Preliminary Assessment of Adverse Health Effects from Carbon Monoxide and Implications for Possible Modifications of the Standard

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STAFF PAPER

I. PURPOSE

The purpose of this paper is to evaluate the key studies in the EPA document "Air Quality Criteria for Carbon Monoxide"[1] and identify the critical elements to be considered in the possible revision of the primary carbon monoxide (CO) National Ambient Air Quality Standard (NAAQS). The paper also identifies critical factors that must be considered in selecting an adequate margin of safety for the CO air quality standard.

II. BACKGROUND

The Clean Air Act Amendments of 1977 provide authority and guidance for setting and revising NAAQS, where appropriate. Primary standards must be based on health effects criteria and provide an adequate margin of safety to ensure protection of public health. Economic or related impacts cannot be considered in the selection of the standard level. Further guidance provided in the legislative history[2] of the Clean Air Act indicates that margins of safety should be defined such that standards are set at "the maximum permissible ambient air level ... which will protect the health of any [sensitive] group of the population." Also, margins of safety are to be defined such that the standards will provide "a reasonable degree of protection ... against hazards which research has not yet identified."[2] In the final analysis, the primary standard is set by the EPA Administrator based on his judgment of the implications of all the health effects evidence, and the need for an adequate margin of safety.

The primary (health-based) and secondary (welfare-based) NAAQS for CO are both presently set at 9 parts per million (ppm) and 35 ppm for 8-hour and 1-hour averaging times, respectively, not to be exceeded more than once per year. This paper considers only the primary NAAQS revision since there is no data to support setting a secondary standard more stringent than the primary NAAQS.

III. APPROACH

The approach used in this paper is to identify the critical factors to be considered in the standard-setting process for carbon monoxide, specifically those points where judgments or decisions must be made and where careful interpretation of incomplete or uncertain evidence is required. Where possible, the paper states our understanding of the evidence as it relates to a particular judgment or, in some cases, proposes alternative choices that might be made. The essential elements that are addressed in this process include the following:

(1) the most probable mechanism(s) of toxicity,

(2) a description of the adverse effects attributed to carbon monoxide and a judgment on the critical effect of concern for standard-setting,

(3) a description of the most sensitive population groups,

(4) the level at which the indicator of adverse effects (blood carboxyhemoglobin) signals a danger to public health in the sensitive population,

(5) the CO exposure which could give rise to a critical carboxyhemoglobin level,

(6) other aspects of the standard, and

(7) a discussion of the uncertainties in the medical evidence and other factors which should be considered in selecting an adequate margin of safety and a final standard level.

IV. CRITICAL ELEMENTS IN THE STANDARD REVIEW

A. Mechanism of CO Toxicity

We interpret the existing health effects evidence[2a] to indicate that the principal mechanism of CO toxicity is through hypoxemia (deficient oxygenation of the blood). This mechanism suggests that adverse effects on the body result from the strong affinity of blood hemoglobin for CO (over 200 times greater than for oxygen), which results in the formation of carboxyhemoglobin (COHb). Thus, the oxygen-carrying capacity of the blood is reduced since hemoglobin that has combined with CO in this manner is not available to transport oxygen; furthermore, the presence of COHb inhibits the release of oxygen from the remaining hemoglobin. Effects on the cardiovascular, central nervous, pulmonary, and other systems are directly related to this reduction in the ability of the blood to deliver oxygen to these systems.

The COHb in an individual's blood stream reflects input from endogenous (produced by the metabolic breakdown of hemoglobin and other heme-containing materials) and exogenous (derived from the external environment) sources. The physiologic norm for endogenous COHb levels has been estimated to be in the range of 0.3 - 0.7 percent,[3] but endogenous production may be significantly increased in persons with hemolytic anemias[4], in women during pregnancy and during the menstrual cycle[5], and in persons taking certain types of drugs.[6] Our judgment is that increments above the physiologic norm, with the above-mentioned exceptions, result

from exogenous sources such as cigarette smoking (which can result in COHb levels ranging from 2 or 3 percent up to as high as 15 to 17 percent)[6a] or community air pollution.

Some researchers have suggested an alternative mechanism for carbon monoxide toxicity that results from a blocking of the energy flow at the cellular level through the cytochrome system[7-11]. Discussion of some of these studies by the CO subcommittee of the Clean Air Scientific Advisory Committee (CASAC)[12] raised the possibility that the results found by these researchers could be more readily explained on the basis of the test protocols than as an alternative mechanism of toxicity. Several of these studies exposed animals to very high CO concentrations (greater than 100,000 ppm) for short time periods, with the result that the animals died at a total-body COHb level lower than that which would be required if the CO dose had been administered as a lower concentration given over a longer period of time. The CASAC discussion[12] indicated that the hypoxemia mechanism probably provides an adequate explanation of this phenomenon as a manifestation of the "bolus effect" wherein a high concentration inhaled over a short period of time results in a portion of the blood supply that is essentially devoid of oxygen reaching the heart, with life-threatening consequences. Since the CASAC questioned the sufficiency of the information base on which the cytochrome system toxicity mechanism has been proposed, we have decided to focus this NAAQS review on the hypoxemia mechanism and related COHb levels associated with observed adverse health effects.

B. Description of Adverse Effects

1. Cardiovascular System Effects. Angina pectoris is a cardio-

vascular disease in which mild exercise or excitement produces symptoms of pressure and pain in the chest because of insufficient oxygen supply to the heart muscle. Angina patients have been reported to experience heart pains earlier during exercise after a resting exposure to low levels of CO.[13-16] We consider aggravation of angina to be an adverse health effect because it may result in cardiovascular damage. Aggravation of angina has been convincingly demonstrated at COHb levels of 2.5 - 3 percent,[13,14] which are lower than those associated with any other measurable adverse effect of CO exposure. A 1978 study by Aronow[17] has reported angina aggravation at COHb levels in the range of about 1.8 - 2.3 percent, but these COHb levels were obtained through a passive smoking exposure regime, with possible confounding factors. The appropriate utilization of this study in the standard-setting process will be discussed in a subsequent section.

Patients having peripheral vascular disease may also have this condition aggravated by CO exposure. The one clinical study[18] examining such an effect involved the exposure of 10 persons with occlusive arterial disease to 50 ppm CO for 2 hours followed by exercise until leg pain occurred. The COHb levels produced by this exposure (about 2.8 percent) significantly decreased the time to onset of pain and cessation of activity.

