REVIEW OF THE NAAQS FOR CARBON MONOXIDE: 1983 REASSESSMENT OF SCIENTIFIC AND TECHNICAL INFORMATION

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I. PURPOSE

The purpose of this paper is to evaluate the key studies and scientific information contained in the draft EPA document, "Revised Evaluation of Health Effects Associated with Carbon Monoxide Exposure: An Addendum to the 1979 EPA Air Quality Criteria Document for Carbon Monoxide,"[1] and to identify the critical elements that the EPA staff believe should be considered in the review and possible revision of the current primary and secondary national ambient air quality standards (NAAQS) for carbon monoxide (CO). The paper also provides staff recommendations on alternative regulatory approaches.

II. BACKGROUND

A. Legislative Requirements

Since 1970 the Clean Air Act has provided authority and guidance for the listing of certain ambient air pollutants which may endanger public health or welfare and the setting and revising of NAAQS for those pollutants. Primary standards must be based on health effects criteria and provide an adequate margin of safety to ensure protection of public health. As several recent judicial decisions have made clear, the economic and technological feasibility of attaining primary or secondary standards are not to be considered in setting them, although such factors should be considered in the development of state plans to implement the standards.[2,3]

The requirement that primary standards provide an adequate margin of safety was intended to address uncertainties associated with inconclusive scientific and technical information available at the time of standard setting as well as to provide a reasonable degree of protection against

hazards that research has not yet identified.[2,3] Thus in providing an adequate margin of safety, the Administrator is regulating not only to prevent pollution levels that have been demonstrated to be harmful, but also to prevent pollutant levels for which the risks of harm, even if not precisely identified as to nature or degree, are considered unacceptable. In weighing these risks for margin of safety purposes, EPA considers such factors as the nature and severity of the health effects involved, the size of the sensitive population(s) at risk, and the kind and degree of other uncertainties that must be addressed. The selection of any particular approach to providing an adequate margin of safety is a policy choice left specifically to the Administrator.[2]

Secondary standards must be based on the welfare effects criteria and must protect the public welfare from any known or anticipated adverse effects associated with the presence of the pollutant in the ambient air. Welfare effects are defined in section 302(h) of the Clean Air Act to include effects on soil, water, crops, vegetation, man-made materials, animals, weather, visibility, hazards to transportation, economic values, personal comfort and well-being, and similar factors.

The Clean Air Act requires periodic review and, if appropriate, revision of existing criteria and standards. If, in the Administrator's judgment, the Agency's review and revision of criteria make appropriate the proposal of new or revised standards, such standards are to be revised and promulgated in accordance with section 109(b) of the Act. Alternatively, the Administrator may find that revision of the standards is not appropriate and conclude the review by reaffirming them.

B. Original CO Standards and Proposed Revisions of the Standards

Original CO Standards. On April 30, 1971, the Environmental Protection Agency promulgated NAAQS for CO under section 109 of the Clean

Air Act (36 FR 8186). Identical primary and secondary standards were set at levels of 9 ppm, 8-hour average, and 35 ppm, 1-hour average, neither to be exceeded more than once per year. The scientific and medical bases for these standards are described in the 1970 document, "Air Quality Criteria for Carbon Monoxide."[4] The standards set in 1971 were primarily based on work by Beard and Wertheim (1967)[5] suggesting that low-level CO exposures resulting in carboxyhemoglobin (COHb) levels of 2 to 3 percent were associated with impairment of ability to discriminate time intervals, a central nervous system effect.

Proposed Revisions of the Standards. In 1979, EPA published a revised Criteria Document for CO[6] and a Staff Paper[6a] in which several key considerations were identified as major factors in the possible revision of the CO standards. As discussed in the August 18, 1980 proposal notice (45 FR 55066), the 1979 Criteria Document,[6] and the Staff Paper,[6a] the Beard and Wertheim study[5] is no longer considered a sound scientific basis for the primary CO standards. However, medical evidence published since 1970 indicated, at the time of proposal, that aggravation of angina and other cardiovascular diseases may occur at COHb levels as low as 2.7 to 3.0 percent. Assessment of this and other medical evidence led EPA to propose: (1) retaining the 8-hour primary standard level of 9 ppm, (2) revising the 1-hour primary standard level from 35 ppm to 25 ppm, (3) revoking the existing secondary CO standards (since no adverse welfare effects have been reported at or near ambient CO levels), (4) changing the form of the standard from deterministic to statistical (i.e., EPA proposed to state allowable exceedances as expected values rather than as explicit values), and (5) adopting a daily interpretation for exceedances of the CO standards, so that exceedances would be determined on the basis of the number of days on which the 8- or 1-hour average concentrations were above the standard levels (45 FR 55066).

C. Developments Subsequent to Proposal

On June 18, 1982, EPA announced (47 FR 26407) an additional public comment period concerning several key issues and technical documents related to the review of the CO standards. These issues included: (1) the role of the Aronow (1981) study,[7] (2) consideration of a multiple exceedance 8-hour standard, (3) the technical adequacy of the revised draft sensitivity analysis[8] on the Coburn model predictions of COHb levels, and (4) the technical adequacy of the revised exposure analysis.[9] The Clean Air Scientific Advisory Committee (CASAC) met on July 6, 1982 to provide its advice on these issues. CASAC's recommendations arising from that meeting are summarized in an August 31, 1982 letter to the Administrator.[10]

The 1980 proposal (45 FR 55066) was based in part on several health studies conducted by Dr. Wilbert Aronow.[11-17] Based largely on evaluation of these studies in 1979 by EPA staff and CASAC, it was concluded at the time of proposal that COHb levels of 2.7-3.0 percent represent a health concern for individuals with angina and other types of cardiovascular heart disease.

