125311

BY THE U.S. GENERAL ACCOUNTING OFFICE

Report To The Chairman, Subcommittee On Oversight And Investigations, Committee On Energy And Commerce, House Of Representatives

Status Of EPA's Air Quality Standards For Carbon Monoxide

The Clean Air Act requires the Environmental Protection Agency (EPA) to establish, and periodically review and revise national air quality standards. EPA established standards for carbon monoxide in 1971 and in August 1980 proposed updated revisions to those standards. Seven of the eight key studies EPA used to support the revisions were authored by a cardiologist employed by the Veterans Administration.

In March 1983 EPA was about to issue its revised standards when it learned that the cardiologist had been under investigation by the Food and Drug Administration and the Veterans Administration since 1979 for, among other things, alleged falsification of research. As a result, EPA delayed issuing the standards, conducted an audit of the research data, and concluded that it could not rely on the cardiologist's research. Even without this research, EPA believes that there is a sufficient scientific basis to support revised standards but has not yet decided what those standards will be.

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WASHINGTON, D.C. 20548

RESOURCES, COMMUNITY,
AND ECONOMIC DEVELOPMENT
DIVISION

B-216003

The Honorable John D. Dingell
Chairman, Subcommittee on
Oversight and Investigations
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

As requested in your letters of September 20 and October 18, 1983, and subsequent discussions with your office, this report discusses the Environmental Protection Agency's (EPA's) development of its carbon monoxide standards. EPA proposed revised standards for carbon monoxide in 1980 but has not yet published final standards. This report discusses the research base supporting the proposed standards and communication between several agencies concerning a researcher upon whom EPA was relying when developing revised standards.

As arranged with your office, unless you publicly release its contents earlier, we will make this report available to other interested parties 30 days after the issue date. At that time copies of the report will be sent to appropriate congressional committees; the Administrator, EPA; the Secretary, Health and Human Services; the Administrator, Veterans Administration; and the Director, Office of Management and Budget.

Sincerely yours,

J. Dexter Peach
Director

BY THE U.S GENERAL ACCOUNTING OFFICE
REPORT TO THE CHAIRMAN, SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS, HOUSE COMMITTEE ON ENERGY AND COMMERCE

STATUS OF EPA'S AIR QUALITY STANDARDS FOR CARBON MONOXIDE

D I G E S T

The Clean Air Act of 1970 required the Environmental Protection Agency (EPA) to establish air quality standards. These standards were to protect the public health and welfare and were to be based on the latest available scientific data. In 1977, the Congress amended the act to require EPA to review and revise, as necessary, all air quality standards before the end of 1980 and at 5-year intervals thereafter.

Carbon monoxide is one of the pollutants that EPA regulates under the act. Carbon monoxide is toxic because, when inhaled, it combines with certain elements in the blood, which reduces the blood's capacity to carry oxygen.

EPA initially issued carbon monoxide standards in 1971 and in August 1980 proposed revisions to these standards. After considering various alternatives, EPA was about to issue the revised standards when it learned in 1983 that its primary researcher, Dr. Wilbert S. Aronow,[1] had been investigated by the Veterans Administration (VA) and the Food and Drug Administration (FDA) for, among other things, alleged falsification of research results. This raised doubts about seven studies conducted by Dr. Aronow that were used by EPA as the primary support for its proposed revision to the carbon monoxide standards.

The Chairman, Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, asked GAO to provide information on the following issues:

--EPA's development of the carbon monoxide standard and the research supporting the standard in its present form; and

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[1]Dr. Aronow worked as a cardiologist at the VA Medical Center in Long Beach, California, from 1964 until he resigned in 1982. From 1973 he served as Chief of the Medical Center's Cardiovascular Section.

--FDA and VA reviews and investigations of research conducted by Dr. Aronow and how these agencies communicated the results of their investigations to EPA. (See p. 3.)

RESEARCH SUPPORTING EPA'S DEVELOPMENT OF THE CARBON MONOXIDE STANDARD

The carbon monoxide standards established in 1971 were based primarily on a study which suggested that low-level carbon monoxide exposure would affect the central nervous system. Subsequent to 1971, several researchers attempted unsuccessfully to replicate this study, raising questions about its reliability. While EPA recognized the limitations of its data regarding carbon monoxide's effect on the nervous system, it took no action to change the standards during the 1970's because new studies conducted during this time showed that the standards were still needed to protect persons with certain heart conditions. These studies were conducted primarily by Dr. Aronow and showed that low levels of carbon monoxide exposure had an adverse effect on the cardiovascular system, specifically on angina patients. (See pp. 6-8.)

EPA was about to issue revised carbon monoxide standards using these studies when the Washington Post published an article in March 1983 concerning an FDA investigation of Dr. Aronow's drug-related research. (See pp. 10 and 22.)

Because of the potential implications of this investigation for all of Dr. Aronow's research, EPA delayed issuing the revised standards and assembled a peer review committee of experts in April 1983 to evaluate Dr. Aronow's carbon monoxide research. The committee subsequently expressed concern about the validity of results reported, concluded that EPA could not rely on Dr. Aronow's data, and recommended that similar carbon monoxide research be conducted by other independent research groups. (See pp. 10-12.)

With the Aronow research results in question, EPA is left with one study which supports its proposed revision to the carbon monoxide standards. Published in 1973, this study demonstrates that low levels of carbon

monoxide adversely affect the health of angina patients. Because of criticisms of this study by various business organizations and state and local governments, EPA assessed the study in 1983, identified some flaws in its design and conduct, and suggested that it be replicated. EPA concluded, however, that overall, the study is scientifically valid. (See pp. 13-16.)

EPA currently believes that this study and three other carbon monoxide studies--which show that low levels of carbon monoxide exposure affect the endurance of healthy subjects--provide a sufficient scientific basis to support a regulatory decision on carbon monoxide. Nevertheless, EPA is currently sponsoring carbon monoxide research that, among other things, will attempt to replicate or verify Dr. Aronow's studies. The results of this research are expected to be available during the 1985-86 time frame. (See pp. 12-13 and 16.)

On August 9, 1984, EPA published a notice in the Federal Register that summarized events surrounding the development of the proposed carbon monoxide standards. The notice stated that EPA is inclined to issue the proposed standards, but, because of the questions raised about its supporting scientific evidence, EPA is requesting public comment by September 24, 1984. After receiving and considering the comments, EPA will decide whether to issue the standards as proposed, revise the standards, or wait until 1985-86 when results of the ongoing research will be available. (See pp. 19-20.)

COMMUNICATION BETWEEN EPA, FDA, AND VA AFFECTED REEXAMINATION OF THE CARBON MONOXIDE STANDARDS

While employed at VA, Dr. Aronow conducted research on certain new drugs for pharmeceutical companies. VA normally allows this type of research if it is approved in advance by the VA medical center where the research is to be conducted. In June 1979 while reviewing an application to approve the use of certain drugs, FDA began an inspection of some of Dr. Aronow's drug research and disclosed a number of problems, including incorrect patient selection, conflicting data, and possible falsification of records. In October

1979 FDA provided the VA Inspector General's Office with a report of its inspection. Subsequent VA inspections of Dr. Aronow's research in 1980 resulted in VA directing him to discontinue all research activities. (See pp. 21-24.)

In addition, FDA and Dr. Aronow signed a consent agreement in October 1982 limiting Dr. Aronow's access to certain new drugs and his right to serve as a clinical investigator of those drugs. FDA also placed Dr. Aronow's name on a list of those who have agreed to restrict or cease their role as investigator of these drugs for pharmaceutical companies. (See pp. 23-24.)

During the 1979-80 time frame, EPA was attempting to establish a formal interagency agreement with VA under which Dr. Aronow would conduct carbon monoxide exposure research. EPA signed the proposed interagency agreement on October 9, 1979, and sent it to VA for approval in January 1980. (See pp. 27-28.)

In August 1980 there were written and telephone contacts between EPA and VA regarding the proposed interagency agreement. At that time VA declined to approve the agreement because Dr. Aronow had already completed the research using VA funding. In reviewing these contacts, GAO could not find any indication that anyone in VA notified EPA of Dr. Aronow's research problems. In explaining this lack of notification, VA's Assistant Chief Medical Director for Research and Development told GAO that VA considered the problems concerning Dr. Aronow to be an internal personnel matter and did not have any reason to doubt the quality of Dr. Aronow's carbon monoxide research. Therefore, unaware of the VA and FDA investigations, EPA began using the results of Dr. Aronow's studies as a basis for revising carbon monoxide standards. (See pp. 28-29.)

FDA, however, did send a letter to EPA in July 1982 concerning its investigation of Dr. Aronow. This was done after an FDA official read a Federal Register notice requesting comments on Dr. Aronow's carbon monoxide research. However, because of a breakdown in communications within EPA, officials in the office responsible for developing the carbon monoxide standards said that they never

received the letter. These officials told GAO that, had they received the FDA letter or had any other earlier indication of Dr. Aronow's research problems, they would have established a peer review committee at that time to review his carbon monoxide research and would have begun earlier to reexamine the data base supporting the standards. (See pp. 29-31.)

AGENCY COMMENTS

GAO did not obtain EPA, VA, or FDA written comments on this report.

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ABBREVIATIONS

CASAC	Clean Air Science Advisory Committee
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
ppm	parts per million
VA	Veterans Administration

CHAPTER 1

INTRODUCTION

The Clean Air Act of 1970 requires the establishment and revision of national air quality standards. Section 108 of the act directs the Environmental Protection Agency (EPA) to identify all pollutants that may reasonably be anticipated to endanger public health or welfare and to issue air quality criteria that reflect the latest available scientific information and serve as a basis for standard setting for such pollutants. Section 108(c) of the act requires periodic review, and, if appropriate, revision of existing criteria and standards. Section 109(d), added by the Clean Air Act Amendments of 1977, requires that EPA review and revise, as necessary, all air quality standards prior to the end of calendar year 1980 and at 5-year intervals thereafter.

Carbon monoxide is one of six pollutants that EPA regulates under these sections of the act. It is a colorless, odorless gas which is toxic because of its tendency, when inhaled, to bind with hemoglobin in the blood and form carboxyhemoglobin. Because hemoglobin in this form is unable to transport oxygen, the oxygen-carrying capacity of the blood is reduced. Furthermore, the presence of carboxyhemoglobin inhibits the release of oxygen from the remaining hemoglobin. EPA believes that the reduction in the ability to deliver oxygen has effects on the cardiovascular, central nervous, pulmonary, and other systems. EPA promulgated national air quality standards for carbon monoxide on April 30, 1971. These standards set carbon monoxide limits at 9 parts per million (ppm) for an 8-hour average and 35 ppm for a 1-hour average, neither to be exceeded more than once a year.

In developing these standards and proposing revisions, EPA has attempted to identify the lowest concentration of carboxyhemoglobin that credible studies have associated with human health effects for sensitive persons. The selection of this critical carboxyhemoglobin blood level is a key element in establishing the final standards.

The primary sources of carbon monoxide emissions are automobile, truck, and bus exhausts. Carbon monoxide is regulated under a combination of federal and state programs under the Clean Air Act. Under the act, the states are responsible for ensuring attainment and maintenance of the carbon monoxide and all other air quality standards. Section 110 of the act requires states to submit to EPA State Implementation Plans that explain how the state will meet air quality standards.