Another cardiovascular system effect of concern is the possible detrimental effect of increased blood flow that occurs as a compensatory response to CO exposures.[19,20] This response could result in coronary damage or other vascular effects due to the cardiovascular system being pushed beyond its capabilities.

Cardiovascular damage and electrocardiogram abnormalities have been reported in persons who have experienced acute non-fatal CO poisoning

episodes (20 percent COHb)[21] or who have been chronically exposed to CO in the workplace.[22,23] Chronic exposure to average CO levels of 70 ppm, with peak levels of about 300 ppm (no COHb levels reported), has been associated with increased mortality from heart failure in a Japanese population.[24] Some epidemiological studies in Los Angeles[25-27] have suggested the possibility that increased mortality from myocardial infarction (death of heart tissue) is associated with high ambient air concentrations of CO (sufficient to produce COHb levels in the range of 8-17 percent),[26] but a similar study in Baltimore[28] failed to find such a correlation with considerably lower ambient CO levels (sufficient to produce COHb levels in the range of 1-10 percent). Another study[29] evaluated patients admitted to the myocardial infarction research unit at the Johns Hopkins University. While the investigator's diagnoses were consistent with both acute and chronic effects on the myocardium of long-term exposure to CO, the effects observed could not be clearly related to that factor. Therefore, the possibility of an association between CO levels in the ambient air and incidence of myocardial infarction or of sudden deaths due to arteriosclerotic heart disease remains in question; more research is needed to clarify this issue.

A recent epidemiology study[30] reported an increase in the frequency of cardiorespiratory complaints by patients at the emergency room of a Denver hospital on "high CO days" when the maximum 1-hour mean ambient CO concentrations at a nearby monitoring site averaged 27 ppm as compared to "low CO days" when the corresponding concentration was 12 ppm. However, the CASAC expressed a need for caution in the interpretation of this study because (1) the cardiorespiratory complaints evaluated in this study are inadequate indicators of cardiovascular

disease aggravation, (2) the authors did not report any COHb levels for the patients evaluated and (3) the single monitoring site near the hospital is inadequate to determine the exposures sustained by the patients.[31]

2. Central Nervous System Effects. Some studies[32-35] have reported that CO exposures resulting in COHb levels of 1.8-7.6 percent have produced decrements in vigilance (the individual's ability to detect small changes in his environment that take place at unpredictable times). The effects of CO on vigilance are in considerable dispute, however, since similar studies[36-41] have failed to observe similar effects. Our judgment of the evidence is that, if relevant variables are controlled, CO exposures at a threshold level of about 4-6 percent COHb may produce decrements in vigilance. Decrements in visual function and sensitivity have been reported at COHb levels as low as 4 to 5 percent.[42,43]

We consider vigilance and visual function effects to be important since these functions are components of more complex tasks, such as driving, and reduced alertness or visual sensitivity could lead to increased accidents. Several studies[41,44-58] have suggested that elevated COHb levels adversely affect the performance of complex tasks, and suggestive (but not conclusive) evidence has been reported indicating that a greater proportion of drivers in fatal accidents have COHb levels above 5 percent.[59] In this respect, the possibility of an interactive effect between alcohol and CO that has been suggested by some experimentation[55] seems to be of particular concern.

3. Pulmonary Function and Exercise Effects. In studies using submaximal exercise for short periods (5 to 60 minutes), oxygen uptake

during work does not appear to be affected by COHb levels as high as 10 to 20 percent,[60-69] although several of these studies have shown that these COHb levels produce increased heart rates. In maximal exercise protocols of several minutes duration, COHb levels in the range of 5-33 percent have been demonstrated to produce a linear decline in maximal oxygen uptake (and hence work capacity).[67-75] One study[76] has reported that competitive swimmers have impaired performance when events are held in atmospheres containing 30 ppm CO originating from traffic (COHb level not reported), but these results may reflect interaction with other pollutants since ambient air exposures were examined in this study rather than systematic, controlled exposures to CO.

Although few studies have been conducted to examine the effects of CO exposure on persons with chronic obstructive pulmonary disease (e.g., asthma, emphysema, and chronic bronchitis), this group is presumably at high risk to CO exposures. A reduction in oxygen supply due to increased COHb levels could exacerbate existing effects of low oxygen levels caused by impaired respiratory system functioning. However, such persons may absorb less CO due to their disease and may have compensated for their respiratory deficiencies by increased production of red blood cells and by other adaptations. One study[77] exposed ten persons with chronic obstructive pulmonary disease for 1 hour to sufficient CO to produce 4.1 percent COHb. A 33 percent reduction in time to onset of marked dyspnea (difficulty in breathing) occurred during exercise as compared to COHb levels of 1.5 percent. The investigators concluded that the limited exercise performance after CO exposure was probably a cardiovascular limitation rather than a respiratory one.

4. Fetal Development. Several experimental animal studies[78-84] have exposed pregnant females to CO and in general have shown deleterious effects in the offspring even when the mothers were not affected. For example, one study[84] exposed pregnant rabbits to 90 ppm CO continuously for 30 days, with resultant maternal COHb levels of 9 to 10 percent. Birth weights decreased 11 percent and the newborn mortality rate increased to 10 percent from a control value of 4.5 percent. In another study,[81] the offspring of rats exposed to 150 ppm CO throughout gestation (maternal COHb levels of 15 percent) weighed slightly (3 percent) less at birth and failed to gain weight as rapidly after birth. Reduced brain protein levels at birth and lower behavioral activity levels through the preweaning period were observed. In many cases the deleterious effects have been shown to disappear by adulthood, but the inference that such effects may occur in humans during maturation is of concern with respect to possible impacts on learning and social behavior development.