In March 1983 EPA learned that the Food and Drug Administration (FDA) had raised serious questions regarding the technical adequacy of several studies conducted by Dr. Aronow on experimental drugs, leading FDA to reject use of the Aronow drug studies data. While there was no direct evidence that similar problems might exist for Dr. Aronow's CO studies, EPA concluded that an independent assessment of these studies was advisable prior to a final decision on the CO NAAQS. An expert committee was convened by EPA and met with Dr. Aronow to discuss his studies and to examine the limited available data and records from his CO studies. In its report,[18] the Committee (chaired by Dr. Steven M. Horvath, Director of the Institute of Environmental Stress, University of California - Santa Barbara) concluded

that EPA should not rely on Dr. Aronow's data due to concerns regarding various problems asociated with the studies which substantially limit the validity and usefulness of the studies results.

The Environmental Criteria and Assessment Office (ECAO) has prepared a draft Addendum[1] to the 1979 CO Criteria Document which re-evaluates the scientific data base concerning health effects associated with exposure to CO at or near ambient exposure levels, in light of the diminished value of the Aronow studies and taking into account any new findings that have become available beyond those reviewed in the 1979 CO Criteria Document.

III. APPROACH

The approach used in this paper is to assess and integrate information derived from the draft Addendum to the 1979 CO Criteria Document and other staff analyses in the context of those critical elements which the staff believes should be considered in the review of the primary (health based) standards. Only the primary standards are addressed, because, as explained in the proposal notice (45 FR 55066), no standards appear to be requisite to protect the public welfare from any known or anticipated adverse effects from ambient CO exposures. Particular attention is drawn to those judgments that must be based on careful interpretation of incomplete or uncertain evidence. In such instances, the paper states the staff's evaluation of the evidence as it relates to a specific judgment, sets forth appropriate alternatives that should be considered, and recommends a course of action.

Section IV reviews and integrates important scientific and technical information relevant to review of the primary CO standards. The essential elements with regard to the primary standards that are addressed in Section IV include the following:

(1) identification of possible mechanisms of toxicity;

(2) description of effects of concern including reported effect levels;

(3) identification of the most sensitive population groups and estimates of their size;

(4) discussion of uncertainties in estimating COHb levels that result from exposures to CO;

(5) estimates of the number of sensitive persons that would reach various COHb levels upon attainment of alternative standards; and

(6) discussion of margin of safety considerations.

Drawing from the discussion and information presented in Section IV, Section V identifies and assesses the factors that should be considered in selecting among alternative regulatory approaches. Preliminary staff recommendations on alternative policy options also are presented.

IV. CRITICAL ELEMENTS IN THE PRIMARY STANDARDS REVIEW

A. Mechanisms of Toxicity

At the time of proposal of the NAAQS for CO, the primary mechanism for toxic effects from CO exposure was thought to be hypoxia resulting from COHb formation. Several other possible mechanisms of toxicity were addressed in the 1979 Criteria Document but at the time of publication were not considered of major importance compared to COHb hypoxia at ambient CO exposure levels.

Presently, the most important mechanism of CO toxicity at low-level CO exposures is still thought to be COHb hypoxia. This mechanism involves diffusion of exogenous CO through the lungs into the blood with resultant formation of COHb. CO hypoxia results from preferential binding of CO by hemoglobin, thus reducing the amount available to bind oxygen (O_2). The CO bound to hemoglobin affects the binding of O_2 to the remaining hemoglobin and, thus, further reduces the O_2 delivery to tissues. Because the affinity constant for CO is between 200 and 250 times that for O_2, blood levels of 2 to 4.5 percent COHb can result from continued exposure to concentrations of CO as low as 20 to 150 ppm within two hours for individuals engaged in moderate activity (ventilation rate = 20 liters per minute). Models designed to estimate COHb levels arising from CO exposure have been developed by Coburn et al. (1965).[19]

Other possible mechanisms of toxicity have been discussed by Coburn (1979).[20] These alternative mechanisms involve binding of CO to such hemoproteins as cytochrome oxidase, myoglobin, tryptophan deoxygenase, and tryptophan catalase. Because the affinity constants for these proteins are much less than that for hemoglobin, it is unlikely that they play a major role in CO hypoxia. However, in tissues with a high O_2 gradient

between blood and tissue, it is reasonable to assume that the interaction of CO with these proteins (particularly with myoglobin in heart muscle) may play a role in CO toxicity. The conclusion drawn in the draft Addendum[1] is that regardless of the mechanism of toxicity, COHb levels provide a meaningful and useful physiological marker to estimate both endogenous production of CO and exposure to exogenous sources of CO. Presently COHb levels provide the best marker available for CO toxicity.

B. Reported Effects, Levels of Effects, and Severity of Effects

Table 1 is a summary of key clinical studies reporting human health effects associated with low-level exposures to CO. This table is based on evidence discussed in the 1979 Criteria Document[6] and in the Draft Addendum[1] but excludes a series of studies by Dr. Aronow due to problems which substantially limit the validity and usefulness of the Aronow studies.[18] Table 1 is intended to be used in conjunction with the following discussion, but each study should be viewed in light of the qualifications, if any, discussed in the 1979 CO Criteria Document, in the draft Addendum, and in this staff reassessment.

1. Cardiovascular Effects

The lowest observed CO exposure levels producing human health effects have been reported in individuals suffering from chronic angina pectoris. Angina pectoris, commonly referred to simply as angina, is a symptom of cardiovascular stress in which mild exercise or excitement can produce pressure or pain in the chest due to insufficient oxygenation of heart muscle.

