardiovascular disease, or any other group of interest, there is a distribution for each of the physiological parameters used in the CFK model. Past work (Biller and Richmond, 1982) has shown that these variations are sufficient to produce noticeable deviations from the COHb levels in Table V-1. Second, predictions based on exposure to constant CO concentrations can underestimate the

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* It has been estimated that a smoker may be exposed to 400 to 500 ppm CO for the approximately 6 min that it takes to smoke a typical cigarrette, producing an average COHb of 4%, with a typical range of 3 to 8%. Heavy smokers can have COHb levels as high as 15 %. (CD, p. 11-39)

Table V-1. Predicted COHb Response to Exposure to Constant CO Concentrations

	Percent COHb Based on Nonlinear CFK Model[1]			
	1-hour Exposure		8-hour Exposure	
CO (ppm)	Intermittent Rest/Light Activity	Moderate Activity	Intermittent Rest/Light Activity	Moderate Activity
7.0	0.7	0.7	1.1	1.1
9.0	0.7	0.8	1.4	1.4
12.0	0.8	1.0	1.7	1.8
15.0	0.9	1.1	2.1	2.2
20.0	1.1	1.4	2.7	2.9
25.0	1.3	1.7	3.4	3.6
35.0	1.6	2.2	4.6	5.0
50.0	2.1	3.0	6.4	7.0

[1]assumed parameters: alveolar ventilation rates = 10 STPD liters/min (intermittent rest/light activity) and 20 STPD liters/min (moderate activity); hemoglobin = 15 g/100 ml (normal male); altitude = sea level; initial COHb = 0.5 percent; endogenous CO production rate = 0.00 STPD ml/min; blood volume = 5500 ml; Haldane coefficient (measure of affinity of hemoglobin for CO) = 218; lung diffusivity for CO = 35.9 and 44.3 STPD ml/min/loss at 10 and 20 STPD liters/min alveolar ventilation rates respectively.

response of individuals exposed to widely fluctuating CO levels that typically occur in the ambient environment (Biller and Richmond, 1982).

Section VII and Appendix C discuss the use of the nonlinear CFK model to estimate the distribution of COHb levels in persons with ischemic heart disease in Denver, Colorado under "as is" conditions and where the current 9 ppm, 8-hour CO NAAQS is just attained. A more detailed discussion of the EPA's application of the CFK model can be found in Biller and Richmond (1992).

D. Health Effects and Effect Levels of CO

Health effects information which is pertinent to review of the NAAQS for CO has been thoroughly reviewed in Chapters 10 and 11 of the CD. The CD has reviewed hundreds of health effects studies, some of which were conducted at extremely high levels of CO (i.e. much higher than typically found in ambient air). However, the focus of this Staff Paper is only on those key health studies, which generally were conducted with human subjects at COHb levels that are most relevant to regulatory decision making.

Health effects associated with exposure to CO include cardiovascular system, central nervous system (CNS), and developmental toxicity effects, as well as effects of combined exposure to CO and other pollutants, drugs, and environmental factors. Cardiovascular effects of CO are directly related to reduced O_2 content of blood caused by combination of CO with Hb to form COHb and resulting in tissue hypoxia. Most healthy individuals have mechanisms (e.g. increased blood flow, blood vessel dilation) which compensate for this reduction in tissue O_2 levels, although the effect of reduced maximal exercise capacity has been reported in healthy persons even at low COHb levels. Several medical conditions such as occlusive vascular disease, chronic obstructive lung disease, and anemia can increase susceptibility to potential adverse effects of CO during exercise.

The best documented cardiovascular effects in patients with angina pectoris are decreased time to onset of chest pain and ST segment depression during exercise stress. The commonly accepted criterion of exercise-induced myocardial ischemia is 1 mm or greater ST segment depression. The ST segment is a portion of the electrocardiogram (ECG), depression of which is an indication of insufficient O_2 supply to heart muscle tissue. Other cardiovascular effects of CO such as increased blood flow, arrhythmogenic effects, or effects on individuals with chronic anemia or chronic obstructive lung disease either have not been studied adequately or do not appear to pose a significant health threat.

Effects of CO on the CNS involve both behavioral and physiological changes. These include modification of visual perception, hearing, motor and sensorimotor performance, vigilance, and cognitive ability. Developmental toxicity effects of CO, though not well studied in humans, do pose a potentially serious threat to the fetus. Finally, environmental factors (e.g. altitude), drug interaction, and pollutant interaction also can play a role in the public health impact of ambient CO exposure.

Table V-2 is a summary of key health studies which have been identified by staff as being most pertinent to a regulatory decision on the NAAQS for CO and is not intended to be comprehensive. Each of the key studies is considered in light of limitations discussed in the CD and this Staff Paper. Due to the fact that most of the studies used optical methods, COHb levels are presented as optical measurements.

1. Effects on Persons with Cardiovascular Disease

Five key studies on cardiovascular effects of CO (Allred et al., 1989a,b, 1991; Kleinman et al., 1989; Adams et al., 1988; Sheps et al., 1987; Anderson et al., 1973) have provided evidence of the potential for CO to enhance development of exercise-induced myocardial ischemia in patients who suffer from angina pectoris. (Angina pectoris is a disease marked by brief,

Table V-2
KEY HEALTH STUDIES FOR ESTABLISHING NAAQS
FOR CARBON MONOXIDE

COHb Concentration Percent[a]	Health Effects	Reference[b]
2.3-7.0	Decreased short-term maximal exercise duration in young healthy men	Drinkwater et al. (1974) Ekblom and Huot (1972) Horvath et al. (1975) Raven et al. (1974a,b) Weiser et al. (1978)
2.9-5.9	Decreased exercise duration due to increased chest pain (angina) in patients with ischemic heart disease	Adams et al. (1988) Allred et al. (1989a,b, 1991) Anderson et al. (1973) Kleinman et al. (1989) Sheps et al. (1987)
5.0-20.0	Decreased maximal oxygen consumption with short-term strenuous exercise in young healthy men	Ekblom and Huot (1972) Klein et al. (1980) Pirnay et al. (1971) Stewart et al. (1978) Vogel and Gleser (1972) Weiser et al. (1978)
5.0-20.0	Equivocal effects on visual perception, audition, motor and sensorimotor performance, vigilance, and other measures of neurobehavioral performance	Benignus et al. (1977, 1987, 1990a,b) Bunnell and Horvath (1988) Christensen et al. (1977) Gliner et al. (1983) Harbin et al. (1988) Hudnell and Benignus (1989) McFarland (1970, 1973) McFarland et al. (1944) Mihevic et al. (1983) O'Donnell et al. (1971) Putz et al. (1976, 1979) Roche et al. (1981) Rummo and Sarlanis (1974) Seppannen et al. (1977) Von Post-Lingen (1964) Winneke (1974)

[a]Blood COHb levels determined by optical methods.
[b]References also found in U.S. Environmental Protection Agency (1991).

recurrent attacks often precipitated by deficient oxygenation of heart muscle tissue.) As was noted in Section II.C (pp. 3-5) of this Staff Paper, earlier angina studies conducted by Dr. Wilbert Aronow reporting decreased time to onset of exercise- induced angina for COHb levels in the range of 2-3% (CO-Ox) have been called into question. Only one other early study by Anderson et al. (1973) reported decreased time to onset of angina pain for COHb levels as low as 2.9 (CO-Ox), representing a 1.6% increase in average COHb levels over baseline. Details of this study were reported at length in the Addendum (U.S. EPA, 1984a).

Recent controlled exposure studies of angina patients have provided substantial new evidence of decreased exercise duration due to early onset of chest pain. (See discussion in CD, pp. 10-21 to 10-35). A study which provides strong evidence of the health effects of CO is the multicenter study of Allred et al. (1989a,b, 1991). There are several reasons why this study is important to the CO NAAQS review: 1) dose-response relationships are shown; 2) information on ST-segment depression of subjects is available; 3) both GC and CO-Ox measurements were taken; 4) a large number of subjects was used; and 5) it was conducted at multiple laboratories around the U.S. This study involved 63 males (ages 41-75) with coronary artery disease living in three different U.S. cities. The objective was to assess the impact of exposure to CO on time to onset of significant ischemia during a standard treadmill test. Unusual care was taken to establish presence of coronary artery disease in all subjects prior to testing. The protocol for the study was quite similar to that used in the Aronow studies; i.e. two exercise tests were performed on the same day separated by a recovery period and a double-blind exposure period. Subjects were exposed to either clean air, 117 ppm CO, or 253 ppm CO for 50 to 70 minutes while performing symptom-limited exercise on a treadmill. Time to onset of angina and time to ST segment depression were determined for each test following exposure to both CO levels and compared to clean air (< 2 ppm CO) exposure. After exposure to 117 ppm

and 253 ppm CO, COHb levels measured before the exercise stress test were 2.4 and 4.7% COHb (GC) and 3.2 and 5.6% COHb (CO-Ox), respectively. After the stress test COHb levels were 2.0 and 3.9% (GC) and 2.7 and 4.7% (CO-Ox). Using the objective measure of time to ST-segment depression, CO exposure which produced 3.2% COHb (CO-Ox, pre-test) resulted in a 5.1% ($p = 0.01$) decrease in time to the ST criterion, and 5.6% COHb (CO-Ox, pre-test) decreased time to the ST criterion by 12.1% ($p<0.0001$) relative to clean air exposure. Combining slopes for the 62 individuals yielded a significant ($p<0.005$) regression which indicates that there was a 3.9% decrease in time to ST criterion for every 1% increase in COHb. Time to onset of angina, signalled by chest pain, also was reduced in the same subjects, and regression analysis yielded a significant relationship ($p<0.025$). Both endpoints (time to angina and time to ST change) were highly correlated.