Experimental animal studies[78,82] have shown that short-term maternal CO exposure results in lower COHb levels in the fetus than in the mother, but may have greater detrimental effects on the fetus than on the mother. One study[85] examining long-term maternal CO exposures has shown that fetal COHb levels exceeded maternal values after an uptake lag of a few hours following initiation of exposure. At equilibrium, fetal COHb levels significantly exceeded maternal values, and fetal elimination of CO after cessation of exposure was slower than maternal elimination. The COHb concentration in human fetal blood has been reported to vary from 0.7 to 2.5 percent (for non-smoking mothers), with the ratio of fetal to maternal COHb levels varying from 0.6 to 1.6.[86]

The biologic effects of CO exposure on fetal tissues during intrauterine development require clarification. The ability of CO to decrease

the oxygen transport capacity of maternal and fetal hemoglobin may result in interference in fetal tissue oxygenation during important developmental stages. Whereas a normal adult has reserve capacity and compensatory responses that enable him to handle moderately high COHb levels without irreversible consequences, the fetus may under normal situations be operating close to the critical levels in terms of tissue oxygen supply. Thus, even moderate CO exposures may have a deleterious effect on fetal development.[86]

Some verification of this hypothesis has been suggested in studies examining the impact of maternal smoking and altitude on the unborn child. Several studies have demonstrated that babies born to smoking mothers have reduced birth weight,[87-94] as do children born at higher altitudes.[95,96] Some question remains as to the relationship of fetal deaths to maternal smoking, but several studies[92-94,97-102] using data from large population samples have concluded that perinatal deaths do increase in the infants of mothers who smoke when these data are corrected for other factors affecting perinatal death rates (e.g., maternal age, the number of children previously borne, race, and social status). The causes of this increased perinatal mortality have not been adequately identified.

The role of CO in the effects of maternal smoking on surviving children is not well understood. One study[103] has reported almost a two-fold increase in the incidence of congenital heart disease in the infants of mothers who smoke. British studies[104,105] of large population groups have found highly significant differences in reading attainment at seven years of age between the children of mothers who smoked and those who did not. A follow-up study[106] of these children at 11 years of age found several months retardation in general

ability, reading, and mathematics between the children of mothers who smoked (0.5 pack of cigarettes or more per day; average COHb levels, though not reported, may have been 3 to 4 percent or more) and those who did not. While the fact that cigarette smoke contains substances other than CO prevents a direct application of the results of these studies in setting the CO standard, the studies do suggest the need for caution in protecting unborn children from such potentially deleterious effects of CO exposure.

C. Population Groups Most Sensitive to Low Levels of CO

On the basis of the previous section's description of the principal adverse effects associated with low levels of CO exposure, we have concluded that the following groups may be particularly sensitive to exposures of CO: angina patients, individuals with other types of cardiovascular disease, persons with chronic obstructive pulmonary disease, anemic individuals, fetuses, and pregnant women. While there is no evidence in the criteria document that healthy children are particularly sensitive to CO, concern exists that they may also be at increased risk to CO exposure because of the increased oxygen requirements that result from their higher metabolism rates.

In our judgment, the available health effects data identify persons with angina and those with other types of cardiovascular disease as the groups at greatest risk from low-level, ambient exposures to CO. Aggravation of angina has been convincingly demonstrated to occur at COHb levels (about 2.5-3 percent)[13,14] which are lower than those associated with any other measurable adverse effect of CO exposure. The low threshold to CO effects results from the fact that the angina condition is due to an insufficient oxygen supply to cardiac tissue, so that such persons have an inadequate reserve capacity and an impaired ability to compensate for the effects of CO.

The second group of prime concern consists of individuals suffering from other cardiovascular diseases, such as peripheral vascular disease. While much less information is available concerning the effects of CO on this group, one clinical study has shown significantly decreased exercise time to onset of leg pain at COHb levels of about 2.8% for persons with peripheral vascular disease.[18]

A wide variation exists in the estimates of the number of persons who have angina and other types of cardiovascular disease. It has been estimated that 2.1% of the population has stable angina,[107] while some cardiologists believe the total number of angina patients may range up to 25% of the national population.[108] The U.S. National Health Survey Examination reported that of the population aged 18 to 79 years, 3.1 million persons have definite heart disease and another 2.4 million are suspected to have heart disease.[109] Another National Health Survey estimated that 12% of the population has arteriosclerotic disease.[110] In addition, data from autopsies has indicated that nearly 25% of persons dying from coronary disease have had no prior recognized symptoms of heart disease.[111]

On the basis of the available effects data, we are focusing on angina patients and those with other types of cardiovascular disease as the most sensitive groups. Other groups such as fetuses, anemics, and persons with chronic obstructive pulmonary disease can reasonably be projected to be affected at CO levels possible in ambient air exposures. Because of the lack of human data for these groups, however, the potential effects on such persons will be considered in determining the margin of safety for the CO standard.

D. Critical COHb Levels

Table 1 provides a summary of the key health effects studies

TABLE 1

ESTIMATED HEALTH EFFECTS LEVELS FOR CARBON MONOXIDE EXPOSURE

Effects	COHb concentration, %[a]	References
Passive smoking aggravates angina pectoris	1.8-2.3	17. Aronow, 1978
Decreased exercise capacity in patients with angina pectoris, intermittent claudication, or peripheral arteriosclerosis	2.5-3.0	13. Anderson et al., 1973 14. Aronow and Isbell, 1973 18. Aronow et al., 1974
Impairment of vigilance tasks in healthy experimental subjects	3.0-7.6	35. Horvath et al., 1971 33. Groll-Knapp et al., 1972 32. Fodor and Winneke, 1972
Decreased exercise performance in normal persons and in patients with chronic obstructive pulmonary disease	3.0-4.9	74. Aronow and Cassidy, 1975 77. Aronow et al., 1977
Increased angina attacks for freeway travel	3.8-8.0	16. Aronow et al., 1972
Changes in heart functioning and possible impairment	3.9	131. Aronow et al., 1974
Linear relationship between COHb and decreasing maximal oxygen consumption during strenuous exercise in young healthy men	5-20	67. Ekblom and Huot, 1972 73. Horvath, 1975 70. Dahms et al., 1975 75. Seppanen, 1977
Statistically significant diminution of visual perception, manual dexterity, ability to learn, or performance in complex sensorimotor tasks (such as driving)	5-17	45. Bender, et al., 1971 46. Schulte, 1973 47. O'Donnell et al., 1971 48. McFarland, 1973 41. Putz et al., 1976 50. Salvatore, 1974 53. Wright et al., 1973 55. Rockwell and Weir, 1975 58. Rummo and Sarlanis, 1974

[a]The physiologic norm (i.e., COHb levels resulting from the normal metabolic breakdown of hemoglobin and other heme-containing materials) has been estimated to be in the range of 0.3 to 0.7 percent.[3]

reporting effects due to elevated blood COHb levels. While the table includes studies reporting effects in three of the basic categories described earlier, the selection of a critical COHb level will be based primarily on the cardiovascular effect category, as discussed previously.