If a state does not meet air quality standards by a specified deadline, EPA may take enforcement measures against the state. Such measures could include requiring a state to develop a vehicle inspection and maintenance program for mobile sources like cars,

economic sanctions, or a construction ban for new or modified stationary sources such as factories.

EPA'S STANDARD-SETTING PROCESS FOR CARBON MONOXIDE

EPA has established a detailed process to review the available health data and regulate pollutants such as carbon monoxide. EPA develops a criteria document and staff paper on the pollutant that are then reviewed by EPA's Clean Air Science Advisory Committee (CASAC).[1] After the review, the EPA Administrator determines what level to set the standards based on the available scientific information and his judgement as to what constitutes an adequate margin of safety. EPA requests public comments at several points during this process.

Specifically, the following steps are taken:

--EPA conducts a search of all known scientific literature concerning a criteria pollutant and consolidates the relevant studies into a criteria document that becomes the scientific basis for the standards (for a discussion of the peer review procedures to which EPA subjects these studies, see app. I);

--EPA develops exposure and sensitivity analyses that compare the relationships between concentrations of the pollutant in the air and the resultant health effects and tests various assumptions regarding the comparisons;

--EPA drafts a staff paper that, among other things, evaluates the key studies in the criteria document and identifies the critical elements to be considered in the revision of the standards;

--CASAC reviews the criteria document and staff paper and drafts a letter of closure advising the EPA Administrator on the scientific adequacy of the documents;

--EPA prepares a proposed Federal Register package that is reviewed at a senior level within EPA before being sent to the Administrator for a final decision.

DR. WILBERT ARONOW

Key research studies EPA used to support its proposed carbon monoxide standards include those conducted by Dr. Wilbert S. Aronow, a cardiologist employed by the Veterans Administration

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[1]CASAC is a standing committee of scientists and engineers external to the federal government, established under section 109 of the Clean Air Act, to advise the EPA Administrator on the scientific bases for air quality standards.

(VA). EPA included seven of Dr. Aronow's studies in its 1979 revised criteria document for carbon monoxide. He worked as a cardiologist at the VA Medical Center in Long Beach, California, beginning in 1964 and was the Chief of the Cardiovascular Section from 1973 until he resigned in 1982. At the VA Medical Center in Long Beach, he was a medical researcher, author, and prominent expert on cardiovascular functions.

In 1979 and 1980, the Food and Drug Administration (FDA) reviewed Dr. Aronow's research on investigational new drugs.[2] In 1982 FDA and Dr. Aronow signed a consent agreement limiting his authority to serve as an investigator for such drugs. Between 1980 and 1982 VA also conducted several reviews of Dr. Aronow's work for, among other things, alleged falsification of research and receiving outside remunerations. After learning of the results of the FDA inspections, EPA delayed implementation of its revised carbon monoxide standards and established a peer review committee to examine some of Dr. Aronow's carbon monoxide studies.

OBJECTIVES, SCOPE, AND METHODOLOGY

In letters dated September 20, 1983, and October 18, 1983, and our subsequent discussions with his office, the Chairman, Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, asked us to provide information on the following issues:

--EPA's development of the carbon monoxide standards and the research supporting the standards in their present form; and

--FDA, VA, and EPA inspections and investigations of research conducted by Dr. Wilbert S. Aronow, including FDA's action concerning Dr. Aronow's compliance with FDA regulations and notification to other federal agencies of the result of its inspections. This also included Dr. Aronow's compliance with VA procedures in performing this research and VA's policies for receipt of outside remunerations by its employees.

Our work was performed between November 1983 and August 1984 at EPA, FDA, and VA headquarters in Washington, D.C.; EPA's Office of Air Quality Planning and Standards in Durham, North Carolina; EPA's Environmental Criteria and Assessment Office and EPA's Health Effects Research Laboratory in Research Triangle Park, North Carolina.

To examine EPA's development of the carbon monoxide standards, including the studies supporting the standards, we reviewed EPA's 1971 standards, the August 1980 proposed revisions, and documentation discussing the various changes to the standards that EPA has since considered. We also examined supporting documentation, including 1970 and 1979 criteria documents, a 1984

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[2]Clinical testing of a new drug or testing for additional uses of an approved drug.

criteria document addendum, EPA staff papers, action memoranda, public comments, transcripts of CASAC meetings, sensitivity and exposure analyses, and other pertinent memoranda and letters.

We discussed the carbon monoxide standards and the studies supporting the standards with the officials responsible for developing the staff paper and other supporting documentation in EPA's Office of Air Quality Planning and Standards. We also discussed the criteria document and the key carbon monoxide studies with officials in EPA's Office of Health and Environmental Assessment. We discussed EPA's past and ongoing research with officials in EPA's Health Effects Research Laboratory. Further, we talked with the executive secretary and selected members of EPA's Clean Air Science Advisory Committee concerning their review of EPA's criteria document and staff paper.

In developing information on the research supporting the current and proposed standards, we talked with the chairman and two members of the peer review committee that EPA established to review Dr. Aronow's research in April 1983. We also reviewed six of the seven carbon monoxide studies by Dr. Aronow. These were the six studies that EPA identified to a peer review committee as being of primary importance when EPA requested a review of his carbon monoxide research in April 1983. We discussed these studies and other peer review-related issues with the editors or other senior officials of each of the four journals in which these articles were published.[3] We also discussed the key carbon monoxide studies and EPA's use of those studies with the principal author of seven of them, Dr. Aronow, and the principal author of another, Dr. Einar Anderson. We also discussed ongoing or planned research on carbon monoxide with officials from the Health Effects Effects Institute in Cambridge, Massachusetts, and the California Air Resources Board.

Finally, we discussed the Aronow studies and other carbon monoxide-related matters with officials from organizations who have commented on the sufficiency of the standards, including the Natural Resources Defense Council, the State and Territorial Air Pollution Program Administrators, General Motors Corporation, the Spokane County Air Pollution Control Authority, and medical doctors in Torrence, California, and Cleveland, Ohio.

To examine FDA's actions concerning Dr. Aronow's compliance with FDA regulations and notification to other federal agencies of the result of its inspections, we reviewed FDA regulations, policies, and procedures for monitoring the clinical testing of drugs and interviewed FDA officials responsible for monitoring this testing. We also reviewed FDA files relating to its inspections of Dr. Aronow's research.

We discussed interagency communication with officials from FDA, VA, and EPA concerning the inspections and investigations

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[3]The American Heart Journal, Circulation, the Annals of Internal Medicine, and the American Journal of Medicine.

conducted by the agencies. Included among them were the writer, recipient, and other relevant parties to a July 12, 1982, FDA letter notifying EPA of its inspection of Dr. Aronow's research.

To develop information on Dr. Aronow's compliance with VA procedures in performing this research and VA's policies for receipt of outside remunerations by its employees, we reviewed VA's policies and procedures applicable to Dr. Aronow's research and interviewed officials at the VA Medical Center in Long Beach and the VA Central Office in Washington. The officials included representatives of the Inspector General's Office, the Department of Medicine and Surgery's Deputy Assistant Chief Medical Director for Research and Development, and the Medical Inspector. We also reviewed files relating to research performed by Dr. Aronow and VA's investigations of Dr. Aronow's activities.

As requested by the Chairman's office, we did not obtain official agency comments on the information in the report. We did, however, discuss the matters contained in the report with officials from EPA responsible for the carbon monoxide standards, and officials in VA and FDA responsible for investigations of Dr. Aronow. Their comments have been incorporated where appropriate. With the exceptions noted above, our review was performed in accordance with generally accepted government audit standards.

CHAPTER 2

RESEARCH SUPPORTING THE DEVELOPMENT OF EPA'S CARBON MONOXIDE STANDARDS

On April 30, 1971, EPA promulgated national air quality standards for carbon monoxide. Based primarily on one key study that linked low levels of carbon monoxide to adverse effects on the central nervous system, EPA established the standards at 9 ppm over on 8-hour average and 35 ppm over a 1-hour average. To be in compliance, neither of these levels can be exceeded by a state or local jurisdiction more than once a year.

As required by the 1977 amendments to the Clean Air Act, EPA began to revise the carbon monoxide standards in late 1978. At that time EPA was aware that the key study supporting the 1971 standards had been questioned by several researchers and that low levels of carbon monoxide might not have as severe an effect on the central nervous system as once thought. EPA, therefore, issued a December 1978 notice in the Federal Register notifying the public that it was reviewing, updating, and revising the criteria document used to develop the carbon monoxide standards. This was followed by another Federal Register notice in August 1980 that announced a proposed revision to the carbon monoxide standards. This proposal would have established the unacceptable level of carbon monoxide at 9 ppm for an 8-hour average and 25 ppm for a 1-hour average. As with the original standards, neither of these limits could be exceeded more than once a year. Unlike the original standards, however, the limits were based on studies conducted primarily in the 1970's which demonstrated that low levels of carbon monoxide affected the cardiovascular system, particularly in people with angina.

These proposed standards have not yet been issued. Between August 1980 and August 1984 EPA analyzed and reconsidered various revisions to the carbon monoxide standards. On August 9, 1984, EPA issued another Federal Register notice proposing the same carbon monoxide standards as originally proposed in August 1980. (For a description of various standards considered by EPA between 1980 and 1984 see app. II.)

This chapter provides the information requested by the Chairman, Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, relating to the research studies supporting the original 1971 carbon monoxide standards and the proposed revision to these standards.

THE KEY RESEARCH STUDY SUPPORTING THE 1971 CARBON MONOXIDE STANDARDS HAS BEEN DISCOUNTED BY EPA

According to EPA officials, the key study supporting the 1971 carbon monoxide standards was published in 1967 by R. R. Beard and

G. A. Wertheim.[1] The study demonstrated low-level effects of carbon monoxide exposure on the central nervous system. The Director of the Office of Criteria and Standards of the National Air Pollution Control Administration[2] in 1970 was responsible for developing the 1970 criteria document that supported the original carbon monoxide standards. During our discussion with the former director in January 1984, he stated that there were questions about the quality of the Beard and Wertheim study at the time it was included in the criteria document. He stated, for example, that the method in which the study was conducted allowed subjective responses from the patients. He also stated that the study had not been replicated by other researchers. He noted, however, that the National Air Pollution Control Administration was directed by the Department of Health, Education, and Welfare to identify and include all research in the criteria document (regardless of quality) that would support the lowest level of carbon monoxide that would affect the public health. Also, at the time that EPA proposed the original standards in January 1971, public comments raised serious questions about the soundness of the research supporting the proposed carbon monoxide standards. Nevertheless, in responding to these public comments, EPA concluded that the evidence of the Beard and Wertheim study had not been refuted and that less restrictive carbon monoxide standards would not provide an adequate margin of safety to protect the public.

Subsequent to the promulgation of the carbon monoxide standards in 1971, several researchers attempted unsuccessfully to replicate the Beard and Wertheim study, raising questions about the reliability of its results. In EPA's 1979 criteria document, EPA concluded that the study no longer provides credible evidence of the effects of carboxyhemoglobin on the central nervous system and therefore does not represent a sound scientific basis for the carbon monoxide standards.

EPA RELIED EXTENSIVELY ON DR. ARONOW'S RESEARCH IN DEVELOPING REVISED CARBON MONOXIDE STANDARDS

With the questioning of the Beard and Wertheim study, EPA took no action during the 1970's to change the standards because several studies conducted by Dr. Wilbert Aronow during this time had demonstrated an adverse relationship between low levels of carbon monoxide exposure and public health. In contrast to the

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[1]Beard and Wertheim were medical researchers at the Stanford University Medical Center, Department of Preventive Medicine, in 1967.