In another study (Sheps et al., 1987), 30 non-smokers with ischemic heart disease (ages 38-75) were exercised during exposure to 100 ppm CO or air using a 3-day, randomized double blind protocol. Following CO exposure average COHb levels were 4.1% (CO-Ox), representing a 2.2% COHb increase from the initial COHb level. (In this and other studies using the CO-Ox, the initial high COHb readings may have been due in part to the inaccuracies of the CO-Ox at very low COHb levels.) In comparing results of air-exposed subjects to CO-exposed subjects as a group, no statistically significant differences were reported in time to onset of angina, maximal exercise time, maximal ST-segment depression, or time to significant ST-segment depression. Although the authors concluded that 4.1% COHb did not produce clinically significant effects in the subject group, 3 of 30 patients did experience angina on CO-exposure days but not on air-exposure days. Further analysis of time to onset of angina that includes these three patients indicated a statistically significant decrease for CO exposure compared to air exposure (Bissette et al., 1986). The same group of researchers (Adams et

al., 1988) exposed 30 subjects with obstructive coronary artery disease to either air or sufficient CO to reach COHb levels of 5.9% (CO-Ox), representing an average increase of 4.2% COHb above initial COHb levels. Results of this study provide evidence that exposure to CO induces earlier onset of angina and ventricular dysfunction as well as poorer exercise performance in patients with ischemic heart disease. As in the earlier study, several patients experienced angina on the CO-exposure day and not on the air-exposure day but never the reverse. "Although the Sheps et al. (1987) and Adams et al. (1988) studies did not observe statistically significant changes in time to onset of angina using conventional statistical procedures, the results of these studies are not incompatible with the rest of the studies reporting an effect of CO." (CD, p. 10-32)

A separate study of the effects of CO exposure was conducted with 26 non-smoking male, angina patients (Kleinman and Whittenberger, 1985; Kleinman et al., 1989). One hour of exposure to 100 ppm CO was sufficient to raise COHb levels to 3.0% (CO-Ox), representing an average increase of 1.5% COHb over initial COHb level. For the group, CO exposure resulted in a decrease in time to onset of angina by 6.9% compared to clean air exposure (Kleinman and Whittenberger, 1985). This was a statistically significant difference ($p=0.03$). Reanalysis, necessitated by dropping two subjects due to inconsistent medical records, resulted in an average decrease of 5.9% ($p=0.046$) in time to onset of angina for CO exposure compared to air exposure (Kleinman et al., 1989). For the eight patients who exhibited depression in the ST segment of ECG traces during exercise there was a decrease of 10% ($p<0.036$) in time to onset of angina and a decrease of 19% ($p<0.044$) in time to onset of ST segment depression.

Allred et al. (1989b, 1991) discuss possible reasons for some differences in results of the above-cited studies. These studies have different designs, types of exercise tests, inclusion criteria (e.g., patient populations), exposure

conditions, and measurement methods for COHb. Of the studies only two (Allred et al., 1989a,b, 1991; Anderson et al., 1973) investigate more than a single target level of COHb, and of those two only Allred et al. (1989a,b, 1991) demonstrate a dose-response effect of COHb on time to onset of angina. Different measurement methodologies for COHb may account for some of the discrepancies between studies. As discussed in Section V.C.1. of this Staff Paper and in the CD (pp. 8-70 to 8-74), only Allred et al. (1989a,b, 1991) used both the GC and CO-Oximeter to measure COHb and found the spread of COHb values to be much greater for the CO-Ox than for the GC. Another difference in the studies was that Allred et al. (1989a,b, 1991) used more rigorous subject entry criteria. All were male subjects, all were required to have stable exertional angina and reproducible exercise-induced ST-segment depression and angina, and all were required to have either a previous myocardial infarction, angiographic disease or a positive thallium test.

The major conclusion which is drawn in the CD regarding all of the studies discussed above is that all ". . . show a decrease in time to onset of angina at postexposure COHb levels ranging from 2.9 to 5.9%. This represents incremental increases of 1.5 to 4.4% COHb from preexposure baseline levels. Therefore, there are clearly demonstrable effects of low-level CO exposure in patients with ischemic heart disease" (CD, pp. 10-34 to 10-35). Across-study comparison is depicted in Figure V-1, which the CD presents (p. 10-33) as an adaptation from Allred et al. (1989b, 1991). For purposes of comparison, optical methods (CO-Ox) are used to avoid confusion. The adverse nature of the effects described in the five key studies is uncertain due to the range of professional judgments on the clinical significance of small performance decrements produced by exercise and CO exposure. Although some physicians may not be greatly concerned about decrements in performance occurring around 3.0% COHb (CO-Ox), consistency across studies of response for both decrease in time to onset of angina and ST-segment depression suggest that the

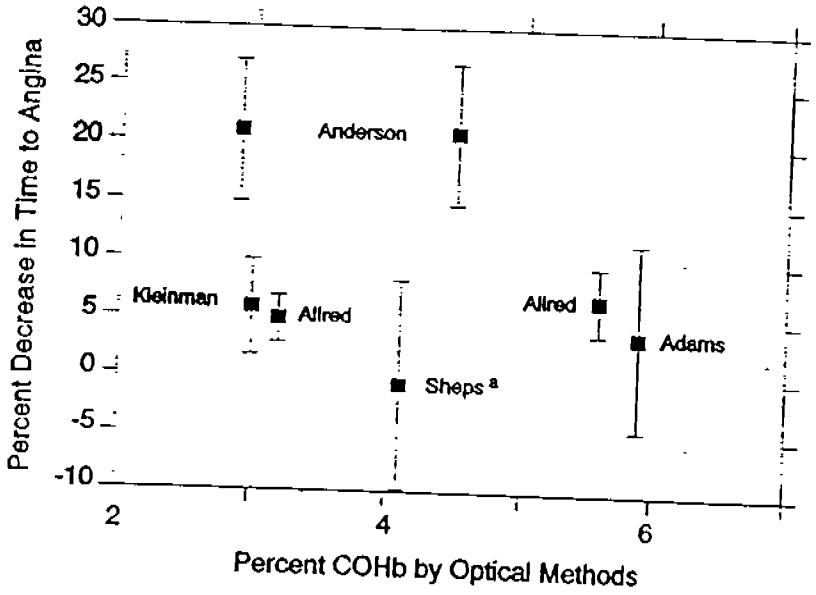

Figure V-1. The effect of carbon monoxide (CO) exposure on time to onset of angina. For comparison across studies, data are presented as mean percent differences between air- and CO-exposure days for individual subjects calculated from each study. Bars indicate calculated standard errors of the mean. Carboxyhemoglobin (COHb) levels were measured at the end of exposure; however, because of protocol differences among studies and lack of precision in optical measurements of COHb, comparisons must be interpreted with caution. (See text and Table 10-2 and Table 10-3 for more details.)

[a]Alternative statistical analyses of the Sheps data (Bissette et al., 1986) indicate a significant decrease in time to onset of angina at 4.1% COHb if subjects that did not experience exercise-induced angina during air exposure are also included in the analyses.

Source: Adapted from Allred et al. (1989b, 1991).

* Figure is a reproduction of Figure 10-3 on page 10-33 of the CD.

effect does occur and may limit activity of persons with ischemic heart disease. Furthermore, Bassan (1990) indicates that 58% of cardiologists believe that recurrent exercise-induced angina attacks are associated with substantial risk of precipitating myocardial infarction, fatal arrhythmia, or slight but cumulative myocardial damage (CD, p. 10-35). Based on discussions in the CD and at the April 30, 1991 CASAC meeting, staff recommends that 2.9 - 3.0% COHb (CO-Ox), representing an increase above initial COHb of 1.5 to 2.2% COHb, be considered a level of potential adversity for individuals at risk.

2. Effects on Exercise Capacity and Oxygen Uptake

Maximal oxygen uptake and maximal exercise capacity are indirect measures of cardiovascular capacity and can provide insight into the impact of CO on the cardiovascular systems of even healthy individuals. Although decreases in these attributes may not be very serious in healthy persons for CO exposures typically found in the ambient air, they can be indicative of the extent to which an individual's ability to function normally may be affected while engaging in activities which require high levels of sustained exercise.