The present NAAQS for CO is not based on the cardiovascular effect category but on central nervous system effects. The Federal Register notice[112] promulgating the existing standard identified 2 percent as the critical COHb level on the basis of a study by Beard and Wertheim[113] which reported an impairment in discrimination of time intervals in subjects having estimated COHb levels of 2 to 3 percent. The revised criteria document states[114] that considerable questions have been raised as to the validity of these observations and points out that attempts to replicate these findings have been less than satisfactory.[47,115-118] As stated previously, we have concluded that other central nervous system effects, i.e. vigilance and visual function decrements, may occur in the range of 4 to 6 percent COHb.

In selecting a standard level, we propose to identify a critical COHb blood concentration which we judge to represent most accurately the lowest concentration that credible studies have convincingly associated with human health effects of concern for sensitive persons. This element of the standard-setting rationale does not include margin of safety considerations, and does not reflect those uncertainties in the medical evidence which must eventually be considered in the margin of safety for the standard.

Selection of the critical COHb blood level is a key element in the standard decision and has a direct effect on the final standard level.

Based on medical evidence presented in the criteria document and summarized in Table 1, it appears that two basic options exist regarding the appropriate COHb levels. These options include:

(1) a COHb level in the range of 2.5 - 3.0 percent or,

(2) a COHb level of approximately 1.8 percent.

Selection between these options is primarily a function of the weight placed on various studies reporting effects and related COHb concentrations. The revised criteria document appears to endorse a range of 2.5 to 3 percent: "It still seems safe to conclude that cardiovascular effects can be demonstrated with CO exposures as low as...(15-18 ppm CO for an 8-hour exposure; 2.5 - 3.0 percent COHb)".[119]

Two studies[13,14] have reported that aggravation of angina pectoris resulted from CO exposures sufficient to produce COHb levels in the range of 2.5 to 3 percent. These studies reported a decrease in the amount of exercise required to induce angina attacks. As stated earlier, we consider this effect to be serious because it may result in heart damage.

A lower COHb level might be selected if more weight were given to the 1978 Aronow passive smoking study.[17] This study suggests that a COHb level of approximately 1.8 percent is the point where aggravation of angina starts to occur in angina patients. The criteria document does include a cautionary statement regarding interpretation of this study because "it is possible that in addition to carbon monoxide and nicotine, other components of tobacco smoke, including oxides of nitrogen and hydrogen cyanide, and possibly psychological factors, may have contributed to the decrease in exercise performance".[120]

The Clean Air Scientific Advisory Committee (CASAC) debated this issue[121] and characterized the situation as one where there was a preponderance of evidence to support a COHb value of approximately 2.5 to 3 percent and that one new study (Aronow, 1978) reported effects at approximately 1.8 ppm. The issue is essentially whether the 1978 Aronow study should form the basis for selecting a critical COHb level of about 1.8 percent or whether that study should receive less weight and a COHb level of 2.5 percent be selected as a critical value. If the higher COHb level is selected, the 1978 Aronow study would be considered in selecting an adequate margin of safety in the final air quality standards.

E. CO Exposure and Resulting COHb Levels

The primary factors determining the final level of COHb in individuals are inspired CO concentrations, alveolar ventilation rates (which depend on the level of exercise), endogenous CO production, red cell volume in the blood, barometric pressure, and the relative diffusive capability of the lungs. For tobacco smokers, the primary source of CO and the resulting COHb levels is from the intake of tobacco smoke.[122] In the following discussion on the uptake of CO by individuals, smokers have not been considered since "smokers generally are excreting CO into the air rather than inhaling it from the ambient environment."[123]

An approximate relationship between CO exposures and equilibrium COHb levels was stated by Haldane and co-workers[124] in 1912. The Haldane equation shows that the ratio of the concentrations of COHb and oxyhemoglobin (O_2Hb) is proportional to the ratio of the partial pressures of CO and oxygen. For practical purposes, the Haldane equation can be used to

estimate the level of COHb achieved at equilibrium upon exposure to various concentrations of CO from the ambient environment.

The time required to reach equilibrium is influenced by a number of factors, the most important for normal individuals being the level of exercise as measured by the alveolar ventilation rate (V_A). At low levels of activity (resting, V_A = 5-10 L/min) approximately 8-12 hours are needed to achieve equilibrium. For a moderate walk (3 miles per hour, V_A = 20 L/min), the equilibrium level of COHb may be reached in half that time, or around 4-6 hours.

The Haldane equation cannot be used to predict COHb levels that are achieved prior to equilibrium. The non-equilibrium levels of COHb are required to evaluate the COHb levels associated with alternative 1- and 8-hour average standard levels for CO. Thus, we must rely on an alternative model or equation to obtain information on COHb levels resulting from short-term CO exposures.

Coburn et al.[122] have developed an equation which permits the calculation of COHb concentration as a function of time, considering appropriate physiological parameters. Peterson and Stewart[125] have reported excellent correlation between COHb values measured in both male and female subjects and those predicted by the Coburn equation. In addition, at levels of exercise sufficient to increase alveolar ventilation up to 2.5 times above resting levels, they measured COHb levels that were consistent with the theoretical values obtained by use of the Coburn equation. While further

experimental verification is needed to demonstrate that the Coburn equation accurately predicts uptake and excretion of CO under a variety of conditions, it is the best tool available for estimating the COHb levels that will result from short-term (1- to 8-hour exposures to ambient CO concentrations.

Table 2 shows the relationship for non-smokers between percent COHb and various exposures of CO as estimated by the Coburn and Haldane equations. A moderate level of exercise, equivalent to a 3 miles-per-hour walk, has been selected as a reasonable estimate of the maximum exercise level achieved by most individuals with angina or cardiovascular heart disease. These estimates would indicate that CO concentrations at the current standard could lead to COHb levels of about 2.1 and 1.5 percent for the 1-hour (35 ppm) and 8-hour (9 ppm) averages, respectively. For resting individuals, the current 1- and 8-hour standards are reasonably consistent in that both are expected to result in COHb levels of about 1.4 to 1.6 percent.

The impact of exercise level on rates of COHb accumulation is most apparent for shorter duration exposures. As illustrated in Table 2, very little difference exists in the COHb levels for resting and moderately exercising persons for 8-hour exposures to CO concentrations near the current standard level. Consequently, assumptions regarding exercise levels at the 8-hour averaging time are not as critical in estimating COHb levels as for the 1-hour averaging time.