[2]The National Air Pollution Control Administration, which preceded the Office of Air Quality Planning and Standards, was responsible for administering the Clean Air Act in 1970. The Administration was part of the Department of Health, Education, and Welfare in 1970.

Beard and Wertheim study, however, Dr. Aronow's research found that low carboxyhemoglobin levels in the blood (5.1 percent or lower) adversely affected the cardiovascular system, particularly in angina patients.

When EPA proposed new carbon monoxide standards in August 1980, seven of the eight key studies it relied upon were authored by Dr. Aronow. The other key study, authored by Dr. Einar Anderson[3] and four coresearchers, also showed adverse effects of low carboxyhemoglobin levels in angina patients. According to EPA officials, these were the only studies EPA could identify which demonstrated adverse effects of low levels of carbon monoxide exposure on angina patients.

Questions raised about the reliability of Dr. Aronow's studies

Before EPA began relying on the Aronow research to support revisions to the carbon monoxide standards, questions had been raised about the adequacy of his research. For example:

--A physician currently associated with a medical group in Torrence, California, and formerly president of the Lung Association of Los Angeles County, questioned the results of Dr. Aronow's research in 1973. Also, in a 1974 letter to the editor of the Annals of Internal Medicine, he criticized the poor quality, small sample size, and subjectivity of Dr. Aronow's research. Furthermore, he stated that he did not believe the Aronow work was of sufficient scientific reliability to be used as a basis for the carbon monoxide standards.

--Another physician, associated with the Stanford University Medical Center, sent a letter to the editor of the Annals of Internal Medicine questioning the results of research published by Dr. Aronow in that journal in 1972. The specific questions the physician raised included: (1) the validity of the carboxyhemoglobin levels reported, (2) the design of the study, and (3) the overall conclusions of the study.

--In an October 10, 1980, public meeting on the proposed carbon monoxide standards held in Denver, Colorado, the chairman of the Spokane City-County Air Pollution Authority criticized several Aronow studies because, among other things, they had not been replicated, examined a small number of subjects, and/or were conducted with improper controls.

After EPA prepared the 1979 criteria document and staff paper to support its proposed revisions to the carbon monoxide

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[3]Dr. Anderson, an M.D., was a Public Health Officer assigned to EPA's Clinical Studies Branch, Human Studies Laboratory, during the time this study was conducted.

standards, Dr. Aronow completed a study for EPA that demonstrated the adverse effects of carbon monoxide on angina patients at the 2-percent carboxyhemoglobin level. The study (referred to as the "2-percent study") was published in the American Heart Journal in February 1981. This study was important because it showed adverse health effects on angina patients at a lower level of carbon monoxide exposure than that of any other available study. In Federal Register notices dated August 18, 1980, and June 18, 1982, EPA solicited public comments on this Aronow study and the role, if any, the study should play in EPA's final rulemaking. A number of the comments received from industry officials and state and local environmental agencies suggested that the Aronow study should be replicated before EPA relied on it for setting the carbon monoxide standards. Other commenters disagreed with the Aronow study, stating that the results should not be used as the basis for the carbon monoxide standards.

EPA officials from the Health Effects Research Laboratory and Environmental Criteria Assessment Office told us they were aware of these comments and some of the others relating to Dr. Aronow's earlier carbon monoxide studies. They stated that it is not unusual for researchers to disagree or question another's work, especially if the results differ from that researcher's position. These officials also agreed that it is important to replicate research to further validate its results, especially key research that will be used by standard-setting agencies such as EPA. Because of Dr. Aronow's reputation as a renowed cardiologist, however, EPA did not have the studies replicated by other independent researchers, including EPA researchers.

In addition, several of the public comments received on the 2-percent study, including those from state agencies, reacted favorably to the study. For example, on August 6, 1982, the California Air Resources Board wrote to EPA stating that the Aronow 2-percent study is "a timely and significant contribution to (carbon monoxide) health effects data carried out by a physician widely acknowledged to be a leading expert in the field." Nevertheless, based on the public comments it received, EPA decided not to rely on the Aronow 2-percent study to determine the adverse health-effects level; rather, EPA relied upon it to ensure an adequate margin of safety when proposing the standards. The margin of safety is the difference between the level at which EPA sets the standards and the research results that show the lowest observable adverse health effects.

According to an April 13, 1984, EPA memorandum regarding the handling of information concerning Dr. Aronow, by the summer of 1982 EPA staff was aware of considerable criticism of Dr. Aronow, but believed there was little reason to question his integrity. They were aware, for example, that Dr. Aronow received an award from the American College of Chest Physicians for his 2-percent study and that a highly respected research scientist who was a member of CASAC had defended Dr. Aronow's data as being solid and irrefutable.

EPA established peer review panel to examine Dr. Aronow's research studies

EPA was about to finalize the revised carbon monoxide standards when a March 1983 Washington Post article appeared about FDA's investigation of Dr. Aronow's research practices and FDA's suspension of him from certain drug research. EPA officials from the Office of Air Quality Planning and Standards, Office of Research and Development, and the Environmental Criteria and Assessment Office met on March 31, 1983, to discuss the impact of the Aronow situation relative to EPA's extensive use of Dr. Aronow's research to support revisions of the carbon monoxide standards. By April 1983 EPA had assembled a special peer review committee of experts to evaluate the quality of Dr. Aronow's research and determine the extent to which EPA should rely on his research to support the carbon monoxide standard.

EPA's mandate to the special review committee was to review the documentation supporting the Aronow studies cited in the carbon monoxide criteria document, to meet with Dr. Aronow to determine the validity of his research, and to decide what reliance EPA could place on his research relative to the revised carbon monoxide standards. The committee was asked, in part, to go beyond the usual peer review procedures and conduct a review, or data audit, of the accuracy of the results reported in his studies. Even though the committee was requested to evaluate six of the Aronow studies, the lack of documentation limited them primarily to the 2-percent study. Based on its review of available documentation and interviews with Dr. Aronow and two of his laboratory technicians, the committee issued its report in May 1983 stating that:

--All documentation supporting the various Aronow studies, had been disposed of except for electrocardiogram strips on subjects in the 2-percent study.

--Log books were not maintained for the studies, and much of the basic data had been collected on "bits of paper" or "looseleaf notepaper."

--There was considerable doubt as to whether appropriate procedures for conducting a double-blind[4] study were maintained.

--No calibration data were available for the instruments used in the studies.

--Dr. Aronow and his technicians had a minimal knowledge of the principles of calibration for the instruments used to measure carboxyhemoglobin.

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[4]The term "double-blind" refers to an experimental procedure by which neither the subjects nor the investigators testing the subjects or recording the resulting data, are aware of the exposure conditions of a given test session.

--There were inconsistencies between diagnosis by Dr. Aronow and other VA physicians concerning patients who participated in the study.

The committee concluded that, based on the limited information available, the issue of possible data falsification could not be resolved. However, the committee expressed considerable concern about the validity of results reported. The committee also questioned the experimental designs employed by Dr. Aronow and whether the experiments were really double-blind. Overall, the committee concluded that EPA could not rely on Dr. Aronow's data due to the concerns they had noted and recommended that similar carbon monoxide research be conducted by other independent research groups.

Dr. Aronow responded to the committee's report in June 1983 by saying that the data he reported were accurate and scientifically valid. Specifically, he stated that:

--Data had been retained for 2.5 to 3 years and only discarded because of insufficient storage space.

--The raw data for the 2-percent study had been offered to EPA for review.

--The data (electrocardiogram tracings) compiled for his research were more than adequate because they clearly supported the results of his studies.

--The exclusion of certain subjects, use of practice exercises, and use of subjects who had participated in previous studies were necessary to decrease the variability in the results of the study.

--The research was conducted under double-blind conditions.

In March 1984 we discussed these issues with Dr. Aronow, who insisted that his carbon monoxide and other research results are valid and accurate. He reiterated his statement that he had offered the raw data for the 2-percent study to EPA, but that the EPA project officer did not want the data. Dr. Aronow also stated that he completed a study in April 1983 showing the harmful effects of carbon monoxide on anemia patients and that the raw data of that study had been audited and found to be impeccable by the Department of Medicine at Creighton University. He said that the study has been published in abstract form in a professional journal and has been accepted by another journal to be published in its entirety. He also stated that he offered the data from

this study to the EPA peer review panel in April 1983, but that the committee was not interested in reviewing the data. In March 1984 we talked with the Chairman of the Department of Medicine at Creighton University who told us that Dr. Aronow's carbon monoxide study on anemia patients was scrupulously conducted and that its results were "perfectly good and publishable."

EPA did not conduct any other peer review of the Aronow research, but relied upon the committee's report in deciding how to handle the situation. The EPA project officer for the 2-percent Aronow study stated that EPA did not request the raw data on the study and that Dr. Aronow never offered the data for EPA's review. According to the project officer, the only documentation Dr. Aronow ever provided EPA was a draft and final report of the study results.

Based on the conclusions of the special peer review committee report, EPA deleted all reference to the Aronow research as support for the lowest adverse health effects in its proposed carbon monoxide standard. However, the revised EPA staff paper continues to cite Dr. Aronow's research as a basis for establishing a margin of safety for the proposed standard. According to the paper, in establishing the margin of safety, EPA must consider several uncertainties regarding the lowest levels at which adverse health effects occur and the levels of carboxyhemoglobin that will result from various levels of carbon monoxide exposure. EPA officials told us that the results of Dr. Aronow's research are among the many uncertainties that EPA will consider in setting the margin of safety.

Ongoing carbon monoxide research will help validate past results

Several new carbon monoxide studies are ongoing or planned which will demonstrate the effect of carbon monoxide on angina patients. These studies will help replicate or validate the Aronow and Anderson research.

EPA's Health Effects Research Laboratory is currently conducting a carbon monoxide exposure study at its Chapel Hill, North Carolina, facility. The study will demonstrate the effects of 4-percent carboxyhemoglobin levels on patients with coronary artery disease. A gamma camera[5] is being used to determine the onset of angina pain. According to officials of the Health Effects Research Laboratory, the gamma camera is more objective when determining the angina pain than the Aronow method, which relied upon the subjects to say when the pain started. On September 5, 1984, Health Effects Research Laboratory officials told us that the study is well ahead of schedule and they estimate that final analysis of the data will be completed about October 1984. They

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[5]The gamma camera records images of the heart to enable the researchers to identify changes in the heart's rhythm. The EPA researchers believe that the changes in the heart rhythm precede the onset of angina pain.

hope to secure publication in a professional journal by the spring of 1985. According to Office of Air Quality Planning and Standards officials, this study will contribute to the carbon monoxide research base, but it will not meet their immediate needs because the carboxyhemoglobin levels being tested are higher than the levels at which adverse health effects have been shown by the Anderson study. The Health Effects Research Laboratory plans to conduct additional research at lower levels, if adverse health effects are found at the 4-percent carboxyhemoglobin level. However, peer-reviewed results at lower levels will not be available until early 1986.