Numerous researchers have studied the effects of CO on oxygen uptake and exercise performance in healthy individuals. Several investigators (Klein et al., 1980; Stewart et al., 1978; Weiser et al., 1978; Ekblom and Huot, 1972; Vogel and Gleser, 1972; Pirnay et al., 1971) found statistically significant decreases (3 to 23%) in maximal oxygen uptake under conditions of short-term maximal exercise at COHb levels ranging from 5 to 20% (CO-Ox). Horvath et al. (1975) found that the lowest level at which COHb marginally influenced maximal oxygen uptake ($p<0.10$) was about 4.3% (CO-Ox); COHb levels of 3.3% and 4.3% (CO-Ox) reduced work time to exhaustion by 4.9% and 7% respectively. Similar results were found following exhaustive treadmill exercise at 5% COHb (CO-Ox) (Stewart et al., 1978; Klein et al., 1980). Short-term maximal exercise duration has been shown to be reduced by 3 to 38% at COHb levels ranging from 2.3 to 7% (CO-Ox)

(Horvath et al., 1975; Drinkwater et al., 1974; Raven et al., 1974a,b; Weiser et al., 1978; Ekblom and Huot, 1972). While these effects may be of only limited concern for healthy individuals, possible impairment of work capacity or of ability to engage in normal activities for persons with respiratory disease should be considered in evaluating whether CO NAAQS provide an adequate margin of safety.

3. Central Nervous System Effects

A variety of central nervous system (CNS) effects have been found to be associated with CO exposures which result in COHb levels of 5 to 20% (CO-Ox). These effects include changes in visual perception, hearing, motor and sensorimotor performance, vigilance, and other measures of neurobehavioral performance.

In a study conducted by McFarland et al. (1944) visual sensitivity was reported to decrease in a dose-related manner at COHb levels ranging from 4.5 to 19.7% (CO-Ox). Subsequent analyses (McFarland, 1970, 1973) were published which suggested that threshold shifts occurred at the end of a CO-exposure period, which resulted in a 17% COHb (CO-Ox) level. However, Hudnell and Benignus (1989) studied dark adaptation and found no difference between CO and air groups, thus leading to the CD (p. 10-108) conclusion that if COHb elevation does affect visual sensitivity, it has not yet been demonstrated.

In other studies, Christensen et al. (1977) failed to find significant vigilance effects at 4.8% COHb (CO-Ox), while Bunnell and Horvath (1988) reported significant impairments in performance at either 7 or 10% COHb (CO-Ox). Critical flicker fusion (CFF) was used as a measure of temporal resolution by estimating a subject's ability to discriminate flashes of light. Even though several studies (Winneke, 1974; O'Donnell et al., 1971a) found CFF not to be affected, Seppanen et al. (1977) and Von Post-Lingen (1964) reported a relationship between decreases of CFF at COHb levels ranging up to 20% (CO-Ox) and higher.

Motor and sensorimotor performance has been investigated using a variety of measures (e.g. fine motor skills, reaction

time, and tracking). Although Winneke (1974) found some effects on steadiness and precision at 10% COHb (CO-Ox), several other investigators (Mihevic et al., 1983; O'Donnell, 1971b; Seppanen et al., 1977) reported no CO effect at COHb levels ranging from 5.5 to 12.7% (CO-Ox). Reaction time was unaffected by COHb levels of 7 and 10% (CO-Ox) (Rummo and Sarlanis, 1974; Winneke, 1974), and the pervasive finding is that COHb elevation does not affect reaction time for COHb levels as high as 20% (CO-Ox) (CD, p. 10-118). Compensatory tracking was not significantly affected by COHb levels of 5.8% (CO-Ox) (Gliner et al., 1983) or by levels of 12 to 13 % (CO-Ox) (O'Donnell et al., 1971); however, tracking tasks were significantly affected by COHb levels of 5% (CO-Ox) (Putz et al., 1976,1979). Results of the Putz et al. (1976) study were confirmed by Benignus et al. (1987) but not by Benignus et al. (1990a) when attempting to demonstrate a dose-effect relationship using the same experimental design. Benignus et al. (1990b) discusses possible reasons for high variability between studies, and the CD (p. 10-121) concludes that COHb elevation produces small decrements in tracking that are sometimes significant.

It can be seen from the discussion above that a wide range of neurobehavioral effects of CO exposure have been investigated but only in healthy young subjects. Even though new information regarding neurobehavioral effects of COHb levels in the range of 5-20% (CO-Ox) has been published during the past decade, conditions under which these effects occur are poorly understood (CD, 10-143). Because neurobehavioral effects have not yet been seen for COHb levels below 5%, (CO-Ox) staff recommends focussing on the cardiovascular effects which have been demonstrated at lower COHb levels. Resulting standards, therefore, should provide an adequate margin of safety against neurobehavioral effects of CO occurring in the exposed population.

4. Developmental Toxicity Effects

Developmental toxicity covers a variety of effects in the developing organism including fetal death, structural

abnormalities, altered growth and functional deficits. The fetus may be particularly vulnerable to the toxic effects of CO exposure because fetal development often occurs at or near critical tissue oxygenation levels (Longo, 1977). COHb levels tend to be naturally elevated in the fetus due to differences in uptake and elimination of CO from fetal hemoglobin.

Human data on developmental toxicity of CO is very limited for obvious ethical reasons. Maternal smoking, however, has been associated with a number of adverse health effects, many of which can be attributed to very high CO exposures (500-1000 ppm) from cigarette smoke. These effects include spontaneous abortion and subsequent fetal death due to depressed birth weight, increased number of hospital admissions during the first 5 years of life, and poorer than predicted school performance during the first 11 years of life. These and other effects of smoking are reviewed in a report to the U.S. Surgeon General (National Institute of Child Health and Human Development, 1979). Current data (Hoppenbrouwers et al., 1981) suggesting a link between environmental CO and sudden infant death syndrome (SIDS) are suggestive, but further study is needed before any causal relationship can be inferred.

Finally, animal studies have provided evidence of fetal mortality, teratogenicity, reduced body weight, morphological changes, altered cardiovascular development, and neurochemical changes. However, animal studies investigating these effects are typically conducted at CO exposures much greater than found in the ambient air, and extrapolation to human health effects remains very difficult. Due to the large uncertainties associated with developmental toxicity effects in humans for ambient CO exposures, staff recommends that these effects be treated as margin of safety considerations.

5. Environmental Factors, Drugs, Other Pollutants

Several additional factors have been investigated for potential interactions with CO that may alter health effects. Among the more important are altitude, drugs, coexposure to other

pollutants and heat stress. Altitude is a matter of concern because of the large populations exposed to CO while living in cities above 1500 m. While there are some data to support the possibility that effects of inhaling CO and effects of high altitude may be additive (Cooper et al., 1985; McDonagh et al., 1986), several studies even at 2,000 m to 4500 m show little or no additivity (McGrath, 1988; Horvath, 1988; Horvath and Bedi, 1989). Most other studies have been conducted at CO levels which are too high to be of regulatory use.

There is evidence that interactions of drug effects with CO toxicity can occur in both directions, i.e., CO toxicity may be enhanced by drug use and toxic or other effects of drugs may be altered by CO exposure. A recent study (Knisely et al., 1989) reported a large interaction of CO exposure and alcohol in mice demonstrating that alcohol doubled the acute toxicity of CO. In the same study CO exposure in combination with administration of barbiturates and other psychoactive drugs produced additive but not synergistic effects. Combined exposures of CO and other pollutants have been investigated primarily using animal subjects with only a few human studies being published. No interaction was observed in humans for CO in combination with common ambient air pollutants such as NO_2, O_3, and PAN (Raven et al., 1974a,b; Drinkwater et al., 1974; Gliner et al., 1975), although a greater decrement in exercise performance was reported in these studies when heat stress was combined with 50 ppm CO. In conclusion, staff recommends that information on CO in combination with other pollutant exposures and environmental stress be treated as a margin of safety consideration.

E. Populations Potentially at Risk to Carbon Monoxide

This section identifies subpopulations most likely to be susceptible to low-level CO exposures based on the health effects evidence reviewed in the revised CD and Section V-D of this Staff Paper. Table V-3 summarizes the population groups at risk to low level CO exposures (i.e., resulting in COHb levels below 5%)

based on current evidence and mechanistic considerations. The table includes the coronary artery disease group, which is most clearly defined as an "at risk" population based on the collection of studies discussed in Section V-D, and other groups which may be more susceptible to CO based on more limited and uncertain evidence and plausible biological mechanisms. Except for persons with ischemic heart disease and peripheral vascular disease, there is little specific experimental evidence to clearly demonstrate increased risk for CO-induced health effects at levels below 5% COHb. However, it is reasonable to expect that individuals with preexisting illness or physiological conditions which limit oxygen absorption or oxygen transport to body tissues would be somewhat more susceptible to the hypoxic (i.e., oxygen starvation) effects of CO. Table V-3 provides population estimates for each subpopulation and a brief summary of why each group is suspected of being more susceptible than average to CO exposures.

The current health effects evidence suggests that the population group at greatest risk from exposure to ambient levels of CO is individuals with stable exercise-induced angina. Given the likely mechanisms of CO effects on the cardiovascular system, individuals with other indications of ischemic heart disease and those with silent ischemia are considered to be similarly at risk for low-level ambient CO exposures.