TABLE 2

PERCENT COHb AS A FUNCTION OF CO EXPOSURE

CO (ppm)	% COHb Based on Coburn Equation[a]								% COHb at Equilibrium Based on Haldane Equation
	Exposure Time (Hours)								
	1		2		4		8		
	Resting	Moderate Exercise	Resting	Moderate Exercise	Resting	Moderate Exercise	Resting	Moderate Exercise	
5.0	0.6	0.6	0.7	0.7	0.8	0.8	0.9	0.9	0.9
9.0	0.7	0.8	0.9	1.0	1.2	1.3	1.4	1.5	1.6
15.0	1.0	1.1	1.3	1.5	1.8	2.0	2.2	2.4	-
20.0	1.1	1.4	1.6	2.0	2.3	2.6	2.9	3.1	3.5
25.0	1.3	1.6	1.9	2.4	2.8	3.2	3.6	3.8	-
35.0	1.6	2.1	2.5	3.2	3.8	4.5	4.9	5.3	-
50.0	2.2	2.9	3.5	4.5	5.2	6.3	7.0	7.6	8.2

[a]Assumed conditions: Alveolar ventilation rates: resting = 10 L/min, moderate exercise = 20 L/min (equivalent to 3 mph walk on level ground or light industry or housework); hemoglobin = 15 g/100 mL (normal); altitude = sea level; endogenous COHb level = 0.5 percent.

Accumulation rates and related COHb levels could be higher than indicated in Table 2 for individuals with anemia, pregnant women, fetuses, and individuals taking certain types of medication or drugs. For example, because of their reduced hemoglobin (Hb) levels, anemic individuals approach equilibrium levels of COHb more rapidly than those with normal Hb levels, and consequently attain a higher COHb level for a given exposure to CO. The Coburn equation predicts that for moderately exercising individuals, exposure to 35 ppm CO for 1 hour would result in 3.3 percent COHb in a person with severe anemia (Hb = 7 g/100 mL), compared to an anticipated level of 2.1 percent for normal individuals. The preceding calculations are based

on persons with a normal endogenous COHb level (0.5 percent); however, persons with hemolytic anemias may attain even higher COHb levels for a given exogenous CO exposure due to their significantly (2- to 9-fold) increased endogenous CO production.[126,127]

Table 2 portrays the COHb levels that may be achieved upon exposure to various CO concentrations for 1 or more hours. Exposure to much higher CO concentrations (50-200 ppm) for very short periods of time (1-60 minutes) may also result in significant localized COHb blood levels (bolus effect). For instance, moderately exercising individuals exposed to 50 ppm CO for 40 minutes or 200 ppm for 10 minutes may reach COHb levels in excess of 2.5 percent. These unusually high levels of CO may result from any of the following scenarios:[128] (1) in heavy traffic that has come to a halt, the ambient CO level may exceed 40-50 ppm; (2) inside a closed auto where cigarettes are being smoked, CO concentrations may exceed 87 ppm; (3) in enclosed, unventilated garages, CO levels in excess of 100 ppm have been found; (4) in a heavily-traveled vehicular tunnel, a 1-hour maximum of 218 ppm CO was recorded; and (5) for certain occupational exposures, such as those encountered by firefighters, foundry workers, miners, toll collectors, and taxi drivers, CO concentrations of 200 ppm for short periods and 60 ppm for 8 hours have been reported.

F. Other Aspects of the CO Standard

Selection of the averaging time, form of the standard, and allowed number of exceedances are all key elements in the standard decision and have a direct effect on the required level of control. The NAAQS for CO is presently 9 ppm and 35 ppm for 8-hour and 1-hour averaging times, respectively, not to be exceeded more than once per year.

The original 8-hour averaging time was selected primarily because most individuals achieve equilibrium or near-equilibrium levels of COHb after 8 hours of exposure. As mentioned previously, approximately 4-12 hours are required to achieve an equilibrium level of COHb upon continuous exposure to CO. The time to reach equilibrium is influenced primarily by the exercise level of the individual, with shorter times required for greater exercise. Another basis for the 8-hour averaging time is that most people are exposed in approximately 8-hour blocks of time (e.g., work, sleep). With respect to the 1-hour averaging time, the health effects rationale is now stronger than in 1971. Aronow has conducted several studies[14,17,18,77] which have reported health effects for persons with cardiovascular disease or chronic obstructive pulmonary disease after 1- to 2-hr exposures. In light of the above considerations we see no need to change the current 1-hour and 8-hour averaging times for the CO NAAQS.

As was noted in the preceding section, short-term (1-60 minute) peak CO concentrations (50-200 ppm) that have been observed in ambient situations may result in COHb levels of concern due to the bolus effect. However, analyses of existing air quality data suggest that attainment of a longer averaging time standard will limit the magnitude of short-term peak concentrations. For example, air quality data obtained in 1974-1976 at a site in Los Angeles that is 6 meters (m) high and 3 m from the curb of a highway bearing an average traffic load of 25,000 vehicles per day were analyzed to determine for various averaging times the peak concentra-

tions that would be expected if the present NAAQS were just attained. The maximum values observed were 46 and 30 ppm for 1- and 8-hour averaging times. Using a 2-parameter averaging time model,[128a] we have calculated that attainment of the 8-hour standard would result in peak 5- and 10-minute concentrations of 36 and 29 ppm, respectively. Although this site might not represent the worst possible situation, this analysis does seem to indicate that attainment of longer averaging time standards would tend to limit short-term peaks.

No decision has been reached on a recommendation regarding the need for, or nature of, any modification of the standard. However, in the event that a recommendation were made to retain the current 8-hour standard level, a question would remain as to the appropriateness of retaining the current 1-hour standard level. As indicated by the COHb levels anticipated for moderately exercising individuals for the current 1- and 8-hour standard levels, arguments could be made for some change in the 1-hour standard level. On the other hand, a case could be made for leaving the standard essentially unchanged on the basis that attainment of the existing 9 ppm 8-hour standard level also protects against shorter averaging times of concern. The latter choice might be attractive because it would limit disruptions in the existing air quality management program without any apparent health liabilities.