The Health Effects Institute--a Cambridge, Massachusetts, based research organization funded equally by EPA and the automobile industry--was established to perform quality health-effects research on motor vehicle pollutants. In a July 1983 letter EPA requested that the Institute conduct an independent study of carbon monoxide effects on angina patients at 2- to 4-percent carboxyhemoglobin levels. The letter stated that EPA needs to determine whether Dr. Aronow's observations, an important part of the basis for the 1980 standards, can be duplicated. The Institute has contracted with three laboratories across the country to conduct exposure studies. The approaches of the three studies will be identical, and the results will be completed and analyzed about June 1985. According to the Deputy Executive Director of the Institute, peer-reviewed results will hopefully be available by the fall of 1985.

A third carbon monoxide research effort is being sponsored by the California Air Resources Board. The study will be conducted at the 2-percent carboxyhemoglobin level and at a higher level. The research is being performed at the University of California at Irvine. According to a California Air Resources Board official, the research should begin about October 1, 1984, and take about 6 months to complete. Peer-reviewed results should be available about 9 months after completion of the research.

EPA'S REVISIONS TO THE CARBON MONOXIDE STANDARDS ARE BASED ON OTHER RESEARCH

With the Aronow research being questioned and the results of several planned or ongoing studies not yet available, EPA has looked to other published research to support a decision on what level to set carbon monoxide standards. EPA reevaluated the pre-1979 carbon monoxide research, identified and reviewed the post-1979 data, and prepared an addendum to the criteria document. The Office of Air Quality Planning and Standards also prepared a revised staff paper based on the new data in the addendum. In Federal Register notices dated August 18, 1983, and September 16, 1983, EPA announced the availability of these documents and solicited public comments on them.

The Anderson research became the focal study supporting EPA's proposed carbon monoxide standard since it demonstrated the adverse health effects of carbon monoxide on angina patients at the 2.9-percent carboxyhemoglobin level. The revised staff paper also emphasized three other studies which showed what EPA calls "significant" health effects on healthy subjects at low carboxyhemoglobin levels (as opposed to adverse effects on angina patients). Based on the update of the criteria document and staff paper and the CASAC endorsement of these documents as scientifically adequate, EPA believes there is sufficient research to support a regulatory decision on the carbon monoxide standards.

The Anderson study has been questioned by various organizations

While the Anderson study is currently the focal study supporting EPA's proposed carbon monoxide standards, it has been questioned by various people and organizations. For example, in September 1983, General Motors Corporation challenged EPA's reliance on the Anderson study in light of several alleged flaws in its design and execution, the small number of subjects, and the inconsistent results. Furthermore, General Motors officials recommended the Anderson study be subjected to the same scrutiny as the Aronow research. EPA researchers did not agree that the Anderson study should be subjected to a special peer review. They stated that the study was not designed to be a definitive study and the records are not available since the research was done more than 10 years ago. The Spokane City Council and Spokane County Air Pollution Control Authority have criticized the Anderson study in several forums, including the September 1983 CASAC meeting. According to the Spokane groups, no work is scientifically valid until it has been replicated, and the Anderson study must be replicated by several independent groups before they believe it should be used to set national standards.

The Anderson study was coauthored by five researchers and published in the Annals of Internal Medicine in 1973. The published report of the study indicated that the carbon monoxide gases were administered to the subjects continuously for 4 hours by means of face masks. In August 1983 and January 1984 EPA contacted two of the authors to verify the method of administering the gases. The principle investigator, Dr. Anderson, stated that all subjects were required to take 10-minute rest breaks during each hour of the 4-hour test. Additionally, he stated that using face masks to administer the gases may have allowed the gases to leak. In contrast, one of the coauthors stated that comfort breaks were allowed, but they were not rigidly scheduled. According to an official from the Spokane County Air Pollution Control Authority, the whole point of a scientific experiment, published in a reputable journal, is that all procedures are made so clear and explicit that they can be replicated by other investigators. She stated that the fact that the authors cannot agree as to the administration of carbon monoxide means that there is no way to replicate the study and, therefore, it should be discarded.

According to the EPA project manager for the carbon monoxide criteria document, research with lengthy exposure periods, such as 4 hours, is considered to be continuous even though breaks are allowed. However, the research methodology was not as descriptive in 1973 as it is today. Therefore, the Anderson study was described as a continuous exposure. According to the project manager, if the methodology of the Anderson study were described today, all the details about the number and duration of the breaks would be included.

The significance of the subjects in the Anderson study taking breaks or their face masks leaking during the test is whether they were exposed to carbon monoxide for 4 continuous hours as reported or something less than 4 hours due to the comfort breaks and mask leaks. The carboxyhemoglobin levels reported in the Anderson study were lower then the predicted levels based on the Coburn Equation.[6] For example, after exposure to 4 hours of 50-ppm carbon monoxide in the Anderson study, the subjects measured an average of 2.9 percent carboxyhemoglobin. However, in applying the Coburn Equation and assuming 4 continuous hours of carbon monoxide exposure, the predicted carboxyhemoglobin level should have been 3.3 percent. The Environmental Criteria and Assessment Office and Health Effects Research Laboratory officials explained the difference between the Anderson study and the Coburn Equation by saying that the Anderson subjects were not exposed to 4 continuous hours of carbon monoxide because of the breaks and face mask leaks. These officials believe the results to be accurate based on less than 4 hours of exposure to carbon monoxide.

According to a February 1, 1984, evaluation by the Chief of the Clinical Research Branch in EPA's Health Effects Research Laboratory, the Anderson study is a good paper, is carefully done, seems reasonable, and is well written. However, this critical review identified some flaws in the design and conduct of the research.

--The study would have been strengthened by more careful selection of a homogeneous subject population.

--The small number of subjects (10) and the missing data points for three subjects weakened the study.

--The use of loose-fitting face masks to administer the gases may have allowed leaks.

--During the study the subjects were allowed to take rest breaks at liberty that reduced exposure time and the final carboxyhemoglobin levels.

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[6]The Coburn Equation is a recognized tool which enables researchers to predict the carboxyhemoglobin levels of subjects after exposure to measured carbon monoxide gases for specific time periods.

The EPA official's overall conclusion was that several aspects of the study were above average quality. Specifically, the double-blind fashion was commendable, and selecting the small number of variables to study minimized the possibility of outside variables accidently influencing the carbon monoxide effects. Despite these positive features of the study, the EPA evaluation concluded the study was in need of replication and extension, and it would be rash to rely entirely upon one study with 10 subjects to set national carbon monoxide standards. On January 24, 1984, a health scientist in EPA's Environmental Criteria and Assessment Office spoke with Dr. Anderson who reaffirmed the study's conclusions, but added that the study should be replicated as soon as possible to confirm these results.

In July 1984 we spoke with Dr. Anderson who told us that his study was a good one and that the independent variable in the study was the carboxyhemoglobin levels, not the exposure conditions. He therefore believes that criticisms of the study's exposure conditions are not relevant to the study's conclusions. He also told us that, while it was a pilot study, it tested enough subjects to result in statistically significant findings.

EPA is also relying on other key carbon monoxide studies

To further substantiate a decision on the carbon monoxide standards, EPA has identified the results of three additional studies by Horvath, Drinkwater, and Raven that demonstrate the effects of carbon monoxide on healthy subjects.[7] The key studies previously cited by EPA to support the revised standards showed the adverse health effects of carbon monoxide on the cardiovascular system of angina patients. In contrast, these three studies show statistically significant decreased activity before exhaustion in exercising healthy males.

More specifically, the studies show observable effects of carbon monoxide exposure at carboxyhemoglobin levels as low as 2.3 to 4.0 percent. EPA believes that the health effects demonstrated in these studies may be of lesser concern than those shown in the angina studies. EPA believes, however, that the results of these studies are significant enough to be considered in setting carbon monoxide standards and complement the Anderson study in demonstrating the effects of carbon monoxide on humans. Therefore, EPA has included these three studies in the 1984 criteria document addendum and, as part of its August 9, 1984, Federal Register notice, requested comments on whether they should be used as part of the basis for establishing revised carbon monoxide standards.

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[7]Horvath was a Ph.D. and the Director of the Institute of Environmental Stress at the University of California at Santa Barbara. Drinkwater and Raven were Ph.D.'s also affiliated with the Institute.

CASAC's review supports EPA's basis for revised standards

According to the May 17, 1984, closure letter to the EPA Administrator, CASAC concluded that, even without the use of the Aronow studies to determine a critical effects level from carbon monoxide exposures, there remained a sufficient and scientifically adequate basis on which to finalize the carbon monoxide standards. The letter also stated that the critical carboxyhemoglobin level for carbon monoxide standard-setting purposes is approximately 3 percent (not including a margin of safety). This is somewhat different from CASAC's October 9, 1979, closure letter on carbon monoxide that stated that, based on a review of the criteria document and staff papers, both of which relied heavily on Dr. Aronow's studies, the critical carboxyhemoglobin level is 2.7 to 3.0 percent. According to the Director of CASAC, the exclusion of the Aronow studies does not impact greatly on CASAC's views of the critical carboxyhemoglobin levels.

In its May 17, 1984, closure letter CASAC recommended that the EPA Administrator consider choosing the carbon monoxide standards to maintain approximately the same levels of protection as established in the 1971 standards. The closure letter also stated that, while CASAC treats the Anderson study with caution, it can find no substantive reason to dispute the reported values, and it recommends that EPA "not disregard" the Anderson study's findings. The CASAC letter also agreed on the importance of replicating the study, but rejected the notion that a study has no validity until it has been replicated. CASAC also stated that other studies, including those by Raven and Drinkwater, are significant and should be factored into EPA's standard-setting decision.

EPA HAS SEVERAL OPTIONS FOR PROMULGATING CARBON MONOXIDE STANDARDS

EPA believes there is sufficient scientific research to support its regulatory decision for the carbon monoxide standards. EPA published a notice in the August 9, 1984, Federal Register that stated that EPA is inclined to promulgate the revised standards proposed in 1980, but wants to withhold its decision until after it receives and analyzes public comments.

The Clean Air Act allows the EPA Administrator to exercise his judgment relative to what level the carbon monoxide standards will be set. The Administrator must be satisfied that the criteria document, staff paper, and other supporting documents are accurate representations of all available carbon monoxide research. Also, the Administrator must ensure there is an adequate margin of safety between the lowest observed adverse health-effect level and the level which is eventually proposed. To

illustrate, EPA documentation shows the 2.9-percent carboxyhemoglobin level of the Anderson study as the lowest observed adverse health-effect level. The EPA documentation also states that the proposed 8-hour standard of 9 ppm with one allowable exceedance would protect 99 percent of the sensitive population at a 2.0-percent carboxyhemoglobin level. Thus, 0.9 percent becomes the margin of safety between the research showing adverse health effects and EPA's proposed standards. Similarly, EPA's documentation shows that a standard of 12 ppm with one allowable exceedance would protect the sensitive population at the 2.5-percent carboxyhemoglobin level, and therefore the margin of safety would be 0.4 percent.

EPA has three options for resolving the impasse on promulgating the revised carbon monoxide standards. The options are to:

--promulgate the 1980 proposed standards,

--propose standards with new levels, or

--delay proposing standards until the results of the new carbon monoxide studies are known.