Anderson et al. (1973)[21] reported that experimental subjects with angina exhibit statistically significant reduced time to onset of exercise-induced

TABLE 1. Lowest Observed Effect Levels For Human Health Effects Associated With Low Level Carbon Monoxide Exposure

Effects	COHb concentration, %[a]	References
Statistically significant decreased exercise capacity (i.e., shortened duration of exercise before onset of pain) in patients with angina pectoris and increased duration of angina attacks	2.9-4.5	Anderson et al., 1973[21]
Statistically significant decreased (~5-7%) work time to exhaustion in exercising young healthy men	3.3 and 4.3	Horvath et al., 1975[30]
Statistically significant decreased maximal oxygen consumption and exercise time during strenuous exercise in young healthy men	5-5.5	Klein et al., 1980[33] Stewart et al., 1978[32] Weiser et al., 1980[78]
No statistically significant vigilance decrements after exposure to CO	Below 5	Haider et al., 1976[35] Winneke, 1973[36] Christensen et al., 1977[37] Benignus and Otto, 1977[38] Putz et al., 1976[39]
Statistically significant decreased maximal oxygen consumption during strenuous exercise in young healthy men	7-20	Ekblom and Huot, 1972[29] Pirnay et al. 1971[76] Vogel and Gleser, 1972[77]
Statistically significant impairment of vigilance tasks in healthy experimental subjects	5-7.6	Horvath et al., 1971[44] Groll-Knapp et al., 1972[45] Fodor and Winneke, 1972[46] Putz et al., 1976[39]
Statistically significant diminution of visual perception, manual dexterity, ability to learn, or performance in complex sensorimotor tasks (such as driving)	5-17	Bender, et al., 1971[47] Schulte, 1973[48] O'Donnell et al., 1971[49] McFarland et al., 1944[41] McFarland, 1973[50] Putz et al., 1976[39] Salvatore, 1974[51] Wright et al., 1973[52] Rockwell and Weir, 1975[53] Rummo and Sarlanis, 1974[54] Putz et al., 1979[42] Putz, 1979[43]

[a]The physiologic norm (i.e., COHb levels resulting from the normal catabolism of hemoglobin and other heme-containing materials) has been estimated to be in the range of 0.3 to 0.7 percent (Coburn et al., 1963).[28]

angina after exposure to low levels of CO resulting in mean COHb levels of 2.9 (range 1.3-3.8 percent) and 4.5 percent (range 2.8-5.4 percent). In the same study, it was reported that subjects experienced statistically significant increases in duration of angina attacks during exercise at a mean COHb level of 4.5 percent. As discussed in the draft Addendum[1], the Anderson et al. (1973)[21] study provides reasonably good evidence for the above effects occurring in angina patients at mean COHb levels of 2.9 to 4.5 percent. There remain some concerns about the study findings due to ambiguities regarding the design and conduct of the study and the small number of subjects (N=10) examined.

In similar studies Aronow et al. (1973)[12] and Aronow (1981)[7] report decreased time to onset of angina for exercising subjects with reported COHb levels in the range of 2 to 3 percent. In addition, Aronow et al. (1974)[13] reported that subjects with peripheral vascular disease had reduced time to onset of leg pain at similar COHb levels. As discussed earlier, however, these results should be considered only in developing a margin of safety for effects below 3 percent COHb. Until independent studies attempting to replicate the Aronow studies have been completed, more conclusive statements are not possible concerning effects on individuals with angina or peripheral vascular disease at COHb levels below 2.9 percent COHb.

In another controlled human experimental study, Davies and Smith (1980)[22] reported possible effects on cardiac function in healthy individuals exposed continually to 0 ppm CO (0.5 percent COHb), 15 ppm CO (2.4 percent COHb), or 50 ppm CO (7.1 percent COHb) for 8 days. P-wave changes taken from EKG tracings were reported in 3 of 15 subjects at 15 ppm CO, in 6 of 15 at 50 ppm CO, and 0 of 14 at 0 ppm CO. One subject showed marked S-T

segment changes at 15 ppm CO. It was suggested by the authors that P-wave changes reported were due to interference by CO of normal atrial pacemaking or conducting tissue activity. Although they hypothesize that CO specifically affects the myocardial tissue as well as reduces blood oxygenation, the P-wave changes reported in this study have not yet been identified as adverse.

Increased blood flow was reported by Ayres et al. (1969, 1970, 1979).[23,24,79] This effect occurs as a compensatory response to CO exposure and may be related to coronary damage or cerebrovascular effects at very high blood flow rates due to the added stress on the vascular system. Community epidemiology studies which may have provided supporting evidence for these effects, however, have instead provided inconclusive results. In the Goldsmith and Landau (1968),[25] Kurt et al. (1978),[26] and Kurt et al. (1979)[27] studies the relationships between CO exposure and mortality from myocardial infarction (heart attack), sudden death due to atherosclerotic heart disease, and cardiorespiratory complaints remain in question.

Maximum aerobic capacity (VO_{2max}) and exercise capacity are indirect measures of cardiovascular capacity which have been reported to be reduced in several carefully conducted studies involving normal healthy adults exposed to CO. These effects, while not as serious as the possible impact of CO on angina, are still a matter of some concern since they have been found to occur in healthy individuals.

A decline in $\dot{V}O_{2max}$ for healthy individuals with COHb levels ranging from 5-20 percent was reported in a series of studies (Ekblom and Huot, 1972;[29] Weiser et al., 1980;[78] Stewart et al., 1978;[32]), reviewed in the 1979 Criteria Document[6]. Horvath et al., (1975)[30] found decreases ($p < .10$) in $\dot{V}O_{2max}$ when COHb levels were 4.3 percent. Also COHb levels

of 3.3 percent and 4.3 percent reduced work time to exhaustion by 4.9 and 7 percent respectively. Similar results were also found (Stewart et al., 1978;[79] Klein et al., 1980[33]) following exhaustive treadmill exercise at 5 percent COHb.