The current CO standard has a deterministic form, allowing only one exceedance per year. This deterministic approach has several limitations, one of which is that it does not adequately take into account the random nature of meteorological variations. The original purpose of permitting a single exceedance was to allow for unique meteorological conditions that were not representative of air quality problems in a given area. However,

since the present form of the standard specifies, in effect, that there be zero probability that the second-highest concentration measured in a year exceed the standard level, it does not achieve this purpose because when a single exceedance of the standard is permitted, a definite possibility exists that a second or third exceedance will also occur. The only way to be certain that subsequent exceedances will not occur is to permit no initial exceedances of the standard. The limitation of the current deterministic form means that compliance with the standard, and consequently pollutant emission control requirements, would be determined on the basis of exceedingly rare weather conditions. These are the same arguments that prompted EPA to change the ozone standard from a deterministic to a statistical form.[129] Because of these arguments, we believe that the CO standard also should be stated in a statistical form. This would mean that the allowable number of exceedances of the standard would be expressed as an average or expected number per year. The emission reductions to be achieved in the required control implementation program would be based on a statistical analysis of monitoring data over the preceding 3-year period.

We are also considering changing the form of the CO standard to permit one calendar day in which the 1-hour standard could be exceeded. No health effects rationale exists to support such a change; however, as in the case of the ozone standard revision, this form of the standard has several advantages, such as (1) requiring less interpretation of data in calculating attainment or non-attainment and (2) achieving greater stability in the design statistics needed for control strategy development. We are still studying alternative forms for the 8-hour standard before making a decision on how to handle the problem of overlapping or running averages.

V. FACTORS TO BE CONSIDERED IN SELECTING A MARGIN OF SAFETY AND A STANDARD LEVEL

Selecting an ambient air quality standard with an adequate margin of safety requires that the Administrator consider and account for uncertainties in the health effects evidence in arriving at the standard. In the case of CO, these effects are principally associated with the evidence leading to a critical COHb level and with the relationship between ambient CO exposures and the resultant COHb levels in selected population groups under various environmental conditions and levels of stress. These factors include: (1) the relevance of the 1978 Aronow study, (2) the implications for humans from animal study findings, (3) the predictability of the relationship between ambient CO concentrations and elevated COHb levels, (4) the altitude effect, (5) the increased risk of adverse effects in persons with anemia, and (6) the bolus effect.

A. Role of the 1978 Aronow Study in Selecting a Critical COHb Level

The preponderance of evidence indicates that adverse effects in angina patients are associated with COHb levels in the range of 2.5 - 3.0 percent. The 1978 Aronow study (previously discussed) is an exception and suggests that effects can occur in angina patients at COHb levels of approximately 1.8 percent. If this study is given full weight and is interpreted as showing adverse effects down to COHb levels of 1.8 percent, a more stringent 1-hour standard must be considered. Such a standard would need to protect against COHb levels below 1.8 percent in order to provide an adequate margin of safety.

The fact that the 1978 Aronow study has not been replicated, as well as the possibility that effects may have been enhanced by exposure to toxic agents other than CO, argues for giving this study less weight in selecting the final air quality standard. In that case, 2.5 - 3.0 percent would be considered the critical COHb level and the 1978 Aronow study

would serve as an element for consideration in selecting an adequate margin of safety but not in identifying the specific critical COHb level.

B. Animal Studies

Although the findings of animal studies currently cannot be extrapolated directly to identify a CO or COHb concentration that will cause an effect in man, much of the evidence compiled from animal studies tends to reinforce the findings obtained in human studies. One important area of concern still exists, however, where little human data are available. This evidence relates primarily to animal studies showing that the developing fetus is exposed to COHb concentrations considerably higher than the pregnant mother for long-term CO exposures. Because the COHb levels may well be elevated in the fetus, and because the fetus is probably more susceptible to the adverse impacts of impaired oxygen delivery, findings from these animal studies denote a need for caution in assessing possible human effects and in establishing an adequate margin of safety for the standard. Even moderate CO exposures may have a harmful effect on fetal development, as has been suggested in studies of smoking mothers.

C. Uncertainty Regarding the Relationship Between Ambient CO Exposure and Resulting COHb Levels

No simple model is available that can provide a foolproof method of predicting COHb levels that result from alternative CO exposure concentrations and patterns. Not only do we lack a perfect model to provide this information, but numerous confounding factors, such as altitude, smoking habits, exercise levels, and individual health status, make the task even more difficult. While projections must be made of ambient CO concentrations that could produce critical COHb levels, the uncertainty in these projections must be accounted for in the margin of safety.

D. Altitude

Hypoxemia can occur at higher altitudes due to the reduced oxygen pressure in the atmosphere; in addition, altitude can increase the rate of accumulation of COHb in the blood. However, normal residents of high-altitude locations appear to have adjusted to the elevation and do not seem to exhibit an interaction between the effects of altitude and CO exposures.[130] Still of concern are impaired visitors from lower altitude locations who may be adversely affected by altitude hypoxemia and by COHb concentrations which are higher than those reached at lower elevations for the same ambient CO concentration. The possible adverse effect on impaired visitors to high-altitude areas should be considered in selecting an adequate margin of safety for the CO standard.

E. Individuals with Anemia

Little quantitative data are available on the COHb concentrations that result in anemic individuals for CO exposures near or below the current standards. The Coburn equation predicts little difference in the final COHb level achieved by anemics and normal individuals for 8-hour exposures to 10 ppm, but a more significant difference for shorter-term exposures at higher concentrations. For example, persons with severe anemia (Hb = 7 g/100 mL) who are moderately exercising and are exposed to 35 ppm CO for 1 hour may reach 3.3 percent COHb, compared to an anticipated level of 2.1 percent for normal individuals. In addition to their more rapid equilibration with a given exogenous CO exposure, persons with hemolytic anemia may be expected to attain even higher COHb levels due to their higher initial COHb values (due to increased endogenous CO

production). While dietary anemia is no longer as widespread a disease as it was some years ago, anemias resulting from various pathological conditions are still major health problems and low levels of CO exposure could pose a health threat to such groups. Anemic individuals who also suffer from angina or who are pregnant would seem to be particularly high-risk categories. However, since very little data exist regarding the effects of CO exposure on anemic individuals, we must base our assessment of the critical COHb level on the available evidence for persons with angina and other cardiovascular diseases, in whom the lowest CO effect level has been observed. Nevertheless, the increased risk for anemics, and other individuals whose uptake of CO is greater, should be considered in determining an adequate margin of safety.