Promulgating the 1980 proposed standards

According to officials in EPA's Office of Air Quality Planning and Standards, promulgating the standards that were proposed in 1980 would offer several advantages to EPA. They stated that the quickest and easiest way for EPA to complete its revisions of the carbon monoxide standards would be to promulgate the same standards that were proposed in August 1980. The Chief of the Ambient Standards Branch of the Office of Air Quality Planning and Standards told us that in taking this option EPA will not have to re-propose the standards through a Federal Register notice and the only delay would be EPA's own administrative procedures and the required Office of Management and Budget review before it promulgates the standard. Office of Air Quality Planning and Standards officials estimate that 3 to 6 months would be needed to promulgate the 1980 standards.

According to officials in the Ambient Standards Branch, there are advantages to the cities and states in promulgating the standards proposed in 1980. For example, there are several technical improvements that the standards set in 1971 do not offer. Among these improvements is the shift in the method of expressing the standards. The proposed method for determining the number of times a locality can exceed the standards gives that locality added flexibility in complying with its State Implementation Plan over the method allowed in the 1971 standards. (See app. II.)

The disadvantages of promulgating the standards proposed in 1980 include having to rely on a research base which has been

questioned since those standards were proposed. As discussed earlier, EPA has received some public comments stating that the Anderson study is not sufficient to support carbon monoxide levels equivalent to the 1980 proposed standards.

Propose standards with new levels

A second option available to EPA is to use the bases of the 1980 proposed standards, but to change the levels of the standards. Because of the questions raised about the Aronow research and the Anderson study, a number of public comments suggested that EPA relax the 8-hour carbon monoxide standards from 9 ppm to at least 12 ppm with one allowable exceedance. EPA's Office of General Counsel officials believe that, in order to relax the carbon monoxide standards, EPA may have to re-propose the standards through the Federal Register and solicit public comments. Furthermore, the Chief of the Ambient Standards Branch in the Office of Air Quality Planning and Standards believes that the additional time needed to re-propose the standards would probably force EPA to prepare a new criteria document since the original critical document of 1979 was prepared nearly 5 years ago. Similarly, the other documents, such as the staff paper, exposure analysis, and sensitivity analysis, would probably have to be updated or prepared anew. According to Office of Air Quality Planning and Standards officials, to change the levels of the carbon monoxide standards would place a burden on the states and localities to revise their State Implementation Plans to conform to the revised carbon monoxide standards and possibly be faced with another change in 2 to 3 years when the results of several new carbon monoxide studies are published.

Office of Air Quality Planning and Standards officials estimated that this option would require a minimum of 15 months to promulgate the standards fully if the criteria document did not have to undergo a full revision. (A new criteria document would essentially start the whole 5-year review cycle over.) By the time EPA completes this process, the publication dates for several new carbon monoxide studies would be near.

Delay proposal until new studies are completed

A third option available to EPA is to delay promulgating revised carbon monoxide standards until the results from several new carbon monoxide studies have been published. EPA officials believe that by waiting until the results of these new studies are available, EPA would be assured of having more current and reliable carbon monoxide data on which to base its decision. However, these studies are just starting and, based on estimated completion and publication dates, it will be at least mid-1985 before the first of these studies is published. Thus, EPA would have to wait at least until late 1985 or early 1986 before it could rely upon

these studies in proposing revised carbon monoxide standards. According to Office of Air Quality Planning and Standard officials, new documents--such as the criteria document, staff paper, exposure and sensitivity analyses--would have to be prepared for the carbon monoxide standards if this option is chosen.

In the meantime, the present carbon monoxide standards, which do not have the technical improvements reflected in the 1980 proposed standards, would remain in place. Office of Air Quality Planning and Standards officials estimate that it would require 3 to 5 years to fully promulgate new standards under this option.

EPA's notice requests further public comment

On August 9, 1984, EPA published a notice in the Federal Register that summarized what has occurred since the August 1980 proposed carbon monoxide revisions, reviewed the basis for EPA's proposal to revise the standards, and solicited additional public comment. After receiving these public comments EPA plans to take final action on carbon monoxide. Comments are due September 24, 1984. The notice stated that, based on the available information including the CASAC closure letter, EPA is inclined to issue the standards proposed in 1980. The notice stated that because of the changes in the interpretation of the scientific evidence since proposal and the significance of the decision, EPA believes it important to encourage public participation and obtain further comment.

CHAPTER 3

COMMUNICATION PROBLEMS BETWEEN FDA, VA, AND EPA HAVE DELAYED THE REEVALUATION OF CARBON MONOXIDE RESEARCH

According to EPA officials, communication problems between FDA, VA, and EPA have delayed EPA's reevaluation of the carbon monoxide research data base. FDA advised VA in June 1979 that it was going to investigate research performed by Dr. Aronow and subsequently advised VA of the results of that investigation. However, FDA did not advise EPA of its investigation until about 3 years after the investigation began because, according to FDA officials, they were unaware that Dr. Aronow had performed research for EPA. Despite a letter from EPA to VA indicating that EPA was relying heavily on research performed by Dr. Aronow in developing its carbon monoxide standards, VA did not inform EPA that it had ordered Dr. Aronow to cease performing research involving human subjects in 1980. The VA official involved believed that VA's problem with Dr. Aronow was an internal VA personnel matter not related to EPA. Even though FDA advised EPA of its concerns about Dr. Aronow's research on July 12, 1982, EPA officials responsible for development of the carbon monoxide standards told us they were not aware of any problems with Dr. Aronow's work until an article appeared in the Washington Post on March 23, 1983.

FDA AND VA CONDUCTED REVIEWS OF DR. ARONOW BETWEEN 1979 AND 1982

FDA and VA independently conducted extensive reviews of Dr. Aronow's research during the period 1979-82. These investigations were ongoing at the same time that Dr. Aronow was conducting research for EPA under a proposed interagency agreement with VA. Between June and October 1979, FDA investigated research performed by Dr. Aronow on several investigational new drugs. FDA notified Dr. Aronow of the results of its inspections in a June 1980 letter and, in October 1982, FDA and Dr. Aronow signed a consent agreement limiting the latter's access to these drugs and his rights to serve as a clinical investigator of new drugs. FDA notified VA of its inspection and, based partly on the FDA results, VA conducted several investigations of Dr. Aronow's work in 1980 and 1981.

FDA conducted inspections of Dr. Aronow's investigational drugs research

While employed at VA, Dr. Aronow conducted research on investigational new drugs for certain pharmaceutical firms. VA permits this type of research if it has prior approval from the appropriate VA medical center's Research and Development Committee

and, if applicable, the center's Human Studies Committee. The drug companies make a contribution of a gift or a donation designated for the conduct of the research to the medical center's General Post Fund.[1] On June 26, 1979, FDA's Division of Scientific Investigations and its Los Angeles District Office began an inspection of research performed by Dr. Aronow on two investigation new drugs. The inspection was performed at the request of the FDA division responsible for reviewing new drug applications relating to cardiac drugs partly because the division questioned the results of one of his studies. Furthermore, the division had received an application for approval to market a drug for an additional use, and Dr. Aronow's study was to be pivotal in the decision whether to approve the drug.

After being notified of the inspection, but before the inspection began, Dr. Aronow called FDA's Associate Director for New Drug Evaluation and, according to a memorandum prepared by the FDA official, told her that he had "fudged" the chest x-ray reports on two of the drugs he had studied. That is, the reports he submitted to the sponsoring pharmaceutical firms were different from the radiologists' interpretation of those x-rays. One of the drugs was included in the proposed FDA inspection. Dr. Aronow later told FDA that he could not remember whether or not he "fudged" the x-rays.

The FDA inspection, which was completed on August 15, 1979, disclosed a number of problems, including incorrect patient selection, conflicting data between hospital records and reports to the sponsor (pharmaceutical firms for which Dr. Aronow performed research), lack of raw data records, and failure in some cases to report patients' adverse reactions to the drugs being studied.

The same FDA officials who conducted the June-August inspection performed a follow-up inspection from September 24, 1979, to October 3, 1979, for three additional studies performed by Dr. Aronow. The deficiencies noted were generally the same as those noted during their first inspection. Closeout meetings were held with Dr. Aronow at the completion of each inspection.

FDA formally notified Dr. Aronow of the results of its inspections in a letter dated June 19, 1980. The letter stated that "we believe that you have repeatedly or deliberately violated regulations pertaining to the proper conduct of clinical studies involving investigational new drugs." The letter went on to spell out the specific regulations FDA alleged had been violated. As provided for in its regulations, FDA offered Dr. Aronow the choice

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[1]According to a VA evaluation report on its research program, General Post Funds refer to nonappropriated funds available to VA medical centers provided by donations by private organizations. The major drug companies who provide such funds for research on new drugs are the biggest source of such funds. Most of these funds are channeled to medical research investigators to conduct research along specific lines.

of responding in writing or at an informal conference. Dr. Aronow opted for an informal conference which was held on September 16, 1980.

As a result of that conference, FDA advised Dr. Aronow on March 20, 1981, that while he had satisfactorily explained some of the alleged violations, he had not satisfactorily explained others. Therefore, in accordance with its regulations, FDA offered Dr. Aronow the opportunity for a regulatory hearing to determine whether he was entitled to receive investigational drugs. Dr. Aronow declined the regulatory hearing.

Subsequently, FDA considered taking criminal action against Dr. Aronow for maintaining inadequate records. FDA believed that this could have been interpreted as causing the pharmaceutical firms sponsoring his studies to fail to establish or maintain records, or make reports as required by sections 505 (i) and (j) of the Federal Food, Drug and Cosmetic Act. Failure to maintain such records or make required reports is prohibited under section 301(e) of that act.

According to an August 3, 1981, memorandum prepared by an FDA compliance officer, FDA decided not to prosecute Dr. Aronow for several reasons, including:

--The U.S. Attorney's Office in Los Angeles had declined to accept a case from VA which had recommended prosecuting Dr. Aronow for false statements to VA on acceptance of outside remunerations. (See pp. 25-26 for a discussion of Dr. Aronow's acceptance of outside remunerations.)

--One of the studies on which Dr. Aronow had admitted "fudging" data had passed the statute of limitations, and there was concern that other studies would pass the statute of limitations before a case could be brought, considering the speed with which other cases had progressed.

FDA's Associate Commissioner for Regulatory Affairs, Deputy Commissioner, and Commissioner Concurred in a proposal to accept an agreement from Dr. Aronow not to participate in any further clinical testing of investigational drugs without explicit FDA approval rather than continuing with the formal process of disqualifying Dr. Aronow. This approach, according to the Commissioner's June 15, 1982, memorandum to the Acting Director of the Bureau of Drugs, was taken for several reasons, including (1) the agreement would ensure that the violations committed by Dr. Aronow would not be repeated and FDA's notification of sponsors would ensure that no reliance would be placed on any of Dr. Aronow's studies, and (2) similar agreements had been entered into with other researchers.

The agreement was signed by Dr. Aronow, his attorney, FDA's Associate Commissioner for Regulatory Affairs, and an FDA attorney in October 1982. The consent agreement provided that

--Dr. Aronow would not seek to obtain investigational new drugs and would not serve as a clinical investigator of investigational new drugs, unless, among other things, he obtained specific permission from FDA;

--FDA could declare Dr. Aronow ineligible to receive investigational new drugs if FDA established that Dr. Aronow breached the agreement; and

--Dr. Aronow would be included on FDA's list of investigators who had voluntarily agreed to restrict or cease their use of investigational new drugs. The list would not be routinely distributed but would be made available under Freedom of Information Act requests.

Although Dr. Aronow did not admit to FDA's overall allegation that he had repeatedly or deliberately violated FDA regulations, or that formal disqualification would be justified, he decided to accept the agreement.