The effects of CO on the fibrinolytic system have been reported in numerous publications and may be related to heart attacks and strokes, although evidence at this time is very limited. In a series of studies Kalmaz et al. (1977;[55] 1978;[56] 1980[57]) concluded that prolonged exposure of rabbits to low levels of CO may change circulating platelet counts and/or congenital platelet function disorders, however, this has not been confirmed in man. Accelerated clot lysis time suggestive of enhanced blood fibrinolytic activity in humans was reported by El-Attar and Sairo (1968),[58] while others reported relationships between CO exposure and increases in fibrinogen and blood coagulation (Alexieva et al., 1975;[59] Panchenko et al., 1977[60]). Haft (1979)[61] reported that smoking increases the activity of platelets and that cigarette smokers have shortened platelet survival time. Neither this study nor others clearly implicate acute CO exposure in observed alterations in fibrinolytic activity and chronic exposure studies of humans are too poorly controlled to confirm coagulation system effects. Thus, this area of cardiovascular effects research needs to be developed far beyond the present state of knowledge before being acceptable even as suggestive evidence.

2. Neurobehavioral Effects

Central nervous system (CNS) effects have been reported in numerous studies (Bender et al., 1971[47]; Schulte, 1973[48]; O'Donnell et al., 1971[49]; McFarland et al., 1944;[41] McFarland, 1973;[50] Putz et al., 1976;[39]

Salvatore, 1974;[51] Wright et al., 1973;[52] Rockwell and Weir, 1975;[53] Rummo and Sarlanis, 1974[54]) for CO exposures resulting in COHb levels of 5-17 percent. The range of effects included impaired vigilance, visual perception, manual dexterity, learning ability, and performance of complex tasks.

While Beard and Grandstaff (1975)[34] have suggested vigilance effects may occur at levels of COHb as low as 1.8 percent COHb, several other studies (Haider et al., 1976[35]; Winneke, 1973[36]; Christensen et al., 1977[37]; Benignus and Otto, 1977[38]; and Putz et al., 1976[39]) have not found any vigilance decrements below 5 percent COHb. Measurement methods used to detect effects may have been too insensitive to detect changes in the latter vigilance studies, but in the draft Addendum, it was concluded that, at least under some conditions, small decrements in vigilance occur at 5 percent COHb.

Benignus et al. (1983)[40] concluded that no reliable evidence for time discrimination decrements caused by exposure to low levels of CO exists. Concentration-related decrements in dark adaptation at COHb levels as low as 5 percent were reported by McFarland et al. (1944).[41] This effect, however, is not considered to be adverse at ambient levels of CO exposure.

Studies by Putz et al. (1976),[39] Putz et al. (1979)[42], and Putz (1979)[43] reported that 5 percent COHb produced decrements in compensatory tracking, a hand-eye coordination task. These effects are not considered to be of major concern because nonsmokers rarely attain 5 percent COHb at ambient CO exposure levels and the effect only was found during high task difficulty.

3. Perinatal Effects

The 1979 Criteria Document suggests that based on limited animal toxicology data CO may produce perinatal effects on the fetus or newborn.

Long-term exposures to CO may result in a slower elimination of CO by the fetus and may lead to interference with fetal tissue oxygenation during development. Because the fetus may be developing at or near critical tissue oxygenation levels, even exposures to moderate levels of CO may produce deleterious effects on the fetus (Longo, 1977).[62] Although this has not yet been demonstrated in humans, evidence from smoking mothers is suggestive of fetal and newborn effects (Peterson, 1981).[63]

Research on sudden infant death syndrome (SIDS) recently has suggested a possible link between ambient CO levels and increased incidence of SIDS (Hoppenbrouwers et al., 1981).[64] It has been pointed out by Goldstein (1982)[65] that indoor sources of CO, as well as other pollutants (e.g., nitrogen dioxide, lead), may be at least as important as CO in causing SIDS and that the relationship between SIDS and ambient pollution levels may be only coincidental. Because the number of potentially confounding factors makes finding an association between CO and SIDS extremely difficult, further confirmation is needed before any causal relationship can be inferred.

C. Sensitive Population Groups

This section identifies those groups most likely to be particularly sensitive to low-level CO exposures based on the health effects evidence and considerations presented in the draft Addendum[1] and Section B of this paper. Those groups include: (1) individuals with angina, peripheral vascular disease, and other cardiovascular diseases, (2) persons with chronic respiratory disease (e.g., bronchitis, emphysema, and asthma), (3) elderly individuals, especially those with reduced cardiopulmonary functions, (4) fetuses and young infants, (5) individuals suffering from anemia and/or those with abnormal hemoglobin types that affect oxygen

carrying capacity or transport in the blood. In addition, individuals taking certain medications or drinking alcoholic beverages may be at greater risk for CO-induced effects based on some limited evidence suggesting interactive effects between CO and some drugs. Visitors to high altitude locations are also expected to be more vulnerable to CO health effects due to reduced levels of oxygen in the air they breathe. Finally, individuals with some combination of the diseaase states or conditions listed above (e.g., individuals with angina visiting a high altitude location) may be particularly sensitive to low-level CO exposures, although there is no experimental evidence to confirm this hypothesis.

Table 2 briefly summarizes the rationale for the judgments that these groups are more likely to be affected by low-level CO exposures and presents population estimates for each group. For most of the groups listed in Table 2 there is little specific experimental evidence to clearly demonstrate that they are indeed at increased risk for CO-induced health effects. However, it is reasonable to expect that individuals with preexisting illnesses or physiological conditions which limit oxygen absorption into blood or its transport to body tissues would be more susceptible to the hypoxic (i.e., oxygen starvation) effects of CO.

In our judgment, the available health effects evidence still suggests that persons with angina, peripheral vascular disease, and other types of cardiovascular disease are the group at greatest risk from low-level, ambient exposures to CO. This judgment is based principally on the Anderson et al. (1973) study[21] which indicates that individuals with angina may be affected at COHb levels in the range 2.9-4.5 percent. In addition, while there is less confidence in the dose-response relationship reported in Aronow et al. (1974),[13] this study still suggests that individuals with peripheral vascular disease may be at risk from ambient exposures to CO.

