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

May 17, 1984

OFFICE OF
THE ADMINISTRATOR

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

Dear Mr. Ruckelshaus:

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

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

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

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

Sincerely,

Morton Lippmann, Chairman
Clean Air Scientific
Advisory Committee

Enclosure

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

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

Addendum to the CO Air Quality Criteria Document

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

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

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

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

A. The role of the Aronow studies

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

B. The role of the Anderson study

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

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

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

C. Additional studies

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

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

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

E. Summary of cardiovascular effects

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

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

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

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

OAOPS Staff Paper Review of the NAAQS For Carbon Monoxide

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

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

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

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

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