The pharmaceutical firms for which Dr. Aronow had performed research were informed of the agreement in November 1982 and January 1983. FDA was aware of firms for which Dr. Aronow had performed research because FDA maintains records on investigators involved in each drug study. The letters to these firms stated that, in the absence of specific validation of Dr. Aronow's work, FDA would not accept data from his studies performed prior to the date of the letter supporting safety or efficacy claims for products under FDA's jurisdiction. FDA asked the firms to determine what effect removing Dr. Aronow's data would have on claims for the safety and efficacy of the drugs on which Dr. Aronow had performed research. FDA and the firms subsequently determined that removal of Dr. Aronow's data did not influence the outcome of the approval of any drug.

VA investigated Dr. Aronow's activities

Beginning in January 1980, VA also initiated a number of investigations of Dr. Aronow's activities including (1) a Professional Standards Board[2] appointed to consider charges against Dr. Aronow for falsification of research, (2) a Department of Medicine and Surgery investigation, and (3) an Inspector General's investigation into Dr. Aronow's receipt of outside remuneration. These investigations resulted in VA ordering Dr. Aronow to discontinue research involving human subjects, suspending his other research privileges for at least 6 months, and taking administrative personnel actions against him.

On January 8, 1980, after receiving FDA's October 1979 inspection report concerning Dr. Aronow's research, VA's Assistant

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[2]A board established by VA's Chief Medical Director to act on appointments and advancements and to conduct probationary reviews of physicians and other medical personnel.

Chief Medical Director for Research and Development requested that the Director of the VA Medical Center in Long Beach withdraw Dr. Aronow's privilege to perform research until further notice. The Medical Center's Chief of Staff advised Dr. Aronow of this on January 30, 1980, at which time Dr. Aronow agreed to discontinue all human studies and indicated that he had already turned over responsibility for his ongoing research to another investigator. Memoranda and other documents which we obtained show that Dr. Aronow's last involvement in conducting experiments with human patients while employed by VA was on January 11, 1980.

On January 16, 1980, a Professional Standards Board was appointed to consider charges against Dr. Aronow for alleged falsification of research. On April 4, 1980, the Board concluded that Dr. Aronow had falsified scientific data and recommended, among other things, that a reprimand be issued restricting Dr. Aronow's research to non-human studies.

In August 1980, the Assistant Chief Medical Director for Research and Development and the other VA Central Office officials visited the VA Medical Center in Long Beach to review the irregularities in Dr. Aronow's research as specified in FDA's June 19, 1980, letter to Dr. Aronow and the circumstances associated with a proposed interagency agreement with EPA. Based on the results of this visit, the Assistant Chief Medical Director for Research and Development recommended that all of Dr. Aronow's research privileges be suspended for at least 6 months. She also recommended that, at the end of this period, the situation be reviewed and, if appropriate, the restriction be partially lifted. However, after the 6-month period, VA would retain restriction preventing Dr. Aronow from engaging in any investigational drug studies, receiving non-VA research funding, or having access to VA's General Post Funds. The Chief Medical Director issued a letter to Dr. Aronow on August 18, 1980, advising him of these restrictions.

Following the August 1980 visit to the VA Medical Center in Long Beach, one of the Central Office officials was informed of allegations that Dr. Aronow and other VA employees at that VA medical center had received outside remuneration from pharmaceutical firms in violation of VA policy. These allegations led to an investigation by VA's Inspector General.

The Inspector General found that from 1977 to 1980, Dr. Aronow had received a total of $72,351 from two pharmaceutical firms. Although Dr. Aronow declined to tell the Inspector General the purpose of the payments, the VA Medical Center's Chief of Staff stated that Dr. Aronow had advised him that the payments were for consulting services. One of the pharmaceutical firms advised the Inspector General that the payments were for conducting drug research. The Inspector General's report does not show whether an explanation was given by the other firm.

VA expressly prohibits its full-time physicians and certain other medical personnel from engaging in outside professional activities for remuneration except under very restricted conditions and with VA approval. VA also requires certain of its employees, including full-time physicians, to report outside

income annually. Dr. Aronow had signed a document in 1964 certifying that he understood VA's policy prohibiting outside professional remuneration and submitted annual statements for calendar years 1977 through 1980 certifying that he had not received remuneration for outside professional activities, except for $100 received in 1980 for an article published in a technical journal. Receipt of the $100 was approved by appropriate VA officials.

In September 1980, prior to the investigation by the Inspector General, the VA General Counsel submitted a request to the U.S. Attorney in Los Angeles to determine whether criminal action should be taken against Dr. Aronow. On April 16, 1981, the U.S. Attorney declined to accept the case stating that factors considered in their decision included the fact that administrative or civil penalties were available, there was minimum federal interest, and prosecution would have no deterrent value.

In August 1981, VA Central Office began taking administrative personnel actions against Dr. Aronow for the unauthorized receipt of money from pharmaceutical firms. In January 1982 a disciplinary board confirmed a Central Office decision to remove Dr. Aronow from VA employment. Dr. Aronow resigned effective March 23, 1982, before the removal took place.

VA has taken actions to improve controls over receipt of donations for support of medical research

According to VA procedures, VA's professional staff involved with medical research is subject to restrictions and reporting requirements concerning "outside" (non-VA) remunerations. Donors such as pharmaceutical firms who support research at VA medical centers may not be aware of VA's administrative requirements for such donations or VA's prohibition against certain of its professional staff receiving outside remuneration. This lack of awareness could be a reason why firms have made payments directly to individual researchers. In addition, according to an official at the VA Medical Center in Long Beach, donations to VA's General Post Fund in support of medical research have occasionally been sent to individual researchers.

We discussed our concerns about the administrative controls over the receipt of donations for medical research with VA officials. As a result, VA initiated action to routinely inform donors or potential donors of proper procedures for VA's receipt and disposition of such donations. Specifically, VA has revised its instructional circular on "Research General Post Funds" to clarify and strengthen its requirements for the acceptance of donations. The revised circular was issued on May 1, 1984. The revised instructions stipulate that:

--Donations for research are to be made payable to VA.

--Prior approval of the facility's Research and Development Committee and Facility Director will be required before donations may be accepted.

--In written acknowledgements of donations or proposed donations, the donor will be informed of the VA's policies and procedures for the receipt and use of the donation. The circular suggests providing the donor with a copy of the circular.

While these changes may not prevent donors such as pharmaceutical firms from making payments directly to VA research staff, it will make it clear to the donors that such payments are improper.

EPA, VA, AND FDA COMMUNICATION CONCERNING DR. ARONOW

Although FDA and VA began investigating Dr. Aronow's research in 1979 and 1980 respectively, EPA was not informed about potential problems concerning Dr. Aronow's research until about 3 years later. The VA never told EPA of its investigations even though EPA indicated in an August 1980 letter to VA that Dr. Aronow's research was of extreme importance to EPA's regulatory decision process. FDA did not notify EPA of its investigation until July 1982. FDA sent a letter notifying EPA at that time only because one of its staff members saw an EPA Federal Register notice mentioning its reliance on Dr. Aronow's research. However, because of an apparent internal communication problem, EPA did not review Dr. Aronow's carbon monoxide research until the March 23, 1983, Washington Post article was published.

EPA and VA proposed an interagency agreement for a carbon monoxide study

On August 23, 1979, Dr. Aronow submitted to VA for approval a proposed 4-year, four-part research project on the effect of carbon monoxide on cardiovascular function with total requested funding of $97,880. Dr. Aronow stated in his application that an interagency agreement had been requested under which EPA would pay up to $40,000 for the first part of the study. VA research and development funds were requested to fund the balance of the study. VA Medical Center's Research and Development Committee approved the project on October 4, 1979, and the project was submitted to Central Office for funding on December 10, 1979. According to a VA Central Office official, while the VA's merit review board had recommended approval of the project, the VA Central Office never formally approved it because of the Inspector General's investigation of Dr. Aronow for his unauthorized acceptance of payments from pharmaceutical firms.

The portion that EPA had agreed to fund under an interagency agreement was critical to EPA's carbon monoxide data base. The objective of the project, titled "Effect of 2% Venous Carboxyhemoglobin on Exercise-Induced Angina Pectoris," was to measure the

effect of breathing 50-ppm carbon monoxide (to raise the venous carboxyhemoglobin level to approximately 2 percent) on angina patients.

VA procedures provide that if medical research and development funds are not being requested from VA Central Office and a proposed research project has been approved by the Medical Center's Research and Development Committee, the research may commence using resources under local control, including General Post Funds. Under local authorization Dr. Aronow began the 2-percent carboxyhemoglobin study for EPA on November 23, 1979, and completed it on January 11, 1980. Dr. Aronow and/or his staff assistants spent $12,889 of VA local funds for the carbon monoxide project.

The EPA project officer signed the proposed interagency agreement on October 9, 1979, and EPA submitted it to Dr. Aronow on January 2, 1980, for him to process for VA approval. VA Medical Center in Long Beach submitted the proposed agreement to VA Central Office on April 11, 1980. VA Central Office did not approve the proposed agreement because of the then ongoing investigations of Dr. Aronow.

Between October 1979 and August 1980, EPA's project officer continued operating under the assumption that VA would sign the proposed interagency agreement. On January 29, 1980, Dr. Aronow submitted a draft of his carbon monoxide study report to the EPA project manager. The study was reviewed in March and April 1980 by the EPA project manager and a researcher at the University of North Carolina at Chapel Hill. EPA then entered it into the National Technical Information Service on July 3, 1980, and printed the study as an EPA document in March 1981.

As part of the VA Central Office review of Dr. Aronow's work in early August 1980, VA's Assistant Chief Medical Director for Research and Development telephoned a staff member in EPA's Office of Air Quality Planning and Standards. Although she discussed the EPA-VA Interagency Agreement, she did not mention VA or FDA reviews of Dr. Aronow's research. On August 7, 1980, the EPA project officer to the 2-percent study wrote to VA's Assistant Chief Medical Director for Research and Development requesting that VA sign the interagency agreement. The letter expressed appreciation for Dr. Aronow's efforts and stated that Dr. Aronow's research was of extreme importance to EPA for its regulatory decision process. In an August 13, 1980, letter VA's Assistant Chief Medical Director for Research and Development responded that she was pleased that Dr. Aronow's research had been useful to the EPA but declined to approve the interagency agreement because the research had already been completed using local VA resources. Her letter did not mention the FDA inspection or the VA investigations of Dr. Aronow. In January 1984, we asked her about the decision not to inform EPA of these matters; she told us that she had no reason to believe that there was anything wrong with the quality of Dr. Aronow's carbon monoxide research. She also stated that

she considered the situation to be an internal VA personnel matter. The Assistant Chief of Staff for Research at the VA Medical Center in Long Beach told us that he did not consider EPA to be the client for the research because the interagency agreement was never finalized. As a result, no one at that medical center attempted to notify EPA about Dr. Aronow's research problems.

FDA notified other agencies of its inspections

As early as 1979, FDA notified VA of its inspections and the inspection results. It did not notify EPA until July 12, 1982, because, according to FDA officials, they were not previously aware that Dr. Aronow had performed research for EPA.