Table 2. Summary of Potentially Sensitive Population Groups[a]

Group	Rationale	Population Estimates	Percent of Population	Reference
Coronary Heart Disease	Anderson et al. (1973) suggests reduced time until onset of exercise-induced angina in 2.9-4.5% COHb range.	7.0 million (in 1979)	5.0 (of the adult population)	DHEW, 1975[66]
Angina Pectoris		5.6 million (in 1979)	4.0 (of the adult population)	
Chronic Obstructive Pulmonary Diseases	Reduced reserve capacities for dealing with cardiovascular stresses and already reduced oxygen supply in blood likely to hasten onset of health effects associated with CO-induced hypoxia.			DHEW, 1973[67]
Bronchitis		6.5 million (1970)	3.3	
Emphysema		1.5 million (1970)	0.7	
Asthma		6.0 million (1970)	3.0	
Fetuses and Young Infants	Several animal studies (Longo, 1977) report deleterious effects in offspring (e.g., reduced birth weight, increased newborn mortality, and lower behavioral activity levels).	3.1 million live births/year (1975)		DHEW, 1978[68]
Anemia	Oxygen carrying capacity of blood is already reduced increasing likelihood of CO-induced hypoxia effects at lower CO exposure levels than for non-anemic individuals.	3.0 million (1973)	1.4	DHEW, 1977[69]
Pernicious and Deficiency Anemias		.15 million (1973)	0.07	
Peripheral Vascular Disease	Aronow et al. (1974)[13] suggests reduced time until onset of exercise-induced leg pain after exposure to CO.	0.7 million (1979)	0.3	DHEW, 1974[70]
Elderly	CO exposures may increase susceptibility of elderly individuals to other cardiovascular stresses due to already reduced reserve capacities to maintain adequate oxygen supply to body tissues.	24.7 million (1980) > 65 years old		DOC, 1980[71]

[a]All subgroups listed are not necessarily sensitive to CO exposure at low levels.

D. Uncertainty in Estimating COHb Levels

The health effect studies discussed above report the effects observed at varying COHb levels. In order to set ambient CO standards based on these studies, it is necessary to estimate the ambient concentrations of CO that are likely to result in COHb levels at or near those observed in the studies. A model known as the Coburn equation[60] has been developed to estimate COHb levels resulting from CO concentrations as a function of time and various physiological factors (e.g., blood volume, endogenous CO production rate). Table 3 presents baseline estimates (i.e., a typical set of physiological parameters was used) of COHb levels expected to be reached by non-smokers exposed to various constant concentrations of CO for either 1 or 8 hours based on the Coburn model.

There are, however, at least two uncertainties involved in estimating COHb levels resulting from exposure to CO concentrations. First, even among otherwise "normal" (non-anemic) persons with cardiovascular heart disease, there is a distribution for each of the physiological parameters used in the Coburn model in the population. These variations are sufficient to produce noticeable deviations from the COHb levels in Table 3 that were predicted using the typical set of physiological parameters. Second, predictions based on exposure to constant CO concentrations inadequately represent the responses of individuals exposed to widely fluctuating CO concentrations that typically occur in ambient exposure situations.

As discussed in the proposal preamble (45 FR 55066), EPA attempted to represent these uncertainties in a draft Sensitivity Analysis. This analysis used the Coburn model to examine the effects of fluctuating CO concentrations and variations in physiological parameters on COHb estimates.

Table 3. Predicted COHb Response to Exposure to Constant CO Concentrations

Percent COHb Based on Coburn Equation[a]
Exposure Time

CO (ppm)	1 hour exposure		8 hours exposure	
	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	0.9	1.7	1.8
15.0	0.9	1.1	2.1	2.2
20.0	1.1	1.3	2.7	2.9
25.0	1.2	1.5	3.4	3.6
35.0	1.5	2.0	4.6	4.9
50.0	2.0	2.7	6.4	6.9

[a] Assumed parameters: alveolar ventilation rates = 10 liters/min (intermittent rest/light activity) and 20 liters/min (moderate activity); hemoglobin = 15 g/100 ml (normal male); altitude = sea level; initial COHb level = 0.5 percent; endogenous CO production rate = 0.007 ml/min; blood volume = 5500 ml, Haldane constant (measure of affinity of hemoglobin for CO) = 218; lung diffusivity for CO = 30 ml/min/torr.

Since proposal, EPA has revised the Sensitivity Analysis[73] to address concerns raised in several public comments. Table 4 presents estimates of the distribution of COHb levels in the sensitive population based on variations in physiological parameters upon exposure to three different patterns of CO levels which just meet a given CO standard. The estimates given in Table 4 and others contained in the Sensitivity Analysis report[73] are based on the assumption that the entire sensitive population is exposed to CO levels just meeting a given standard.

The impact of fluctuating air quality levels on COHb uptake can be roughly estimated by comparing the result of a constant 9 ppm exposure for 8 hours (1.4 percent COHb from Table 3) with a "typical" (50th percentile) adult exposed to several different air quality patterns that result in the same maximum 8-hour dose (i.e., 9 ppm, 8-hour average). The various patterns examined in the Sensitivity Analysis indicate COHb levels ranging from 1.4 to 1.9 percent (from Table 4) can be reached for the "typical" adult exposed to air quality reaching a 9 ppm, 8-hour average. A similar comparison of the results for air quality with a 12 ppm, 8-hour average peak exposure, indicates that the impact of fluctuating CO levels can increase the peak COHb value by up to 0.5-0.6 percent COHb.

The Sensitivity Analysis results in Table 4 also illustrate the effect of using distributions for each physiological parameter rather than just a representative set of physiological parameters in applying the Coburn model. For any given air quality pattern, the effect of the distribution of physiological parameters is to generate a distribution that is fairly tight around the 50th percentile individual. For example, 95 percent of the population is estimated to be within $\pm$ 0.3 percent COHb of the median adult value after exposure to the midrange pattern with a peak 9 ppm, 8-hour average.