F. COHb Levels of Concern

In selecting the appropriate level for the primary NAAQS for CO, the Administrator must first determine the COHb levels of concern taking into account a large and diverse health effects data base. The scientific quality and strength of health data are assessed in the CD and in Section V of this Staff Paper. Based on these assessments, judgments are made here to identify those studies that are most useful in establishing a range of COHb levels to be considered in standard setting. In addition, the more uncertain or less quantifiable evidence discussed in

Table V-3. Summary of Subpopulations Potentially At Risk[1]

Group at Risk to Low Level CO Exposures	Rationale	Population Estimates	Percent of U.S. Population[2]	References
Coronary Artery Disease	Strongest evidence is for group with symptomatic angina pectoris, although asymptomatic individuals have limited coronary flow reserve and are likely to be sensitive to CO-induced decrease in O_2 carrying capacity.	Prevalence of diagnosed ischemic heart disease = 7.0 million (in 1989). Prevalence of undiagnosed (silent ischemia) estimated to be 3 to 4 million (in 1989). 1.5 million heart attacks/yr (in 1987) 513,700 heart attack fatalities/year (in 1987)	About 2.9% About 1.4%	DHHS, 1990 American Heart Association, 1989 American Heart Association, 1989 American Heart Association, 1989
Peripheral Vascular Disease	This condition is associated with limited blood flow capacity and should be sensitive to CO exposures.	0.75 million (in 1979)	About 0.3%	DHEW, 1974
Cerebrovascular Disease	This condition is associated with limited blood flow to the brain and may be sensitive to CO exposures.	2.5 million persons (in 1983-1985)	About 1%	DHHS, 1988a
Anemia	O_2 carrying capacity of blood is already reduced increasing likelihood of CO-induced hypoxia effects at lower CO exposure levels than for non-anemic individuals	3.2 million (in 1987)	About 1.3%	DHHS, 1988b
Chronic Obstructive Lung Disease	These subgroups have reduced reserve capacities for dealing with cardiovascular stresses and have reduced O_2 supply in blood which may hasten onset of CO-induced hypoxic effects.	Bronchitis - 11.1 million Emphysema - 2.0 million Asthma - 8.6 million (above for 1983-1985)	About 4.6% About 0.8% About 3.5%	DHHS, 1988
Fetuses and Young Infants	Several animal studies report deleterious effects in offspring (e.g., reduced birthweight, increased newborn mortality, and lower behavioral activity levels).	3.6 million live births per year (1983)	About 1.5%	DHHS, 1990

[1]All subgroups listed are not necessarily sensitve to CO exposure at normal ambient levels.

[2]Percentages were calculated based on 1989 U.S. population base of 243.5 million and assumed the absolute numbers in the previous column were the same for 1989. Neither the absolute numbers nor the percentages can be added because of significant overlap among these groups.

Section V are reviewed to determine the lower end of the range that would provide an adequate margin of safety from effects of clear concern. Those judgments relevant to the establishment of an appropriate range of COHb levels are summarized below.

1. Cardiovascular effects, as measured by decreased time to onset of angina pain and by decreased time to onset of significant ECG ST-segment depression, are judged to be the health effects of greatest concern which clearly have been associated with CO exposures at levels observed in the ambient air. Decrease in time to onset of exercise-induced angina pain is well documented in studies of angina patients whose postexposure COHb levels have been raised to 2.9-5.9% (CO-Ox), which represents incremental increases of 1.5 to 4.2% COHb from baseline levels (Allred et al., 1989a,b, 1991; Kleinman et al., 1989; Adams et al., 1988; Sheps et al., 1987; Anderson et al., 1973). Figure V-1, depicted earlier in Section V, shows consistency between percent of time to onset of angina and COHb levels for each of the five studies. Time to onset of significant ECG ST-segment change, which is indicative of myocardial ischemia in patients with documented coronary artery disease and a more objective indicator of ischemia than angina pain, provides supportive evidence of health effects occurring as low as 2.9-3.0% COHb (CO-Ox). In light of the above data and discussions of adverse health consequences in the CD (p. 10-35) and at the April 30, 1991 CASAC meeting, staff concludes that CO exposures resulting in COHb levels of 2.9-3.0% (CO-Ox) or higher in persons with heart disease has the potential to increase the risk of myocardial ischemia, an adverse health effect. It is important that standards be set which appropriately reduce the risk of ambient exposures which may produce such COHb levels.

2. Clinical importance of cardiovascular effects associated with exposures to CO resulting in COHb levels of 2 to 3% remains uncertain. Although one recent study (Allred et al., 1989a,b) provides evidence of a 5.1% decrease in time to ST-segment depression at 2.0% COHb when using the GC, health significance of

this effect is more uncertain than at higher COHb levels. Several earlier studies (Aronow, 1981; Aronow and Isbell, 1973; Aronow et al., 1974) reported that aggravation of angina and peripheral vascular disease may occur at COHb levels as low as 2%; however, only limited use should be made of them because "...results of Aronow's studies did not meet a reasonable standard of scientific quality and, therefore, should not be used by the Agency in defining the critical COHb level at which adverse health effects of CO are occurring." (CD, p. 10-24). It is, therefore, recommended by staff that results suggesting cardiovascular effects in angina patients when COHb levels are between 2.0 and 2.9% be considered by the Administrator in evaluating whether the current CO standards provide an adequate margin of safety.

3. Elevated COHb levels in exercising, healthy, young persons affect exercise performance and reduce oxygen uptake. Numerous studies (Drinkwater et al., 1974; Ekblom and Huot, 1973; Horvath et al., 1975; Raven et al., 1974; Weiser et al., 1978) provide evidence of decreased short-term maximal exercise duration (3-38%) in healthy young males when COHb levels are in the range of 2.3-7.0% (CO-Ox). Submaximal exercise for short periods of oxygen uptake was not affected by COHb levels of 15-20% (CO-Ox) (Raven et al., 1974); however, under conditions of short-term maximal exercise, maximal oxygen uptake was decreased significantly (3-23%) when COHb levels ranged from 5-20% (CO-Ox) (Klein et al., 1980; Stewart et al., 1978; Weiser et al., 1978; Ekblom and Huot, 1972). Although these effects may not be of clear health significance in the healthy population, possible impairment of work capacity of individuals with respiratory illness should be considered in evaluating whether CO standards provide an adequate margin of safety.

4. <u>There are several other factors which staff believes should be considered in evaluating the adequacy of the current CO NAAQS</u>.

(a) The wide range of human susceptibility to CO exposures and ethical considerations in selecting subjects for experimental purposes together suggest that the most sensitive individuals have not been studied.

(b) Animal studies of developmental toxicity and human studies of the effects of maternal smoking provide evidence that exposure to high concentrations of CO can be detrimental to fetal development, although very little is known about the effects of ambient CO exposures on the developing fetus.

(c) Although little is known about effects of CO on potentially sensitive populations other than those with cardiovascular disease, staff believes there is reason for concern about visitors to high altitudes, individuals with anemia or respiratory disease, and the elderly.

(d) Impairment of visual perception, sensorimotor performance, vigilance or other CNS effects has not been demonstrated to be caused by CO concentrations commonly found in the ambient air; however, short-term peak CO exposures may be responsible for impairments which could be a matter of concern for complex activities such as driving a car.

(e) Limited evidence suggests concern for individuals exposed to CO concurrently with drug use (e.g. alcohol), during heat stress, or coexposure to other pollutants.

(f) Large uncertainties remain regarding modelling COHb formation and estimating human exposure to CO which could lead to over or underestimation of COHb levels in the population associated with attainment of a given CO NAAQS.

(g) COHb measurements made using the CO-Ox may not reflect COHb levels in angina patients studied, thereby creating uncertainty in establishing a lowest effects level for CO.

In summary, staff concludes that the lowest COHb level at which adverse effects have been demonstrated in persons with

angina is around 2.9-3.0%, representing an increase of 1.5% above baseline when using the CO-Ox to measure COHb. These data serve to establish the upper end of the range of COHb levels of concern. Taking into account uncertainties in the data, the less significant health end points and less quantifiable data on other potentially sensitive groups, staff recommends that the lower end of the range be established at 2.0% COHb. Below this level, the potential for public health risk appears to be small.

VI. AVERAGING TIMES

When the EPA promulgated CO primary NAAQS on April 30, 1971 (36 FR 8186), two averaging times -- 1-hr and 8-hr -- were selected. The 8-hr standard was chosen because most individuals, even at rest, appear to approach equilibrium levels of COHb after 8 hr of exposure. In addition the 8-hr period approximates blocks of time for which people are often exposed in a particular location or activity (e.g. sleeping, working) and provides a good indicator for tracking continuous exposures that occur during any 24-hr period. The 1-hr standard was chosen because a 1-hr averaging period provides a better indicator of short-term health effects of CO. The 1-hr standard provides reasonable protection from effects which might be encountered from very short duration peak (bolus) exposures in the urban environment. Review of current scientific information in the CD indicates that these reasons for choosing averaging times for the CO standards remain valid and there are no compelling arguments for selecting new or different averaging times. It is, therefore, recommended by staff that both averaging times be retained for primary CO standards.

VII. EXPOSURE ANALYSIS

A. Overview

This section discusses an exposure analysis intended to provide estimates of CO exposure and their resultant COHb levels for people living in one city for different exposure scenarios. The analysis provides a basis for assessing protection afforded by the current CO standards and preliminary insight into the relative impact of certain indoor sources to total CO exposure, at least for Denver, Colorado, the city chosen for analysis. Denver was chosen because (1) in 1988 it violated both the current 1-hr and 8-hr CO NAAQS (one of only two areas that exceeds both standards; see Section IV.B), (2) it has a relatively high 8-hr design value, 16.2 ppm--the second-highest design value in the U.S., and (3) CO personal monitoring data are available for a rough validity check of the modeling effort. The four scenarios relate to (1) current air quality versus future air quality associated with just-attaining the 8-hr CO NAAQS, and (2) common indoor sources present versus ambient air without internal sources. Only the 8-hr NAAQS is evaluated since previous analyses indicate that it is the controlling standard from a control strategy development viewpoint (EPA, 1979b). In the current analysis indoor sources that are removed include only residential gas stoves and passive smoking. Other indoor sources, such as running automobiles in private or public garages and CO intrusion into a motor vehicle from the vehicle itself, are not removed from the analysis; their inclusion affects the exposure results.