In accordance with its established procedures, FDA notified the Director of VA's Medical Center in Long Beach of its planned visits prior to the inspections in 1979. VA's Office of Inspector General requested a copy of FDA's first inspection report, which it received on October 24, 1979. FDA records also show that an FDA official discussed the Aronow case with a representative of VA's Office of Inspector General in April and July 1981. On November 1, 1982, FDA provided VA a copy of its October 1982 agreement with Dr. Aronow.

However, FDA did not inform EPA of its concerns over the quality of Dr. Aronow's clinical studies until July 12, 1982. We were informed by the FDA medical officer who performed the inspections that he knew that Dr. Aronow had performed carbon monoxide research and that the research had been published in professional journals. He said he did not know that EPA was using Dr. Aronow's research until a coworker showed him a notice in the June 18, 1982, Federal Register in which EPA was soliciting public comment on Dr. Aronow's 2-percent study and the role, if any, the study should play in EPA's carbon monoxide standards. This official said he then drafted a memorandum and submitted it through channels to advise EPA of FDA's problems with Dr. Aronow's work. The letter was signed by the Director of FDA's Bioresearch Monitoring Staff.

FDA, however, did not send the letter to the representative in EPA's Office of Air Quality Planning and Standards, as specified in the Federal Register notice. Instead, it was sent to an official in EPA's Pesticides and Toxic Substances Enforcement Division. The Director of FDA's Bioresearch Monitoring Staff told us that he sent the letter to the Chief of the Compliance Monitoring Branch of EPA's Pesticides and Toxic Substances Enforcement Division because that official is listed as the EPA contact on a Memorandum of Agreement between FDA and EPA on the Good Laboratory Practices Program and data audit cases.

In January 1984 we discussed the matter with the EPA recipient of the letter. He told us that he assigned the matter to one

of his staff members who, after locating the Federal Register notice, telephoned EPA's Office of Air Quality Planning and Standards in Durham, North Carolina, to discuss it with the contact listed in that notice. According to the staff member from the Pesticides and Toxic Substances Enforcement Division, because the individual listed was not available, he passed the information along to another staff member in the Office of Air Quality Planning and Standards and forwarded a copy of the letter. The staff in the Pesticides and Toxics Substances Division did not find any record of the referral to the Office of Air Quality Planning and Standards.

On January 31, 1984, we provided a copy of the FDA letter to the staff of the Strategies and Air Standards Division of EPA's Office of Air Quality Planning and Standards. At that time they could not recall either the telephone conversation or the letter. However, on February 10, 1984, the Chairman of the Subcommittee on Oversight and Investigations, House Energy and Commerce Committee, sent a letter to the EPA Administrator, enclosing a copy of the FDA letter and asking why EPA had not acted when it originally received the letter. EPA's Assistant Administrator for Air and Radiation subsequently established an investigative team comprised of staff members from EPA's Offices of Air and Radiation and General Counsel to review the matter.

When this team began examining the issue, the Chief of the Ambient Standards Branch in EPA's Office of Air Quality Planning and Standards notified us that one of his staff members found an entry in a journal he maintained which acknowledges their receiving a phone call on July 19, 1982, concerning the FDA investigation of Dr. Aronow. After reading the journal entry, a staff member in that office recalled receiving the phone call but stated that his office never received the FDA letter. As a result, EPA did not include the letter in its public docket. According to the staff member, the person who telephoned did not provide him with sufficient information to allow him to follow up on the matter. Officials in the Ambient Standards Branch also told us that their heavy work load at that time may have precluded them from pursuing the issue. As a result, EPA did not take any action to review Dr. Aronow's studies on carbon monoxide or reexamine the health studies data base for carbon monoxide until after publication of the March 1983 Washington Post article.

EPA officials told us that, had they been aware of the various reviews of Dr. Aronow's work by VA and FDA, they would have taken the same action they took in March 1983 upon finding out about the FDA investigations in the Washington Post. According to those officials, if, for example, EPA had become aware of the letter from FDA in July 1982, it would have taken the same steps to reexamine its carbon monoxide research base that it took 9 months later.

On April 13, 1984, the investigative team established by EPA's Assistant Administrator for Air and Radiation issued its

report on EPA's handling of information concerning the Aronow investigation. The report confirms that "it was only by happenstance, the fortuitous spotting by an FDA employee of an EPA Federal Register notice, that EPA learned of the investigation as early as 1982." The report states that, even in the aftermath of the controversy surrounding the Aronow matter, there exists no systematic way for EPA to know which of the researchers on whom it relies for development of regulatory standards may be subject to investigation by other government agencies.

We found one other instance in which EPA was told of FDA's problems with Dr. Aronow before the March 23, 1983, Washington Post article appeared. As part of EPA's internal review of a proposed Federal Register package on the carbon monoxide standards in early 1983, an Environmental Protection Specialist in EPA's Office of Policy and Resource Management reviewed several carbon monoxide documents, including the October 9, 1979, CASAC closure letter. The Specialist told us that she had been reassigned to other duties in early February 1983, but she was still helping out with the review on carbon monoxide. A minority opinion to the CASAC letter was written by a CASAC member who questioned EPA's scientific basis for its carbon monoxide standards.

The EPA Environmental Protection Specialist and other EPA officials met with the CASAC member on February 4, 1983. According to the CASAC member, in the course of his meeting with EPA, he told the Specialist that he had heard rumors that FDA was having problems with some of Dr. Aronow's drug research. The CASAC member suggested that EPA contact FDA to follow up on the matter.

According to the EPA Environmental Protection Specialist, she attempted to telephone an official in FDA's Bureau of Drugs to discuss the matter but was never able to make contact with the FDA official. She told us that on February 9, 1983, she left the country for a 4-week vacation, and when she returned, she assumed new duties. As a result, she did not follow up on the matter.

EPA's Inspector General gathered information on Dr. Aronow

As a result of facts gathered by its Office of Inspector General, EPA is considering taking action to debar Dr. Aronow from conducting grant or contractor-funded research for EPA. Between May and October 1983 the Inspector General's Office gathered information about Dr. Aronow's research activities at EPA, VA, and FDA. On January 26, 1984, the Inspector General forwarded a report to the Assistant General Counsel in EPA's Contracts Information Law Branch who will make a recommendation concerning the debarment to the Director of EPA's Grants Administration Division. Under EPA procurement and grant regulatory procedures, the Director is responsible for deciding whether EPA should debar Dr. Aronow. On September 6, 1984, the Assistant General Counsel in EPA's Contracts Information Law Branch told us that he had not yet made his recommendation as to what action EPA should take

concerning Dr. Aronow, but that he plans to make this recommendation by early October 1984.

Presidential Commission recommended establishing a government-wide list of disqualified researchers

In a December 1981 report, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavorial Research[3] recommended that federal departments and agencies should establish government-wide procedures for making determinations on suspension and debarment of grantees and contractors alleged to have engaged in misconduct in federally supported research with human subjects. The Commission recommended that final determinations and sanctions imposed should be entered onto a consolidated list of individuals and made known to all federal agencies involved with human research, to state licensing boards, and to appropriate professional societies. The Commission's report explains that an individual who is debarred or suspended by one federal agency from receiving further grants or contracts remains eligible to receive research funds from other federal agencies. The report also points out that the other agencies may not have any knowledge of the administrative sanctions imposed by the first. The Commission's study was reviewed by an ad hoc Committee for the Protection of Human Research Subjects and an Interagency Human Subjects Coordinating Committee and will become the basis for a proposed Model Federal Policy for Protection of Human Subjects by the Office of Science and Technology Policy in the Executive Office of the President. According to the draft proposed Model Policy, the ad hoc Committee generally concurred with the recommendation on government-wide procedures for suspension and debarment, but believes that it should be implemented as part of an Executive Branch consideration of government-wide suspension and debarment procedures encompassing misconduct under all types of federal support.

The Executive Branch has undertaken several initiatives in this regard. In June 1982, the Office of Federal Procurement Policy of the Office of Management and Budget issued a policy letter prescribing government-wide policies and procedures for suspension/debarment as it relates to direct federal procurement. These policies and procedures have been effective since October 1982, and the General Services Administration is responsible for maintaining a consolidated listing of suspensions and debarment of contractors. In response to a recommendation in a November 1982 report of the Interagency Project Team on Suspension and Debarment, the Office of Management and Budget established a Task Force on Nonprocurement Suspension and Debarment. Among other things, the Task Force is developing uniform government-wide criteria for determining when an assistance recipient or other

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[3]The Commission was established in November 1978 by Public Law 95-622 and was charged, among other things, with reporting biennially to the President and the Congress on the protection of human subjects of biomedical and behavioral research.

nonprocurement recipient should be excluded from participation on a government-wide basis. The Task Force will also provide the Office of Management and Budget with a recommended approach, management structure, and draft implementation documents for a permanent, government-wide, nonprocurement exclusion system. According to its chairperson, the Task Force will make its recommendations to the Office of Management and Budget in early to mid 1985.

These developments address government-wide information sharing but, had they been operative, they would not have had any impact on the Aronow/carbon monoxide situation. Both the policies for direct federal procurement and those being examined for nonprocurement apply to those instances in which the government is funding the researcher in question. In Dr. Aronow's case, the federal government did not fund his research on investigational new drugs. Furthermore, the October 1982 consent agreement between FDA and Dr. Aronow states that FDA would include Dr. Aronow's name on its list of investigators who have voluntarily agreed to restrict or cease their use of investigational new drugs. According to FDA officials, because the agreement also states that, unless requested, the list will not be routinely distributed, FDA would not have included Dr. Aronow in the government-wide list of debarred or suspended researchers.

EPA'S PEER REVIEW PROCESS FOR RESEARCH SUPPORTING THE CARBON MONOXIDE STANDARDS

All research on which EPA relies to support the carbon monoxide standards must be documented in the carbon monoxide criteria document. EPA will only include research in the criteria document that has been published by a professional scientific journal, such as the American Heart Journal, Science, or Circulation. Additionally, the research included in the criteria document is subjected to several peer review phases beyond publication in a professional journal before being used as a basis for the carbon monoxide standards.

Research submitted to any of the professional journals must be peer reviewed before the journals will publish it. According to several journal editors and EPA officials, this peer review process allows other researchers to review and comment on the overall adequacy and reasonableness of the research. The journal editors must be satisfied that any questions or comments raised by these peer reviewers have been addressed by the author before the editors approve the research for publication in their respective journals.

According to journal editors, this peer review process ensures that the researcher's conclusions are valid and based on the information presented in the report and identifies obvious problems or inconsistencies in work practices. However, an in-depth review of the documentation supporting the research would be necessary to determine that data have been falsified or to identify sloppy research practices. Journal editors stated that there would have to be strong indications of falsified data or improper research practices before subjecting a researcher's work to this in-depth level of data audit.

A second peer review phase for the research supporting EPA's carbon monoxide standards occurred during EPA's development of the criteria document. The various chapters of the 1979 carbon monoxide criteria document were written by a combination of EPA and private researchers. However, prior to writing the document, a workshop was held in January 1978 at which time EPA officials and the researchers decided upon the overall format of the document. Subsequently, meetings were held to select the authors and bring them together to prepare draft chapters of the criteria document. A second workshop was also held in June 1978 during which time EPA, the researchers who drafted the various chapters, and other individuals knowledgeable about carbon monoxide reviewed and commented on the drafts of the criteria document chapters. After some revisions EPA solicited public comments on the criteria document through a June 1979 Federal Register notice, and, in response, the automobile industry submitted a number of technical comments. According to officials in EPA's Environmental Criteria and Assessment Office and Office of Air Quality Planning and Standards, EPA took these technical comments into consideration

when finalizing the document. The addendum to the criteria document was written in-house by EPA. EPA submitted the addendum to several outside researchers for comment and solicited public comments through a Federal Register notice.