F. Smokers

Little or no evidence exists that would suggest the need for a more restrictive national ambient air quality standard to protect smokers from a possible incremental COHb burden from the air. In fact, even in a pristine environment, smokers will have COHb levels ranging from 2 to 17 percent. Furthermore, the existing evidence suggests that cigarette smokers exposed to an environment where CO is at the ambient standard level are generally excreting more CO into the air than they are inhaling from that environment. While these individuals are at a definite risk from accelerated incidence of heart and related disease, these risks are principally associated with cigarette smoking and not with incremental CO levels at or near the standard.

G. Bolus Effect

A factor that should be considered in selecting an adequate margin of safety is the uncertainty relating to adverse health impacts from short duration (5-10 minutes) high-level CO exposures. While the data

base is incomplete regarding the mechanism or effect of the peak short-term exposures, the criteria document and the CASAC have underlined the potential seriousness of CO delivered to the body in this manner. The consequence may well be adverse effects separate and, perhaps, more intense than those associated with elevated COHb concentrations, a phenomenon referred to as the bolus effect. While this factor should be a consideration in establishing an adequate margin of safety for the standard, existing air quality data does indicate that attainment of a longer averaging time standard will limit the magnitude of short-term peak concentrations, as discussed previously. Consequently, the bolus effect, while of concern in selecting a margin of safety, does not appear to be an over-riding consideration in the final standard decision.

REFERENCES

1. U.S. EPA. Air Quality Criteria for Carbon Monoxide. External Review Draft, April 1979. (Hereinafter referred to as Criteria Document.) Environmental Criteria and Assessment Office, Office of Research and Development, U.S. EPA, Research Triangle Park, N.C.

2. A Legislative History of the Clean Air Act Amendments of 1970, p. 410.

2a. Criteria Document, pp. 9-1 to 9-12.

3. Ibid. Chp. 11 Ref. 222 (Coburn et al., 1969).

4. Ibid. Chp. 9 Ref. 15 (Coburn et al., 1966).

5. Ibid. Chp. 11 Ref. 53 (Delivoria-Papadopoulos et al., 1970).

6. Ibid. Chp. 9 Ref. 9 (Coburn, 1970).

6a. Ibid. pp. 11-51 and 11-52.