The model used for exposure analysis is a new version of the CO NAAQS Exposure Model (NEM); see Johnson et al. (1992). Because the new version incorporates Monte Carlo sampling and multiple runs, or realizations, of the model, it is known as pNEM/CO (probabilistic NEM applied to CO).

The major model outputs of interest are estimates of the number of person-days of exposure to various CO levels for the four scenarios mentioned above for adults with cardiovascular

disease in Denver. In addition, estimates also are made of the percentage of the cardiovascular heart disease population in Denver that would exceed selected COHb levels one or more times per year under the four scenarios. These latter estimates are derived by applying a modified version of the CFK equation (see the next Section and Appendix C for a discussion of the new CFK model used in pNEM/CO). It is estimated that there are about 36,800 non-smoking people in Denver with diagnosed or undiagnosed (silent) ischemia. Some of these are children <18 years of age. Excluding them results in a "sensitive population" estimate in Denver of about 36,645 non-smoking adult persons. See Appendix B for a description of model mechanics, cohorts, and microenvironments. Staff does not know to what extent findings of this analyses can be generalized to other U.S. urban areas. It always is speculative to make inferences to a population from a sample size of one, even if that sample is almost the "worst case" as Denver is with respect to ambient CO concentrations. In addition, the functional relationships developed to relate CO monitoriong values to outside-the-microenvironment concentrations rely heavily on the 1982-83 personal monitoring data available in Denver. (The only other place these data exist is in Washington, DC or the same time period.) The "transferability" of these functional relationships is unknown at the present time.

B. Estimating COHb Levels in Exposed Populations

As discussed earlier in this staff paper, the most relevant indicator for evaluating the potential for being at risk to CO-induced health effects is the distribution of blood COHb levels in sensitive populations. The original CO-NEM (Johnson and Paul, 1983) used the CFK model (see Section V.C.2 of this Staff Paper) to estimate population COHb levels for the exposed population. The new exposure analysis also contains a module for computing COHb blood level distributions in exposed populations. The COHb module in pNEM/CO uses the nonlinear solution to the CFK differential equation and assumes a linear relationship between

O_2Hb and COHb. With the assumption of a linear relationship between O_2Hb and COHb there is an analytical solution to the CFK equation (Muller and Barton, 1987). A brief summary of the COHb module used in pNEM/CO is given in Appendix C. A more detailed discussion of how Muller's solution is used to estimate COHb levels within pNEM/CO can be found in Biller and Richmond (1992) and Johnson et al. (1992).

C. Results

Summary results of pNEM/CO exposure modeling appear as Tables VII-1 through VII-3. All three tables focus on the number and relative amount of person-days or person-hours of exposure above specified CO levels or above specified COHb percentages. A person-hour of exposure to 9 ppm, for instance, means that one person is exposed to 9 ppm for one hour. One hundred person-hours of exposure to 9 ppm could mean that 100 people are exposed for 1 hour; 1 person is exposed for 100 hours; or any combination of people exposed and hours of exposure that when multiplied, equals 100. (Ten people each exposed 10 times to 9 ppm is one example.)

Our estimates must be expressed in terms of person-hours (or person-days) because the human activity data base used to model activities is in the form of single days of activity that are "strung together" to represent population cohorts. Thus, the "sampling frame" used in pNEM/CO is a person-day comprised of 24 person-hours, and inferences can thus be made only to person-days or person-hours of exposure. See Appendix B for additional discussion of this point.

As shown in the tables, between 21 and 25 runs of pNEM/CO were made for each of four scenarios. Unfortunately, these are not adequate to obtain tight distributions for the relatively extreme values of interest (i.e., % of person-days $\geq$2.1% COHb). Many of the distributions are generally log-normal in shape and are quite "lumpy." If more runs were made, distributions would become more normalized and "smoother." The practical impact of

this is that nonparametric tests have to be used to compare scenario results, rather than the "usual" tests only suited for random samples from normal distributions.

Table VII-1 presents model results relating to the relative percentage of person-days of exposure to the adult population with heart disease in Denver that would experience air quality concentrations associated with the four scenarios. Remember that the two "just attain" scenarios relate only to attainment of the current 8hr NAAQS of 9 ppm. Four air quality indicators are evaluated:

1-hour daily maximum (1hDM) $\geq$35 ppm

8-hour DM (8hDM) $\geq$9ppm

8hDM $\geq$12 ppm

8hDM $\geq$15 ppm

In all cases, the mean and its 95th percentile confidence interval (C.I.) are presented. If the mean is statistically different than 0 (at a $p \leq 0.05$), it is noted with an @. If the statistic is less than 0.05% (in the case of Table VII-1) but is not 0, the * symbol is used.

The data presented in Table VII-1 indicate that attaining the current 8-hr CO NAAQS greatly reduces the estimated median number and percentage of person-days of exposure to the various 1-hour and 8-hour CO indicators used. The relative reduction from the "as is/all-sources" scenario is approximately 90% for the 1-hr indicators and nearly 100% for the three 8-hr indicators. These percentage reductions hold for both "attain" scenarios: with and without the two internal sources that were explicitly analyzed--gas stoves and passive smoking. Thus, the data presented in Table VII-1 indicate that attaining the current 8-hr NAAQS, and consequently the current 1-hr NAAQS, apparently will result in virtually all persons with heart disease in the study area receiving CO exposures at or below ambient air quality concentrations of concern.

A Kolmogorov-Smirnov (K-S) test of the two "all sources" scenarios was undertaken to determine if attaining the 8-hr CO

Table VII-1

HEART DISEASE PERSON-DAYS WITH
ONE OR MORE 1H AND 8H DAILY MAXIMUM (DM) EXPOSURES
≥CONCENTRATION LEVEL SHOWN FOR FOUR ALTERNATIVE SCENARIOS
(Any Exercise Level)

	"As Is" Air Quality		"Just Attain" Air Quality	
Exposure Indicators	Ambient Air and Internal CO Sources	Ambient Air w/o Certain Internal Sources	Ambient Air and Internal CO Sources	Ambient Air w/o Certain Internal Sources
1hDM≥35ppm				
Median P-D	67,000	65,900	7,300	6,900
Mean Percent	0.50@	0.49@	0.058@	0.052@
95% C.I.	±0.02	±0.03	±0.007	±0.004
8hDM≥9ppm				
Median P-D	634,300	565,900	1,300	500
Mean Percent	4.75@	4.19@	0.011@	0.004@
95% C.I.	±0.07	±0.06	±0.003	±0.001
8hDM≥12ppm				
Median P-D	113,600	91,900	130	30
Mean Percent	0.89@	0.69@	0.002@	0.001@
95% C.I.	±0.05	±0.02	±0.001	± *
8hDM≥15ppm				
Median P-D	23,200	14,800	10	0
Mean Percent	0.17@	0.11@	*	*
95% C.I.	± *	±0.01	±*	± *
Number of Runs	21	25	23	22

Notes: *: Less than 0.0005% (but not 0).
NA: Not applicable
@: Reject H_o that $\mu = o$ at $p \leq 0.05$
P-D: Person-days of exposure

air quality standard significantly reduced exposures. It does so for all of the exposure indicators shown in Table VII-1. When the K-S test is applied to the sources/no sources scenarios for the "as is" air quality situation, however, not all exposure estimates are statistically different. The three 8hDM exposure estimates are different, but the 1hDM estimates are not (DN = 0.19, ~ p>0.99).

These estimates--and those that follow--have to be used with caution. The validation effort of pNEM/CO described in Johnson et al. (1992) indicates that the model replicates the 1hDM distribution of person-days of exposure fairly well. It also replicates the 8hDM distribution fairly well between the 30th and the 95th percentile levels, but underestimates higher percentile CO concentrations and overestimates lower percentile concentrations. The main reason for the tails of the distribution being different than the monitored data is that the cohort-sampling method of obtaining activity-days (see Appendix B) conflates together people having systematically low CO exposures due to their lifestyle with people having systematically high CO exposures within a particular cohort. Thus, we "lose" the person who systematically cooks for long periods of time using a gas stove. We "lose" the person who consistently spends a lot of time in smoky indoor areas, such as a tavern, or in high CO microenvironments, such as a service station or garage. These people have some probability of being included in our modeling effort, but not often enough to affect the high tail of the person-days of exposure distribution. This must be recognized as a shortcoming of the modeling effort, but there is little alternative to proceeding in the way that we do since year-long human activity data are not available. In fact, such data are likely never to be available, since people would have to account for their activities for an entire year rather than the day or two that they now report on. The reporting burden is too great to ensure cooperation for that length of

time. All exposure modeling efforts face this shortcoming whether or not they acknowledge it explicitly.