Table 4. Percentage of Sensitive Persons with Carboxyhemoglobin Greater than or Equal to Specified Peak Value When Exposed to Air Quality Associated with Alternative Eight-Hour Daily Maximum Carbon Monoxide Standards[a,b,c]

Peak COHb %	9 ppm, 8-hr 1 Expected Exceedance			12 ppm, 8-hr 1 Expected Exceedance		
	Low Pattern	Midrange Pattern	High Pattern	Low Pattern	Midrange Pattern	High Pattern
3.7						<0.01
3.5						0.01
3.3						0.1
3.1					<0.01	0.6
2.9			<0.01		0.01	2
2.7			0.02	<0.01	0.2	9
2.5		<0.01	0.2	0.01	2	36
2.3		0.02	2	0.2	12	84
2.1	<0.01	0.4	10	4	49	100
1.9	0.05	5	53	36	88	100
1.7	3	35	98	91	99	100
1.5	39	88	100	100	100	100
1.3	97	100	100	100	100	100
1.1	100	100	100	100	100	100

[a]COHb responses to fluctuating CO concentrations were dynamically evaluated using the Coburn model prediction of the COHb level resulting from one hour's exposure as the initial COHb level for the next hour. The series of 1-hour CO concentrations used were from 20 sets of actual air quality data. Each pattern was proportionally rolled back or up so that its peak 8-hour CO concentration equalled the level of the 8-hour standard. Of the 20 selected patterns, results from 3 patterns are presented here. The low pattern tends to give the lowest peak COHb levels, the midrange pattern tends to give a midrange value, and the high pattern tends to give the highest value.

[b]Haldane constant = 218. Alveolar ventilation rate = 10 liters/min. Altitude = 0.0 ft.

[c]The estimation of distributions for each of the physiological parameters used in the Coburn model and the Monte Carlo procedure used to generate these estimates are discussed in Appendix C of the Sensitivity Analysis.[73]

Since proposal, EPA has made considerable improvements in its exposure analysis methodology which, unlike the Sensitivity Analysis, treats movement of people and variation of CO concentration levels through time and space. EPA staff believes that the revised Exposure Analysis,[74] described below, represents the best available tool for estimating the percentage of the sensitive population who would reach various CO concentrations and COHb levels upon attainment of alternative CO standards. Since the Exposure Analysis model simulates the exposure of individuals on an hourly basis and simulates actual air quality patterns, the impact of fluctuating CO levels is taken into account in the Exposure Analysis results. The results of the revised Sensitivity Analysis are useful, however, in characterizing the uncertainties resulting from variations in physiological parameters in the population which at this time are not fully accounted for in the Exposure Analysis.

E. Exposure Analysis Estimates

EPA's revised exposure analysis report, "The NAAQS Exposure Model (NEM) Applied to Carbon Monoxide,"[74] contains estimates of the numbers and percentage of urban American adults with cardiovascular heart disease that would be exposed to various ambient CO levels if alternative 8-hour CO standards were just attained. In addition, estimates have been made of the percentage of this sensitive population that would exceed selected COHb levels each year. These latter estimates were derived by applying the Coburn model, which relates patterns of CO exposure to resultant COHb levels, to the exposure model outputs using a typical set of physiological parameters for men and for women.

In contrast to the Sensitivity Analysis,[73] the Exposure Analysis[74] simulates pollutant concentrations and the activities of people with regard

to time, place, and exercise level. In the exposure model, the population is represented by an exhaustive set of "cohorts" (i.e., age-occupational groups that tend to "track together" in time and space). For each hour of the year each cohort is located in one of five "microenvironments." A microenvironment is a general physical location such as indoors-at-home or inside a transportation vehicle. CO levels in each of the microenvironments are estimated by the use of multiplicative "transformation factors," which relate CO levels recorded at the nearest monitor to estimated CO levels for each microenvironment. The multiplicative transformation factors are based on the growing literature on (1) indoor and inside-motor-vehicle air pollution and (2) statistical analyses of monitoring data (e.g., how ambient values change with height and distance from a monitor). A more detailed description of the approach, input data, and assumptions used to derive exposure estimates appears in the Exposure Analysis report.[74]

The exposure analysis model described above was applied to four urban areas: Chicago, Los Angeles, Philadelphia, and St. Louis. Exposure estimates for the sensitive population living in urban areas in the United States were obtained primarily by associating each urban area in the United States having a population greater than 200,000 with one of the four cities mentioned above. The association was made on the basis of geographic proximity to one of the base areas, average wind speed, peak CO concentrations, observed climate, and general character of the area.

Table 5 provides estimates for 1987 of the percentage of the sensitive population living in urban areas who would exceed various COHb levels upon attainment of two alternative 8-hour standards. For example, less than 0.1 percent of the sensitive population in urban areas

Table 5. Cumulative Percent of Sensitive Population in Urban Areas Whose COHb Levels Would Exceed Specified COHb Values Upon Attainment of Alternative 8-Hour Standards[a,b,c]

	8-Hour Standards		
	9 ppm 1 Expected Exceedance	12 ppm 1 Expected Exceedance	15 ppm 1 Expected Exceedance
COHb Level Exceeded (Percent)			
3.0	-	<.01	1.1
2.9	-	.02	2.5
2.7	-	0.1	5.9
2.5	-	0.8	9.7
2.3	<0.1	4.1	14
2.1	0.1	8.6	20

[a]Projected cardiovascular and peripheral vascular disease population in all urbanized areas in the United States for 1987 is 5,300,000 adults.

[b]These exposure estimates are based on air quality distributions which have been adjusted to just attain the given standards.

[c]These exposure estimates are based on best judgments of microenvironment transformation factors. Projections for one urban area based on lower and upper estimates of the microenvironment transformation factors are provided in the Exposure Analysis report.[74]

is estimated to exceed 2.1 percent COHb due to CO exposures associated with attainment of a 9 ppm standard with 1 expected exceedance allowed per year and approximately 20 percent of the sensitive population is estimated to exceed 2.1 percent COHb upon attainment of a 15 ppm standard with 1 expected exceedance allowed per year. It should be noted that the estimates given in Table 5 are based on air quality distributions which have been adjusted to just attain the given standards.