7. Ibid. Chp. 9 Ref. 53 (Ramirez et al., 1974).

8. Ibid. Chp. 9 Ref. 25 (Goldbaum, 1977).

9. Ibid. Chp. 9 Ref. 27 (Goldbaum et al., 1976).

10. Ibid. Chp. 9 Ref. 28 (Goldbaum et al., 1976).

11. Ibid. Chp. 9 Ref. 29 (Goldbaum et al., 1975).

12. CASAC Transcript, Jan. 30-31, 1979, pp. 67-89.

13. Criteria Document. Chp. 11 Ref. 2 (Anderson et al., 1973).

14. Ibid. Chp. 11 Ref. 5 (Aronow & Isbell, 1973).

15. Ibid. Chp. 11 Ref. 9 (Aronow & Rokaw, 1971).

16. Ibid. Chp. 11 Ref. 7 (Aronow et al., 1972).

17. Ibid. Chp. 11 Ref. 2b (Aronow, 1978).

18. Ibid. Chp. 11 Ref. 6 (Aronow et al., 1974).

19. Ibid. Chp. 11 Ref. 14 (Ayres et al., 1970).

20. Ibid. Chp. 11 Ref. 15 (Ayres et al., 1969).

21. Ibid. Chp. 11 Ref. 48 (Corya et al., 1976).

22. Ibid. Chp. 11 Ref. 221 (Zenkevic, 1973).

23. Ibid. Chp. 11 Ref. 57 (Ejam-Berdyev, 1973).

REFERENCES

24. Ibid. Chp. 11 Ref. 123a (Komatsu, 1959).

25. Ibid. Chp. 11 Ref. 42 (Cohen et al., 1969).

26. Ibid. Chp. 11 Ref. 76 (Goldsmith & Landau, 1968).

27. Ibid. Chp. 11 Ref. 103 (Hexter & Goldsmith, 1971).

28. Ibid. Chp. 11 Ref. 128 (Kuller et al., 1975).

29. Ibid. Chp. 11 Ref. 168 (Radford, 1975).

30. Ibid. Chp. 11 Ref. 128a (Kurt, 1978).

31. CASAC Transcript, pp. 141-143, 186-190.

32. Criteria Document Chp. 11 Ref. 67 (Fodor & Winneke, 1972).

33. Ibid. Chp. 11 Ref. 85 (Groll-Knapp et al., 1972).

34. Ibid. Chp. 11 Ref. 19 (Beard & Grandstaff, 1975).

35. Ibid. Chp. 11 Ref. 107 (Horvath et al., 1971).

36. Ibid. Chp. 11 Ref. 95 (Haider et al., 1975).

37. Ibid. Chp. 11 Ref. 217 (Winneke, 1974).

38. Ibid. Chp. 11 Ref. 218 (Winneke et al., 1976).

39. Ibid. Chp. 11 Ref. 39 (Christensen et al., 1977).

40. Ibid. Chp. 11 Ref. 23 (Benignus & Otto, 1977).

41. Ibid. Chp. 11 Ref 167 (Putz et al., 1976).

42. Ibid. Chp. 11 Ref. 142 (McFarland et al., 1944).

43. Ibid. Chp. 11 Ref. 97 (Halperin et al., 1959).

44. Ibid. Chp. 11 Ref. 21 (Bender et al., 1972).

45. Ibid. Chp. 11 Ref. 22 (Bender et al., 1971).

46. Ibid. Chp. 11 Ref. 186 (Schulte, 1973).

REFERENCES

47. Ibid. Chp. 11 Ref. 158 (O'Donnell et al., 1971).

48. Ibid. Chp. 11 Ref. 141 (McFarland, 1973).

49. Ibid. Chp. 11 Ref. 143 (McFarland et al., 1972).

50. Ibid. Chp. 11 Ref. 183 (Salvatore, 1974).

51. Ibid. Chp. 11 Ref. 114 (Johnson et al., 1974).

52. Ibid. Chp. 11 Ref. 115 (Johnson et al., 1976).

53. Ibid. Chp. 11 Ref. 219 (Wright et al., 1973).

54. Ibid. Chp. 11 Ref. 175 (Ray & Rockwell, 1970).

55. Ibid. Chp. 11 Ref. 177 (Rockwell & Weir, 1975).

56. Ibid. Chp. 11 Ref. 178 (Rockwell & Ray, 1967).

57. Ibid. Chp. 11 Ref. 215 (Weir & Rockwell, 1973).

58. Ibid. Chp. 11 Ref. 181 (Rummo & Sarianis, 1974).

59. Ibid. Chp. 11 Ref. 220 (Yabroff et al., 1974).

60. Ibid. Chp. 11 Ref. 31 (Brinkhaus, 1977).

61. Ibid. Chp. 11 Ref. 35 (Chevalier et al., 1966).

62. Ibid. Chp. 11 Ref. 60 (Ekblom et al., 1975).

63. Ibid. Chp. 11 Ref. 73 (Gliner et al., 1975).

64. Ibid. Chp. 11 Ref. 89 (Guillerm et al., 1963).

65. Ibid. Chp. 11 Ref. 207 (Vogel & Gleser, 1972).

66. Ibid. Chp. 11 Ref. 208 (Vogel et al., 1972).

67. Ibid. Chp. 11 Ref. 59 (Ekblom & Huot, 1972).

68. Ibid. Chp. 11 Ref. 155 (Nielsen, 1971).

69. Ibid. Chp. 11 Ref. 165 (Pirnay et al., 1971).

REFERENCES

70. Ibid. Chp. 11 Ref. 50 (Dahms et al., 1975).

71. Ibid. Chp. 11 Ref. 36 (Chiodi et al., 1941).

72. Ibid. Chp. 11 Ref. 45 (Collier et al., 1972).

73. Ibid. Chp. 11 Ref. 108 (Horvath et al., 1975).

74. Ibid. Chp. 11 Ref. 3 (Aronow & Cassidy, 1975).

75. Ibid. Chp. 11 Ref. 187a (Seppanen, 1977).

76. Ibid. Chp. 11 Ref. 205 (MacMillan, 1976) ~~74 (Goldsmith, 1970)~~.

77. Ibid. Chp. 11 Ref. 4 (Aronow et al., 1977).

78. Ibid. Chp. 10 Ref. 27 (Dykyk et al., 1975).

79. Ibid. Chp. 10 Ref. 29 (Dyer et al.).

80. Ibid. Chp. 10 Ref. 32 (Fechter & Annau, 1976).

81. Ibid. Chp. 10 Ref. 33 (Fechter & Annau, 1977).

82. Ibid. Chp. 10 Ref. 36A (Ginsberg & Myers, 1974).

83. Ibid. Chp. 10 Ref. 86 (Schwetz et al., 1975).

84. Ibid. Chp. 11 Ref. 13 (Astrup et al., 1972).

85. Ibid. Chp. 10 Ref. 55 (Longo & Hill, 1977).

86. Ibid. Chp. 11 Ref. 136 (Longo, 1977).

87. Ibid. Chp. 11 Ref. 138 (McMahon et al., 1965).

88. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 161 (Mulcahy et al., 1970).

89. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 206 (Simpson, 1957).

90. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 143 (Lowe, 1959).

91. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 153 (Meredith, 1975).

92. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 25 (Butler & Alberman, 1969).

REFERENCES

93. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 28 (Butler et al., 1972).

94. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 218 (U.S. Public Health Service, 1973).

95. Ibid. Chp. 11 Ref. 131 (Lichty et al. 1957).

96. New Mexico State Department of Health. "Birthweight and Altitude." New Mexico Department of Health, Albuquerque, NM, 1975, pp. 7-16.

97. Criteria Document, Chp. 11 Ref. 136 (Longo, 1977) Ref. 48 (Comstock et al., 1971).

98. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 156 (Meyer et al, 1976).

99. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 157 (Meyer et al., 1975).

100. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 170 (Niswander & Gordon, 1972).

101. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 173 (Ontario Dept. of Health, 1967).

102. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 174 (Ontario Dept. of Health, 1967).

103. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 71 (Fedrick et al., 1971).

104. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 55 (Davie et al., 1972).

105. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 86 (Goldstein, 1972).

106. Ibid. Chp. 11 Ref. 136 (Longo, 1977) Ref. 27 (Butler & Goldstein, 1973).

107. Knelson, John H. "General Population Morbidity Estimates from Exacerbation of Angina Pectoris Related to Low-Level Carbon Monoxide Exposure." EPA, Health Effects Research Laboratory, August 1975.

108. CASAC transcript, pp. 150-151.

109. Criteria Document, p. 11-33.

110. U. S. Dept. of Health, Education, and Welfare (DHEW). Prevalence of Chronic Circulatory Conditions, United States, 1970. DHEW Publication No. (HRA) 74-1511. Rockville, MD. 1973.

REFERENCES

111. Lown, Bernard. "Sudden cardiac death: The major challenge confronting contemporary cardiology." Amer. J. Cardiol. 43: 313, 1979.

112. Federal Register Vol. 36, No. 84, p. 8186 (April 30, 1971).

113. Criteria Document, Chp. 11 Ref. 18 (Beard & Wertheim, 1967).

114. Criteria Document, pp. 11-9 and 11-10.

115. Ibid. Chp. 11 Ref. 159 (O'Donnell et al., 1971).

116. Ibid. Chp. 11 Ref. 193 (Stewart et al., 1973).

117. Ibid. Chp. 11 Ref. 197 (Stewart et al., 1970).

118. Ibid. Chp. 11 Ref. 161a (Otto et al., 1978).

119. Ibid. p. 11-83.

120. Ibid. p. 11-28.

121. CASAC transcript, pp. 182-191.

122. Criteria Document Chp. 9 Ref. 12 (Coburn et al., 1965).

123. Ibid. p. 11-52.

124. Ibid. Chp. 9 Ref. 21 (Douglas et al., 1912).

125. Ibid. Chp. 9 Ref. 51 (Peterson & Stewart, 1975).

126. Ibid., Chp. 11 Ref. 41.

127. Ibid., Chp. 11 Ref 134.

128. Ibid. pp. 1-5, 6-46 to 6-53, and 11-77 to 11-81.

128a. Larsen, R.I. A Mathematical Model for Relating Air Quality Measurements to Air Quality Standards. U.S. EPA. Office of Air Programs Publication No. AP-89. 1973.

129. Federal Register Vol. 43, No. 121, p. 26967 (June 22, 1978).

130. Criteria Document Chp. 11 Ref. 216 (Weiser et al., 1978).

131. Ibid. Chp. 11 Ref. 8 (Aronow et al., 1974).