A third peer review phase for the research supporting the carbon monoxide standards is CASAC's review of the criteria document and staff paper. CASAC's review of these documents in June 1979 addressed five major issues:

--Did the criteria document adequately identify, discuss, and evaluate the critical health studies for carbon monoxide?

--Did the document address and assess in sufficient detail the methodologies for measuring carbon monoxide?

--Did the document adequately identify exposure conditions for the population as can best be ascertained from presently available information?

--Did the criteria document adequately address and evaluate the global cycle of carbon monoxide?

--Did the criteria document fulfill the requirements of the law set forth in the Clean Air Act Amendments of 1977?

In September 1983 EPA again asked CASAC to review the addendum to the criteria document and a revised staff paper. CASAC's review of the criteria document and staff paper was open to the public, and individuals and organizations presented a number of comments on these documents. CASAC's review of these documents considered the opinions of its own expert members and the comments from the general public.

EPA'S PROPOSED REVISIONS TO THE CARBON MONOXIDE STANDARDS

The Clean Air Act, as amended, requires that EPA review and revise as necessary all air quality standards prior to the end of calendar year 1980 and at 5-year intervals thereafter. To meet these requirements, EPA issued a notice in the Federal Register in December 1978 notifying the public that EPA was reviewing, updating, and revising the criteria document for the carbon monoxide standards.

Subsequently, EPA developed the draft criteria document which was reviewed and commented upon by CASAC in a January 1979 meeting. CASAC held another meeting in June 1979 to discuss the second draft of the criteria document and also the EPA staff paper. In an October 9, 1979, closure letter, CASAC agreed with EPA's interpretation of the medical evidence and gave a favorable endorsement to the draft criteria document. One member of CASAC submitted a minority report to the closure letter in which he stated his belief that major problems concerning the adequacy of the research remained to be resolved before the criteria document could be used as a scientific basis for proposing the carbon monoxide standards. EPA, however, accepted the opinion of the majority of CASAC members and finalized the criteria document in October 1979.

Chronology of Events Related to the Development of the Carbon Monoxide Standards

Date	Event	Carbon monoxide levels
4/71	Original carbon monoxide standards promulgated	9 ppm/1 exceedance - 8 hrs 35 ppm/1 exceedance - 1 hr
8/80	Federal Register notice announcing proposed carbon monoxide standards	9 ppm/1 exceedance - 8 hrs 25 ppm/1 exceedance - 1 hr
12/80	Carbon monoxide package presented to EPA Administrator	9 ppm/1 exceedance - 8 hrs 25 ppm/1 exceedance - 1 hr
3/82	Revised carbon monoxide package prepared	9 ppm/5 exceedances - 8 hrs 35 ppm/1 exceedance - 1 hr
12/82	Revised carbon monoxide package prepared	7 ppm/5 exceedances - 8 hrs 25 ppm/1 exceedance - 1 hr
3/83	Revised carbon monoxide package prepared	9 ppm/1 exceedance - 8 hrs 25 ppm/1 exceedance - 1 hr

Source: EPA

After EPA promulgated the standards in 1971, new medical evidence being generated shifted EPA's concerns from the neurological effects of carbon monoxide inhalation to effects related to the cardiovascular system. On August 18, 1980, EPA published in the Federal Register a proposed rule to change the carbon monoxide standard based on the new information. Among other things, this rule proposed changing the 1-hour standard and making several technical adjustments to the standards.

EPA proposed maintaining the 8-hour standard at 9 ppm with one allowable exceedance but proposed changing the 1-hour standard from 35 ppm to 25 ppm. In the notice EPA acknowledged that, when establishing the 35-ppm standard in 1971, EPA failed to consider the influence that light exercise would have on angina patients when they are exposed to carbon monoxide. Taking this and other information into account, EPA found that a 25-ppm, 1-hour standard is comparable to the 9-ppm, 8-hour standard in terms of carboxyhemoglobin protection.

EPA also proposed shifting the form of the standards from deterministic to statistical. A deterministic form allows only one exceedance per year and, according to the June 1979 EPA staff paper, has several limitations including the fact that it does not adequately consider the random nature of meteorological variations. Therefore, EPA proposed to change the carbon monoxide standards to a statistical form that would be based on an average of monitoring data over at least the preceeding 3-year period. As a result, the standards would continue to be expressed in terms of one exceedance per year but would allow, for example, two exceedances one year and none the following year. In a March 23, 1983, memorandum to the EPA Administrator, the Assistant Administrator for Air, Noise, and Radiation recognized that this proposal is somewhat less stringent than the deterministic form established in 1971.

In December 1980 the final carbon monoxide package, based on the August 1980 proposals, was given to the EPA Administrator for a promulgation decision. The Administrator decided to defer the decision on carbon monoxide until the incoming administration had a chance to examine the issues.

EPA's consideration of multiple exceedances

After the change in administrations, EPA began to examine the possibility of allowing localities to exceed the EPA-established standard more than once annually. In March 1981 the EPA Acting Administrator requested that the Office of Air Quality Planning and Standards examine the effects of allowing the 9-ppm, 8-hour standard to be exceeded five times annually.

In March 1982 the Assistant Administrator for Air, Noise, and Radiation forwarded a revised final promulgation package for carbon monoxide to the EPA Administrator. This package proposed

that the 9-ppm 8-hour standard could be exceeded five times per year. No change was planned for the existing 35-ppm, 1-hour standard. In a June 18, 1982, Federal Register notice, EPA stated that this change would tend to reduce the impact of unusual meteorological events on air quality values and, by providing more flexibility, would help state and local agency control officials design and implement pollution control programs. The notice also stated that EPA concluded that, on average, a 9-ppm, 8-hour, five-allowable-exceedance standard is approximately equivelent to a 12-ppm, 8-hour, one-allowable-exceedance standard. According to an EPA sensitivity analysis, raising the standard to 12 ppm with one allowable exceedance or retaining a 9-ppm standard level and increasing the number of allowable exceedances to five would keep 99 percent of the sensitive population from achieving carboxyhemoglobin levels of 2.5 percent or higher. As a result, these changes would have represented a relaxation of the standards when compared with the 1971 standards or the August 1980 proposed standards.

EPA was supported in its decision to consider changing to a multiple exceedance standard in the August 31, 1982, CASAC closure letter. CASAC met on July 6, 1982, to discuss the proposed revision and other carbon monoxide issues and agreed that the multiple exceedance standard had both scientific and administrative merit.

EPA received public comments on its consideration of changing to a multiple exceedance standard. These included comments obtained during an August 27, 1982, hearing held in Oregon before the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce. Many of these comments questioned what was perceived as a relaxation of the standards by shifting to the multiple exceedance format.

In September 1982, the Assistant Administrator for Air, Noise, and Radiation considered changing EPA's proposed 8-hour standard to 7-ppm with five allowable exceedances. By December 1982 EPA's Office of Air Quality Planning and Standards had drafted a promulgation package which would have changed the 8-hour standard from 9 ppm with five allowable exceedances to 7 ppm with five allowable exceedances. The promulgation notice would have revised the 1-hour standard from 35 ppm with one allowable exceedance back to the August 1980 proposed level of 25 ppm with one allowable exceedance. EPA was considering this package because it retained the flexibility of using multiple exceedances and, in response to public comments received, would have maintained approximately the same level of protection as that provided by the August 1980 proposed 8-hour standard of 9 ppm with one allowable exceedance.

In February 1983 EPA received comments from the State and Territorial Air Pollution Program Administrators that had adopted a resolution expressing several reservations about a multiple exceedance standard. The organization stated that a single

exceedance standard is more directly related to the health effects of concern and more clearly understood by the public than a multiple exceedance standard. EPA's Assistant Administrator for Air, Noise, and Radiation had also received a letter dated December 23, 1982, from the Natural Resources Defense Council that for these and other reasons urged her not to recommend the 7-ppm, five-allowable-exceedances standard to the Administrator.

EPA action on carbon monoxide since March 1983

In March 1983, the Assistant Administrator for Air, Noise, and Radiation recommended that the Administrator promulgate the single exceedance standards originally proposed in August 1980. According to the Assistant Administrator's memorandum, she recommended the single exceedance standards because of the concern expressed by the State Air Pollution Control Agencies and others.

The new promulgation package was in final senior level review in EPA when, on March 23, 1983, the Washington Post printed an article stating that FDA had banned drug tests by Dr. Wilbert S. Aronow because he might have misrepresented research results. Because EPA was relying heavily on the results of Dr. Aronow's carbon monoxide research, EPA immediately established a committee of independent experts who reviewed the most recent of Dr. Aronow's carbon monoxide studies and concluded that EPA could not rely on Dr. Aronow's data. EPA subsequently withdrew the carbon monoxide package from final internal review and developed an addendum to the 1979 criteria document and a revised staff paper on carbon monoxide which reevaluated the scientific data in light of the diminished value of the Aronow studies. On September 26, 1983, CASAC reviewed the criteria document addendum and the revised staff paper and reached a consensus that they were scientifically adequate. EPA is now in the process of revising its final standards based on the CASAC review, the updated staff paper, and the criteria document addendum.

Because EPA has not yet issued final standards, it has received a notice of possible judicial action. Spokane, Washington, is one of the cities that has been unable to comply with EPA's carbon monoxide standards and, as a result, EPA has ordered Spokane to establish a schedule for developing a motor vehicle inspection program. On May 1, 1984, four Spokane groups, including the city and county of Spokane, notified EPA of their intent to initiate judicial action against EPA after 60 days if EPA does not promulgate new standards. EPA was required by the Clean Air Act to review and, if necessary, revise the carbon monoxide standards by December 1980. According to the Spokane letter of notice, EPA is not in compliance with the statutory deadline, and "it is conceivable that a proper, scientifically based standard would remove any arguable basis for an inspection program in our area." As of August 29, 1984, Spokane had not initiated any legal action.

Cost of developing carbon monoxide standards

As shown in the following table, EPA's Office of Air Quality Planning and Standards and the Environmental Criteria and Assessment Office estimate that they spent $1,769,100 on revisions to the carbon monoxide standards between fiscal years 1978 and 1984. These estimates do not include expenses incurred by other EPA offices. In developing the 1979 criteria document, the Environmental Criteria and Assessment Office officials estimate that they spent $148,500 on outside contracts and $40,000 on in-house staff. They estimate that they spent another $25,000 of in-house expenses on developing the criteria document addendum.

EPA Estimates of the Cost of Revising the Carbon Monoxide Standards[a]

EPA office	Dollars (in thousands)
Office of Air Quality Planning and Standards	
Outside contractors[b]	$ 764.0
In-house staff	691.6
Computer resources	100.0
Total	$1,555.6
Environmental Criteria and Assessment Office	
Outside contractor	148.5[c]
In-house staff	65.0[c]
Total	$ 213.5[c]
Total	$1,769.1

[a]Does not include costs incurred by other EPA offices. However, these two offices are the primary EPA participants in revising national air quality standards.

[b]Includes development of several documents such as the exposure and sensitivity analyses and the cost and benefit analyses.

[c]Cost of developing the criteria documents.

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