Several factors make the nationwide exposure estimates uncertain. They include: (1) the paucity of information on several of the needed inputs (e.g., the microenvironment multiplicative transformation factors), (2) the fact that nationwide estimates were extrapolated from only four urbanized areas, and (3) the use of two representative sets of physiological parameters (one for men and one for women) rather than the distributions of the physiological parameters in applying the Coburn model to derive COHb estimates. The Exposure Analysis report[74] describes some limited sensitivity analysis runs for one urbanized area to give a rough idea of the degree of uncertainty involved in the analysis. In addition, the results of the Coburn Model Sensitivity Analysis,[73] discussed previously in Section D, suggest that the uncertainty introduced by use of two representative sets of physiological parameters rather than the distributions of the parameters is not very large.

F. Margin of Safety Considerations

In determining which standards will provide an adequate margin of safety, the Administrator must consider uncertainties regarding the lowest levels at which adverse health effects occur, as well as uncertainties about the levels of COHb that will result from CO exposure at the levels associated with attainment of alternative standards. The staff recommends

that the following factors and sources of uncertainty be considered in selecting the primary standards:

1. Human susceptibility to health effects and the levels at which these effects occur varies considerably among individuals, and EPA cannot be certain that experimental evidence has accounted for the full range of susceptibility. In addition, for ethical reasons, clinical investigators have generally excluded from their studies individuals who may be especially sensitive to CO exposure, such as those with myocardial infarction or multiple disease states (e.g., angina and anemia). Another factor is that, apart from the Aronow et al. studies,[7,12,13] there are neither positive nor negative human exposure studies testing cardiovascular effects at COHb levels below the 2.9 percent level reported by Anderson et al.[21]

2. Several Aronow et al. studies[7,12,13] report decreased time to onset of angina and peripheral vascular disease at COHb levels in the range of 2.0-3.0 percent. In view of the concerns expressed in the Horvath Committee report,[18] the findings from these Aronow studies are questionable. Therefore, EPA staff recommends that the Aronow et al. findings be considered only as a margin of safety consideration. The Aronow studies suggest the possibility of effects at lower levels of CO but the results remain to be confirmed.

3. There is some animal study evidence indicating that there may be detrimental effects on fetal development (e.g., reduced birth weight, increased newborn mortality, and behavioral effects) associated with CO exposure. Similar types of effects have also been found in studies of the effects of maternal smoking on human fetuses. However, it is not possible at this time to sort out the confounding influence of other components of

tobacco smoke in causing the effects observed in the human studies. While human exposure-response relationships for fetal effects remain to be determined, these findings denote a need for caution in evaluating the margin of safety provided by alternative CO standards.

Other groups that may be affected by ambient CO exposures but for which there is little or no experimental evidence providing exposure-response relationships include: anemic individuals, persons with chronic respiratory diseases, elderly individuals, visitors to high altitude locations, and individuals on certain medications.

5. Uncertainties regarding the uptake of CO, including those related to the accuracy of the Coburn equation in assessing variations in the population due to differing physiological parameters and exposure to varying air quality patterns, should be considered in judging which standards provide an adequate margin of safety.

6. There are several factors contributing to uncertainties about the estimates provided by the Exposure Analysis[74] of the expected number of individuals achieving various COHb levels upon attainment of alternative standards. These factors include: the paucity of information on several of the needed inputs, the fact that nationwide estimates were extrapolated from only four urbanized areas, and the use of two representative sets of physiological parameters (one for men and one for women) rather than the distributions of physiological parameters in applying the Coburn model to derive COHb estimates. The Exposure Analysis report[74] describes some limited sensitivity analysis runs for one urbanized area to give a rough idea of the degree of uncertainty involved.

7. Uncertainty regarding adverse health effects that may result from very short duration, high-level CO exposures (the bolus effect). However,

this factor is probably not a critical consideration because, as discussed in the proposal notice (45 FR 55077), existing air quality data indicate that attainment of an 8-hour averaging time standard should limit the magnitude of short-term peak concentrations.

8. There is some concern about possible interactions between CO and other pollutants, although there is little experimental evidence to document such interactions at this time.

V. FACTORS TO BE CONSIDERED IN SELECTING PRIMARY STANDARDS

This section draws on the previous evaluation of scientific information and summarizes the principal factors bearing on selection of primary CO standard levels and on designating appropriate averaging times and forms. Preliminary staff recommendations for each of these choices also are presented.

A. Averaging Times

Currently there are primary CO standards for both 1-hour and 8-hour averaging times. The original 8-hour averaging time was selected primarily because most individuals achieve equilibrium or near equilibrium levels of COHb after 8 hours of continuous exposure. Another reason for the 8-hour averaging time is that many people are exposed in approximately 8-hour blocks of time (e.g., work, sleep). The 8-hour averaging time provides a good indicator for tracking continuous exposures that occur during any 24-hour period. The 1-hour averaging time provides an appropriate time frame for evaluating health effects from short-term exposures. As discussed in the June 1979 staff paper,[6a] the 1- and 8-hour averaging time standards can also provide reasonable protection against high spikes of less than 1-hour duration ("the bolus effect") in the urban ambient environment. The staff recommends both the 1- and 8-hour averaging times be retained for the primary standards.

B. Form of the Standards

The current CO standards are stated in a deterministic form, allowing only one exceedance per year. The general limitations of the deterministic form are discussed in Biller and Feagans (1981).[75] Recognition of these limitations has led EPA to promulgate a statistical form for the ozone standards (44 FR 8202) and to propose a statistical

form for the CO standards (45 FR 55066). The statistical form of the standard (e.g., stating an allowable number of exceedances of the standard level as an average or expected number per year) offers a more stable target for control programs and is less sensitive than a deterministic form to very unusual meteorological conditions. The emissions reductions to be achieved in the required control implementation program would be based on a statistical analysis of the monitoring data over a multi-year period (e.g., the preceding 3-year period).