The next pNEM/CO series of outputs are depicted in Table VII-2. The indicator of interest is a surrogate measure of CO dose received by exposed individuals--the percentage of COHb in blood. Five COHb levels are analyzed, based on the range discussed in Section V and taking into account those used in past CO NAAQS regulatory actions: 2.1, 2.3, 2.5, 2.7, and 3.0 percent (30 FR 37484). The body of Table VII-2 depicts (1) the median estimate of the number of adult heart disease person-days with at least one hourly COHb $\geq$ the COHb value depicted, and (2) the relative percentage of total heart disease person-days that these estimates represent. There are 13,412,070 total person-days that were modeled (36,645 adults estimated to have heart disease times 366 days).

The absolute estimates of the number of person-days above specified COHb levels are quite large for the lower COHb percentages under the "as is" scenario. Even these estimates are relatively small, however, due to the large base of 13.4 million total person-days. For instance, Table VII-2 shows an estimate of 63,300 person-days $\geq$ 2.1% COHb, but this amounts to only 0.5% of total possible person-days in the Denver heart disease cohort. When the 8-hour DM NAAQS is attained, we only expect 100-200 or so person-days of exposure at a COHb $\geq$2.1%; this is fewer than 0.002% of total person-days in the Denver group.

Attainment of the 8-hr CO NAAQS has a statistically significant impact on COHb estimates. All of the "attain" estimates are significantly lower than their counterpart "as is" estimates using a K-S test of the distribution at ~$p<0.05$. In fact, removing selected indoor sources (gas stoves and passive smoking) also reduces COHb estimates significantly for the "as is" scenario except for the $\geq$3% COHb indicator. The $\geq$3% estimates--small to begin with--are not statistically different (DN = 0.22, ~$p>0.99$). The relative reductions in COHb person-days are between 24-36% for the remaining COHb levels when the

Table VII-2

HEART DISEASE PERSON-DAYS WITH AT LEAST ONE HOURLY COHb ESTIMATE ≥VALUE SHOWN FOR FOUR ALTERNATE SCENARIOS (Any Exercise Level)

Exposure Indicators	"As Is" Air Quality: Ambient Air and Internal CO Sources	"As Is" Air Quality: Ambient Air w/o Certain Internal Sources	"Just Attain" Air Quality: Ambient Air and Internal CO Sources	"Just Attain" Air Quality: Ambient Air w/o Certain Internal Sources
COHb ≥2.1%				
Median P-D	63,300	42,600	200	100
Mean Percent	0.46@	0.32@	0.002@	0.001@
95% C.I.	±0.03	±0.01	±0.001	±0.001
COHb ≥2.3%				
Median P-D	26,800	17,700	80	20
Mean Percent	0.20@	0.13@	0.001@	*@
95% C.I.	±0.02	±0.01	±0.001	±*
COHb ≥2.5%				
Median P-D	11,900	7,600	30	10
Mean Percent	0.09@	0.06@	*@	*@
95% C.I.	±0.01	±0.01	±*	±*
COHb ≥2.7%				
Median P-D	4,600	3,500	0	0
Mean Percent	0.04@	0.03@	*	*@
95% C.I.	± *	± *	±*	±*
COHb ≥3.0%				
Median P-D	1,600	1,700	0	0
Mean Percent	0.01@	0.018	*	*
95% C.I.	± *	± *	±*	±*
Number of Runs				

Notes:
*: Less than 0.0005% (but not 0).
NA: Not applicable
@: Reject H_o that $\mu = 0$ at $p \leq 0.05$
P-D: Person-days of exposure

"w/o certain internal sources" case is compared with the "internal sources included" scenario. Thus, these two types of internal sources play an important, but not dominant, role in total CO exposure.

The final pNEM/CO result table is Table VII-3. It depicts the absolute number and relative percentage of adult heart disease person-hours that exceed the depicted COHb indicators for the four scenarios. There are 321,889,680 adult heart disease person-hours in Denver (36,645 x 366 x 24 hours/day).

Compared with the large base of 322 million person-hours, the absolute and relative estimates shown in Table VII-3 are quite small for all scenarios. Most of the estimates are significantly different than 0 except for those associated with the "just attain" scenarios for the higher COHb percentages. Excluding gas stove and passive smoking indoor sources reduces person-hours of COHb $\geq$2.1% and COHb $\geq$2.3% by 41% for the "as is" air quality case. The comparable figure for the "attain" case is 59% and 73% for the respective COHb values. However, the absolute estimates for the "attain" air quality situation are very small (e.g., <300 person-hours). Again, the relatively large reductions in COHb levels due to removal of certain indoor sources indicates that these sources play an important role in total CO exposure. The limited ability of an ambient standard to affect CO exposures from these sources should be recognized.

As previously noted, estimates of CO emitted from indoor sources are based on limited data. Therefore, CO exposure and COHb estimates associated with these sources should be viewed cautiously. While we used the best data available from the Gas Research Institue on gas stove usage, we have not fully captured the upper end of the usage pattern in pNEM/CO. We also have not captured the distribution of CO concentrations associated with passive smoking in indoor microenvironments.

While uncertainties associated with indoor sources are important for estimating total CO exposure, they are less important in reaching judgments regarding a CO NAAQS because

Table VII-3

HEART DISEASE PERSON-HOURS WITH AN 1H COHb ESTIMATE
≥VALUE SHOWN FOR FOUR ALTERNATIVE SCENARIOS
(Any Exercise Level)

Dose Indicators	"As Is" Air Quality		"Just Attain" Air Quality	
	Ambient Air and Internal CO Sources	Ambient Air w/o Certain Internal Sources	Ambient Air and Internal CO Sources	Ambient Air w/o Certain Internal Sources
COHb ≥2.1% Median P-H	176,800	104,300	270	110
Mean Percent	0.050@	0.033@	*@	*@
95% C.I.	±0.004	±0.002	±*	±*
COHb ≥2.3% Median P-H	63,100	37,200	110	30
Mean Percent	0.019@	0.012@	*@	*@
95% C.I.	±0.002	±0.001	±*	±*
COHb ≥2.5% Median P-H	22,600	15,000	40	10
Mean Percent	0.007@	0.005@	*	*@
95% C.I.	±0.001	±0.001	±*	±*
COHb ≥2.7% Median P-H	8,200	6,800	0	0
Mean Percent	0.003@	0.002@	*	*
95% C.I.	± *	± *	±*	±*
COHb ≥3.0% Median P-H	2,900	2,400	0	0
Mean Percent	0.001@	0.001@	*	*
95% C.I.	± *	± *	±*	±*
Number of Runs	21	25	23	22

Notes:
*: Less than 0.00005% (but not 0).
NA: Not applicable
@: Reject H_o that $\mu = 0$ at $p \leq 0.05$
P-H: Person-hours of exposure

passive smoke and gas stove emissions are not affected by alternative NAAQS levels. The focus of this Staff Paper is not to establish the need for controlling indoor sources but for assessing the adequacy or need for revision of the CO NAAQS.

In conclusion, results from the Denver exposure analysis indicate that the current 8-hr CO standard, if attained, provides adequate protection against ambient exposures to CO. This is true for attainment of the current 1-hr CO NAAQS also, since it is attained when the 8-hr NAAQS is attained. The analysis also reveals that indoor sources of CO exposures that cannot be mitigated by a NAAQS play a role in total CO exposure. Given uncertainties in the database used to estimate indoor source contributions, however, this finding must be viewed with caution.

VIII. SUMMARY OF STAFF CONCLUSIONS AND RECOMMENDATIONS

This summary of staff conclusions and recommendations draws upon the discussions in Section V, VI, and VII of this paper. The key findings are:

1) The staff concludes that the lowest COHb level at which adverse effects have been demonstrated in small populations of persons with angina is around 3.0% as measured by CO-Ox. In these populations, post-exposure COHb levels represent an increase of about 1.5% above baseline. These data serve to establish the upper-end of the range of COHb levels of concern for people with coronary artery disease. Taking into account uncertainties in the data, the less significant health end points, and the less quantifiable data on other potentially sensitive groups, staff recommends that the lower-end of the range be established at 2.0% COHb. Below this level, the potential for public health risk appears to be small, if any.

Based on this assessment, and considering the 1985 review of similar CO effects and effects levels, staff recommends that the evaluation of adequacy of the current CO standards should focus on reducing the number of individuals with cardiovascular disease from being exposed to CO levels in the ambient air that would result in COHb levels of 2.1% or greater. Standards that protect against COHb levels at the lower end of the range should provide an adequate margin of safety against effects of uncertain occurrence as well as those of clear concern that have been associated with COHb levels in the upper-end of the range.

2) The staff again recommends that both the 1-hr and 8-hr averaging times be retained for the primary CO standards.

3) Based on the exposure analysis results described in Section VII, staff concludes that relatively few people of the cardiovascular sensitive population group analyzed will experience COHb levels $\geq$2.1% when exposed to CO levels in the absence of indoor sources when the current ambient standards are attained. The analysis also suggests, however, that certain

indoor sources (e.g. passive smoking; gas stove usage) contribute to total CO exposure. In addition, other indoor CO sources such as wood stoves and fireplaces also contribute to total CO exposure, but they were not explicitly modeled. While the contribution of indoor sources cannot be effectively mitigated by ambient air quality standards, these sources of exposure may be of concern for such high risk groups as individuals with cardiovascular disease, pregnant women, and their unborn children.

The potential contribution of indoor sources to total CO exposure should be examined in greater detail outside the context of the NAAQS review. Such an examination should address all potential indoor sources of CO exposure in greater detail than could be accomplished within this NAAQS review. Until such a detailed review is complete, results of the exposure analysis concerning indoor exposures should be viewed as being preliminary.

In conclusion, based on its assessment of the available scientific and technical information, staff recommends that the current 1-hr (35 ppm) and 8-hr (9 ppm) primary standards be reaffirmed.

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APPENDIX A

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

EPA-SAB-CASAC-91-015

July 17, 1991

OFFICE OF
THE ADMINISTRATOR

The Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Dear Mr. Reilly:

At a public meeting held on April 30, 1991, the Clean Air Scientific Advisory Committee (CASAC) completed its review of the draft EPA Air Quality Criteria for Carbon Monoxide dated March 1990. The Committee unanimously concluded that this document, with minor revisions (currently being incorporated by ECAO Staff), provides a scientifically balanced and defensible summary of the current knowledge of the effects of this pollutant and provides an adequate basis for the EPA to make a decision as to the appropriate primary NAAQS for carbon monoxide.

The first external review draft of this document was released for public comment on April 30, 1990 with the comment period ending on July 31, 1990. CASAC is pleased with the responsiveness of ECAO in producing a comprehensive, well-written document to support Agency decision-making. For the record, I have attached brief responses to the major issues which were addressed in the Committee charge.

The CASAC is ready to review the Staff Paper on Carbon Monoxide as soon as it is available. The Committee urges the Agency to move forward as rapidly as possible with completion of the Staff Paper and, ultimately, the issuance of a reaffirmed or revised NAAQS for carbon monoxide based on the current scientific data.

We appreciate the opportunity to present our views on this important environmental health issue.

Sincerely,

Roger O. McClellan

Roger O. McClellan
Chairman, Clean Air
Scientific Advisory Committee

Attachment

Clean Air Scientific Advisory Committee
Review of
Draft Air Quality Criteria for Carbon Monoxide

On April 30, 1991, the Clean Air Scientific Advisory Committee convened to review the draft document Air Quality Criteria for Carbon Monoxide, dated March 1990. Development of this document stems from requirements of section 108 of the Clean Air Act. This section requires that the Administrator identify pollutants that may reasonably be anticipated to endanger public health or welfare and to issue air quality for them. These criteria must incorporate the latest scientific information available to indicate the type and extent of identifiable effects that may occur from exposure to the pollutant in ambient air.

Section 109 of the Act requires periodic review/revision of existing criteria and standards. If the Administrator concludes that the revised criteria make appropriate the proposal of new standards, such standards are to be promulgated in accordance with section 109(b). Conversely, if the Administrator concludes that the revisions to the standards are unnecessary, they remain unchanged.

In accordance with the Clean Air Act, EPA's Environmental Criteria and Assessment Office is revising the criteria for carbon monoxide, incorporating new data which have become available since the completion of the last criteria document (1979) and the addendum to that document (1984).

The draft carbon monoxide document review consisted of a chapter by chapter review and focused on addressing the following issues:

1) What method of analysis of blood carboxyhemoglobin levels, optical or gas chromatography, should be used to determine lowest observed adverse effect levels for CO? Should end-exposure or end-exercise COHb levels be used as an input to the exposure models of COHb formation developed by Coburn, Foster and Kane?

Due to the large amount of variability in spectroscopic measurement of carboxyhemoglobin by CO oxymeters, gas chromatography should be the method of choice.

Coburn-Foster-Kane-based models yield the expectant net increase in COHb for a given exposure to CO (concentration and duration), and the level of activity/exercise (alveolar ventilation and diffusing lung capacity for CO). Input to the model requires the preexposure COHb level, with the post exposure level

predicted by the model. The model does not accurately predict the rate of appearance of COHb at the blood sampling point because of the lag in the delivery of CO due to lung washing and blood circulation factors.

2) How important is tissue action of CO, given the likelihood of typical ambient exposures of the population to low levels of CO for 1 to 8 hours in duration?

Although it is difficult to expand on the information contained within the document, it should be noted that elevated levels of CO, particularly from bolus exposures, may potentially affect the electron transport chain. Also, some studies conclude that CO dissolved in plasma is more dangerous than elevated COHb levels. Low levels of dissolved CO may be significant in cellular respiration.

3) What fraction of the total population with ischemic heart disease (IHD) is represented by the study populations used in the recent key clinical investigations of Sheps, et al. (1987), Adams et al. (1988), Kleinman et al. (1989) and Allred et al. (1989)?

The study by Allred et al. and the Coronary Artery Surgery Study (CASS) provide a wide representation of patients with ischemic heart disease., and the CASS study is a good source of information on the variability of characteristics of IHD (almost 25,000 patients enrolled). All subjects studied for the effects of CO fall within this variability.However, since no Coronary Artery Disease (CAD) registry was developed for the CO studies, coupled with the change in characterization of CAD in recent years, it is difficult to assess the representativeness of the study populations.

4) Were appropriate statistical analyses used in the key studies on subjects with IHD? Should there be a more rigorous comparison of statistical approaches , including discussion of primary versus secondary analyses, use of trimmed or non-trimmed means, and choice of one- or two-tailed tests of significance? Could other formal techniques (meta-analysis) be used to provide a better assessment of data?

The analyses provided in the document were adequate and appropriate. In general statistical analyses need not be uniform, but should be tailored to the data being collected, and the distinction between one- and two-tailed tests is insignificant. Meta-analysis is useful, but graphic presentations such as those provided in figure 10-2 are satisfactory. However, error bars should be highlighted and made a common basis for data presentation.

5) Could differences in the study designs utilized in the key studies on the subjects with Ischemic Heart Disease account for some of the differences in the results?

It is unlikely that variations in study design resulted in variations in results. The protocols for each study are described in sufficient detail and the authors have done an excellent job of presenting and interpreting the results.

6) Are the small changes reported in the key studies on subjects with Ischemic Heart Disease of clinical significance? What is the definition of an adverse health effect in this population?

There is a wide distribution of opinion concerning this issue. The panel agrees that the effects observed at these levels are small performance decrements and that they are consistent across the populations studied. It is important to note that the ST segment changes and decrements in the time to onset of angina appear to be a consistent response to low levels of CO exposure. Among health professionals there is a range of views as to the clinical significance of these changes with the dominant view being that the changes should be considered as adverse or a harbinger of adverse effects.

APPENDIX B

Appendix B

Overview of Exposure Analysis Model

The exposure analysis simulates CO pollutant concentrations in "microenvironments" (defined below) which people enter as they go through their daily lives. In pNEM/CO, people are represented by a set of eleven demographic groups that are based upon age, sex, occupation, and commuting breakdowns. These groups are further subdivided into "cohorts" that have a distinct combination of: home district, work district (if applicable), and type of residential cooking fuel (natural gas or not). These subdivisions are used because the personal exposure monitoring (PEM) study conducted in 1983 in Denver (Johnson et al., 1984) indicated that these factors contribute significantly to personal CO exposure.

Home and work districts are defined by U.S. Census tract data on where people live and work in Denver. Ambient air quality for each district is defined by "transformed" ambient air quality data monitored at fixed-site stations located in each district.

Cohort daily activities are simulated by sampling from human activity data obtained in Denver, Washington (DC), and Cincinnati. These human activity data bases were combined for pNEM/CO modeling purposes to increase the number of diary-days of data available for analyses. In addition, using all three studies provides more seasonal variation in activities than use of the Denver study alone provides. The human activity data are in the form of a "person-day" of activities specific to the demographic group and cohort being modeled. Since the modeling "sampling frame," so to speak, is a person-day, inferences to the total Denver population CO exposures associated with the air quality scenarios are most appropriately made only to "person-days" or "person-hours" of exposure.

Space is disaggregated into 13 "microenvironments" in pNEM/CO. A microenvironment is a defined location into which a person enters and remains for at least 1 minute. The 13 microenvironments include two related to residences (inside a home and inside a residential garage). There are five microenvironments related to non-residential buildings (generally: auto service stations, malls, offices, schools, and "other"), three outdoor microenvironments (generally: near-road, non-residential garage, and "other" outdoor), and two in-vehicle microenvironments (automobile and "vehicle-other").

Two additional data items are defined for most microenvironments: the type of activity that occurs within that environment and the presence or absence of passive smoking. In the "inside-a-home" microenvironment, these two data items are supplemented by whether or not a gas stove is used for cooking when people are at home. Gas stove usage results in somewhat higher indoor CO levels and it is a common source, so it was explicitly modeled in pNEM/CO. Other sources of CO indoors--such as space heaters and internal combustion engines--are not explicitly considered in pNEM/CO.

The type of activity undertaken in each microenvironment is addressed in pNEM/CO by the "ventilation rate", or breathing rate associated with cohort-specific activities. Four different ventilation rates are used: sleeping, slow, medium, and fast.

CO concentration estimates for outdoor microenvironments are obtained from "transformed" fixed-site monitoring data for the "as is" air quality scenarios. For the "just attaining" scenario, a modified rollback procedure is used to adjust the already transformed hourly fixed-site data. Both processes are further defined in Johnson et al. (1992).