EPA has considered the possibility of setting a multiple expected exceedances standard (47 FR 26407). At a July 6, 1982 public meeting, the CASAC discussed several advantages and liabilities of setting a multiple expected exceedances standard for CO. Based on the discussion at that meeting, the Chairman of CASAC sent a letter to the Administrator recommending adoption of a multiple expected exceedances standard with a standard level suitably adjusted to provide adequate protection of public health.[10] Subsequent to the CASAC meeting, the Agency received a number of comments both for and against multiple exceedances standards. In particular, the State and Territorial Air Pollution Program Administrators (STAPPA) sent a resolution to EPA expressing the view that a single exceedance CO standard would be preferable to a multiple exceedance standard because the former (1) is more directly related to the health effects of concern and (2) is more clearly understood by the public than a multiple expected exceedances standard. The staff recommends that for the CO decision the standards be stated in terms of a single expected exceedance based on (1) the comments made by State air pollution control agencies and others regarding the advantages of a single exceedance standard and (2) the advantages of a statistical (i.e., expected exceedance) standard discussed above.

C. Levels of the Standards

The principal conclusions derived from the scientific evidence described in Section IV of this paper and in the draft Addendum to the 1979 Criteria Document[1] that are relevant to the standard selection process are summarized below:

(1) Cardiovascular effects are judged to be the health effects of greatest concern that have been associated with CO exposure levels observed in the ambient air. In particular, there is no change in the staff's judgment as stated in the 1980 proposal that decreased time to onset of angina and prolonged duration of angina attacks should be considered adverse health effects. The staff concludes from its review of the scientific evidence that aggravation of angina is likely to occur at COHb levels in the range 2.9-4.5 percent. This judgment is based principally on the Anderson et al. (1973)[21] study. The Aronow studies[7,12,13] report that aggravation of angina and peripheral vascular disease may occur at levels below 2.9 percent COHb. However, in view of the concerns expressed by the Horvath Panel[18] about the design and conduct of the Aronow studies, further experimental confirmation is needed on the question of whether these effects occur at levels below 2.9 percent COHb. The Aronow studies should be considered only in developing a margin of safety.

(2) Several controlled human exposure studies[30,79,33] have reported effects on maximum aerobic and exercise capacity for healthy vigorously exercising adults exposed to CO. The staff's assessment of these studies is that small (5-7 percent) reductions in work time are likely to occur at COHb levels in the range 3.3-5.0 percent. It should be noted, however, that the effects observed at these levels are not clearly of health significance. At higher COHb levels (7 percent), one study[29] reported a 38 percent decrease in work time for healthy adults engaged in heavy exercise.

At submaximal exercise levels there appear to be little if any effects on aerobic or work capacity for healthy individuals exposed to COHb levels up to 15-20 percent. However, the possibility that individuals with severe chronic respiratory disease may be affected at COHb levels below 5 percent has not been investigated. The possible impairment of work capacity for individuals with chronic respiratory disease should, therefore be included as a margin of safety consideration in selection of the final standards.

(3) Additional factors which we believe should be considered in selecting CO primary standards which provide an adequate margin of safety include:

(a) there are no valid human controlled experimental studies reporting no adverse health effects at COHb levels below 2.9 percent for cardiovascular effects,

(b) concern about animal study evidence indicating that there may be detrimental effects on fetal development,

(c) concern about other potentially sensitive population groups that have not been adequately tested such as the elderly, anemics, and visitors to high altitude,

(d) uncertainties regarding the uptake of CO and the accuracy of the Coburn equation in assessing uptake under varying conditions,

(e) uncertainties about the Exposure Analysis[74] estimates of the expected number of individuals achieving various COHb levels upon attainment of alternative standards,

(f) uncertainty regarding adverse health effects that may result from very short duration high-level CO exposures (the bolus effect), and

(g) concern about possible interactions between CO and other pollutants.

All of the above factors were previously discussed in greater detail in Section IV-F of this paper.

D. Staff Conclusions and Recommendations

Based on the assessment of the scientific evidence discussed in the draft Addendum[1] and in previous sections of this paper, the staff remains concerned that adverse health effects may be experienced by large numbers of sensitive individuals at COHb levels in the range 2.9 to 4.5 percent. Unless the primary standards are set to keep most of the sensitive population somewhat below these levels, we believe that the Agency would not be exercising the degree of prudence called for by the Clean Air Act requirement that primary standards be set to provide "an adequate margin of safety."

Based on the revised Exposure Analysis[74] estimates summarized in Table 5, 8-hour standards with one expected exceedance allowed per year in the range of 9 to 15 ppm are estimated to keep 99 percent or more of the sensitive population below 3.0 percent COHb. Standards within this range would provide different levels of protection. For example, a 9 ppm, 8-hour average standard is estimated to keep more than 99 percent of the sensitive population below 2.1 percent COHb and a 15 ppm standard would keep almost 99 percent of the sensitive population below 3.0 percent COHb. In using the Exposure Analysis estimates to evaluate the protection afforded by alternative standards, it should be noted that the above exposure estimates are based on best judgments of certain key inputs to the analysis. The uncertainty associated with these estimates should, therefore, also be considered in evaluating alternative standards. To the extent that the uncertainty may lead to underestimates of the protection afforded by any particular standard, selection of a more protective standard is appropriate.

In view of the lack of negative controlled human exposure evidence concerning the impact of COHb levels below 2.9 percent on individuals with cardiovascular disease, the margin of safety considerations discussed in Section IV-F of this paper, and the precautionary nature of the Clean Air Act, the staff is concerned that 8-hour standards at the upper end of the range 9 to 15 ppm would provide little or no margin of safety. Therefore, the staff recommends that the Administrator retain or select an 8-hour standard in the range 9 to 12 ppm. With regard to the 1-hour primary standard the staff recommends that 1-hour standards in the range 25 to 35 ppm be retained or set to provide a comparable level of protection.

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