CO concentration estimates for all non-vehicle, indoor microenvironments are obtained by solving a mass-balance equation following Nagda et al. (1987). This equation requires that a

number of variables be estimated in order to solve for microenvironmental CO concentration. Included are: hourly air changes per hour (ACH), indoor CO generation rate, effective volume of the microenvironment, and net CO removal/decay rate. Values for a number of these variables are obtained via Monte Carlo sampling from distributions obtained from the literature on measured values of the specified variables. See Johnson et al. (1992) for a complete discussion of the variables defined by this sampling procedure.

While Monte Carlo sampling allows OAQPS to explicitly address uncertainty inherent in estimating personal exposure to an ambient pollutant, it also places a large burden on the analyst to obtain data for variables that are not much studied. This situation exists, in particular, for many variables that affect estimates of indoor sources of CO, including gas stove and passive smoking concentrations. A number of assumptions are made in order to explicitly model these sources. While Johnson et al. (1992) were able to estimate CO from indoor sources, additional information most likely exists that will improve these estimates. Staff will solicit information during the public review process of this paper to allow us to further refine the exposure analysis, as appropriate. While uncertainties associated with indoor sources are important for estimating total CO exposure, they are less important in reaching judgments regarding NAAQS because passive smoke and gas stove emissions are not affected by alternative NAAQS levels.

It should be recognized that even though pNEM/CO explicitly addresses many sources of uncertainty in exposure modeling, not all sources of uncertainty are addressed. One of these is the "rollback" procedure used to estimate CO air quality associated with just-attaining the current 8-hr 9 ppm CO NAAQS. Another is the set of factors used to relate outdoor CO concentrations to fixed-site monitor concentrations. (See Johnson et al., 1992

for a discussion of these issues.) Again, if Staff receives information during the public review process on these--or other--sources of uncertainty in pNEM/CO, we will explicitly address the issues in subsequent analyses.

APPENDIX C

Appendix C

Estimating COHb Levels in Exposed Populations

The COHb module computes the COHb level of each cohort at the end of each exposure event using the Muller and Barton solution to the CFK equation (Muller and Barton, 1987). The COHb at the beginning of each exposure event is required as an input to the CFK model. Generally, the COHb level at the end of the previous exposure event is used as the beginning level for the event. The initial COHb is obtained by starting the model one day before the beginning of the exposure period. The effect of the initial COHb value is negligible after about 15 hr (Biller and Richmond, 1992). The model stores COHb levels at the end of each clock hour and generates distribution of COHb levels by cohort and for the total sensitive population.

The COHb module uses an average CO exposure concentration provided by pNEM/CO for each exposure event which is no longer than 1 hour. There is little loss of accuracy in using average concentrations rather than instantaneous CO concentrations to estimate the COHb level at the end of each exposure event due to the sufficiently long time constant for change in COHb (Biller and Richmond, 1992).

Table C-1 summarizes the parameters and variables required as inputs to the CFK model in the COHb module of pNEM/CO. Many of the parameters are physiological variables which vary from individual to individual within the populations of interest. The COHb module assigns a height and weight to the person representing each cohort and keeps this constant for a 24-hr period. The procedure relies on height and weight data collected as part of the National Health and Nutrition Examination Survey (NHANES) (DHEW, 1976). Once height and weight are assigned to the individual representing the cohort, many of the other

Table C-1. Summary of Important Variables Used in COHb Module of pNEM/CO

Parameter	Estimation Procedure or Value	
Haldane Affinity Constant (M)	218	Rodkey et al. (1969)
Alveolar ventilation rate ($\dot{V}_A$)	Multiply Effective Ventilation Rate by Estimated Body Surface Area	
Hemoglobin content of blood (Hb)	Distribution by age group and sex from NHANES data	DHHS (1982)
Blood volume (V_B)	Estimate based on regression equations for men and women by height and weight.	Allen et al. (1956)
Lung diffusion coefficient of CO (DL_{CO})	Estimate based on regression equations for men and women by age and height.	Salorinne (1976) Tikuisis et al. (1992)
Endogenous production rate ($\dot{V}_{CO}$)	Estimate for men and women based on fitting lognormal distribution to empirical data. For women the distributions are different depending on whether in pre- or post-menstrual phase.	
Barometric pressure (P_B)	A single value is estimated for the study area based on average height above sea level.	EPA (1978)

physiological variables can be determined using appropriate correlations and distributions (Biller and Richmond, 1992). For example, relationships have been published to estimate blood volume for men and for women based on height and weight (Allen et al., 1956) and to estimate lung diffusivity of CO (D_LCO) based on height and age (Salorinne, 1976). A further adjustment is made to account for the effect of alveolar ventilation rate on D_LCO (Tikuisis et al., 1992).

One of the most important variables in terms of influencing the rate of formation of COHb is the alveolar ventilation rate (V_A). The main exposure program supplies the COHb module with an effective alveolar ventilation rate (EVR) in liters per minute per unit body surface area for the duration of each exposure event. To obtain V_A the EVR is multiplied by body surface area, which is derived by using a published relationship between surface area and height and body weight.

Another important parameter required as input to the CFK equation is the Haldane affinity coefficient (M). This constant is a measure of the affinity of CO for Hb. While values in the range of 210-250 have been reported in the literature, most modelers have used values in the range 218-220 (Biller and Richmond, 1992). During the last CO NAAQS review, the CASAC endorsed the use of a value of 218 for modeling purposes. This was based on CASAC's judgment that the most careful work done in this field was that by Rodkey et al. (1969) who determined a value of 218 for M. Since there have been no significant advances in estimating M in the last decade, the COHb module of pNEM/CO assigns a value of 218 to this constant.

APPENDIX D

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

EPA-SAB-CASAC-LTR-92-016 August 11, 1992

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M St., S.W.
Washington, D.C. 20460

OFFICE OF
THE ADMINISTRATOR

Subject: Clean Air Scientific Advisory Committee Closure on the OAQPS Staff Paper for Carbon Monoxide

Dear Mr. Reilly:

The Clean Air Scientific Advisory Committee (CASAC) of EPA's Science Advisory Board (SAB) at a meeting on April 28, 1992, completed its review of the document entitled Review of the National Ambient Air Quality Standards for Carbon Monoxide: Assessment of Scientific and Technical Information, OAQPS Staff Paper. The Committee notes with satisfaction the improvements made in the scientific quality and completeness of the staff paper. It has been modified in accordance with the recommendations made by the CASAC in March and April, 1992.

This document is consistent with all aspects of the scientific evidence presented in the criteria document for carbon monoxide. It has organized the relevant information in a logical fashion and the Committee believes that it provides a scientifically adequate basis for regulatory decisions on carbon monoxide. The staff paper concludes, and the CASAC concurs, that a standard of the present form and with a numerical value similar to that of the present standard would be supported by the present scientific data on health effects of exposure to carbon monoxide.

The Committee looks forward to receiving notice of the revised or reaffirmed carbon monoxide standard when it is proposed.

Sincerely,

Roger O. McClellan, D.V.M.
Chairman
Clean Air Scientific Advisory Committee

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

DEC 2 8 1992

THE ADMINISTRATOR

Roger O. McClellan, D.V.M.
Chairman
Clean Air Scientific Advisory Committee
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Dear Dr. McClellan:

Thank you for your letter of August 11, 1992 concerning the Clean Air Scientific Advisory Committee (CASAC) review of the staff document entitled Review of the National Ambient Air Quality Standards for Carbon Monoxide: Assessment of Scientific and Technical Information - OAQPS Staff Paper.

I am pleased that the CASAC found that the document is consistent with the scientific evidence presented in the draft criteria document for carbon monoxide and that it provides a scientifically adequate basis for completing the review of the air quality standards for carbon monoxide. The guidance and recommendations provided by the CASAC greatly facilitated preparation of the staff paper and will greatly assist us in reaching a decision as to whether standard revisions are appropriate at this time.

I want to thank you, the other Committee members, and consultants for your contribution to the review of the carbon monoxide standards.

Sincerely yours,

/s/ William K. Reilly
William K. Reilly

A3B

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO.	2.	3. RECIPIENT'S ACCESSION NO.
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McKee, D.J.; McCurdy, T. R.; Richmond, H. M.	
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15. SUPPLEMENTARY NOTES

16. ABSTRACT

This paper evaluates and interprets the updated scientific and technical information that EPA staff believes is most relevant to the review of primary (health) national ambient air quality standards for carbon monoxide. This assessment is intended to bridge the gap between the scientific review in the EPA criteria document for carbon monoxide and the judgments required of the Administrator in setting ambient air quality standards for carbon monoxide. The major recommendations of the staff paper include the following: (1) There continues to be a need to control ambient levels of carbon monoxide to protect public health; (2) Both 1-hour and 8-hour averaging times should be retained for primary carbon monoxide standards; (3) Exposure analysis results indicate relatively few individuals with angina pectoris would experience carboxyhemoglobin (COHb) levels of 2.1 % or greater when exposed to carbon monoxide levels in ambient air only if current standards are attained; (4) Public health risk for COHb levels of 2.0 % or lower appears to be small, if any; (5) Current 1-hour (35 ppm) and 8-hour (9 ppm) standards for carbon monoxide should be reaffirmed.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group
Carbon Monoxide Air Pollution Ambient Air Quality Air Standards Health Effects	Air Quality Standards	

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